persons who have selection, hiring, placement or supervisory responsibilities for public service employment participants.

* * * * *

§ 98.24 General benefits and working conditions.

(a) (1) Each participant in an on-the-job training, work experience or public service employment program under the Act shall be assured of workers' compensation at the same level and to the same extent as other employees of the employer who are covered by a State or industry workers' compensation statute. Whether provided through the State's compensation agency or a private insurance carrier, this coverage includes medical and accident insurance as well as income maintenance insurance.

(2) Where a participant is employed or engaged in any CETA program activity, i.e., work experience, public service employment, on-the-job training, classroom training, services to participants and other activities where others similarly employed or engaged are not covered by an applicable workers' compensation statute, the participant shall be provided with medical and accident insurance coverage. Whether provided through the State's workers' compensation agency or a private insurance carrier, the prime sponsor shall provide such participants with medical and accident insurance coverage equivalent to the medical and accident insurance provided under the applicable State workers' compensation statute. However, prime sponsors shall not be required to provide these participants with the income maintenance insurance coverage in the statute.

* * * * *

§ 98.41 Review of plans and applications, violations.

(a) The Secretary shall not finally disapprove any Comprehensive Manpower Plan or Application for financial assistance submitted under any title of the Act (except where other procedures are set forth e.g., Sec. 97.292), or any modifications, or amendments thereof, without first affording the grantee submitting the plan or application reasonable notice and opportunity for a hearing as provided in section 98.47 et seq.

* * * * *

Signed in Washington, D.C., this 30th day of June 1977.

ERNEST G. GREEN,
Assistant Secretary for Employment and Training Administration.

[FR Doc.77-19558 Filed 7-7-77;8:45 am]

federal register

FRIDAY, JULY 8, 1977

PART V



DEPARTMENT OF LABOR

Employment and Training Administration

■

MIGRANT AND SEASONAL FARMWORKER PROGRAMS

Fiscal Year 1978 State Planning Estimates, Programs and Areas To Be Renewed Without Competition, and Areas Open for Competition

DEPARTMENT OF LABOR

Employment and Training Administration

MIGRANT AND SEASONAL FARMWORKER PROGRAMS

Fiscal Year 1978 State Planning Estimates, Programs and Areas To Be Renewed Without Competition, and Areas Open for Competition

AGENCY: Employment and Training Administration, Labor.

ACTION: Notice.

SUMMARY: Pursuant to 29 CFR 97.211, the Employment and Training Administration is required to announce State planning estimates of resources available to implement programs funded under title III, section 303 of the Comprehensive Employment and Training Act (CETA) of 1973, as amended. This notice also announces the States and/or areas open for competition as provided in 29 CFR 97.219.

FOR FURTHER INFORMATION CONTACT:

Paul A. Mayrand, Chief, Division of Farmworker Programs, DOL/ETA, 601 D Street NW., Washington, D.C. 20213, Phone: (202—376-7288).

SUPPLEMENTARY INFORMATION:

1. *Fiscal Year 1978 State Planning Allocations.* Planning estimates are announced for planning purposes only and are subject to congressional action on the Fiscal Year 1978 appropriation for the Department of Labor, Employment and Training Administration, CETA. The total amount of planning estimates listed below, $63,920,000, is 85 percent of the total amount planned for all section 303 purposes in Fiscal Year 1978.

The apportionment of the planning estimate amounts for 49 States and Puerto Rico is based on each State's percentage of the nation's farmworkers and on each State's hold harmless level of 90 percent of the Fiscal Year 1977 allocation. These estimates are based upon the same data source utilized for the Fiscal Year 1977 estimates. (A description of this data source and the rationale for using it are set forth in the FEDERAL REGISTER, Volume No. 144, page 31293, July 25, 1975.)

Eligible applicants should use the following State planning estimates in developing Fiscal Year 1978 funding requests:

State:	*Fiscal year 1978 allocation*
Alabama	$967,200
Arizona	931,500
Arkansas	916,100
California	11,911,400
Colorado	690,900
Connecticut	235,700
Delaware	81,000
Florida	3,113,600
Georgia	1,471,600
Hawaii	324,000
Idaho	791,100
Illinois	1,532,200
Indiana	1,208,100
Iowa	1,934,400
Kansas	855,200
Kentucky	1,110,200
Louisiana	685,300
Maine	302,900
Maryland	517,100
Massachusetts	320,500
Michigan	1,239,800
Minnesota	1,768,900
Mississippi	916,100
Missouri	1,173,600
Montana	402,900
Nebraska	828,400
Nevada	103,600
New Hampshire	77,500
New Jersey	453,000
New Mexico	656,100
New York	1,526,500
North Carolina	3,880,700
North Dakota	264,900
Ohio	1,265,200
Oklahoma	736,800
Oregon	1,096,800
Pennsylvania	1,527,200
Rhode Island	40,500
South Carolina	1,029,200
South Dakota	555,100
Tennessee	810,800
Texas	4,962,900
Utah	335,300
Vermont	290,200
Virginia	1,297,600
Washington	1,980,900
West Virginia	499,500
Wisconsin	2,166,200
Wyoming	245,900
Puerto Rico	1,887,900
Total	63,920,000

2. *Programs and areas to be renewed without recompetition.* The Secretary of Labor will exercise the option contained in 29 CFR 97.219(a), to negotiate Fiscal Year 1978 grants without recompetition for existing sponsors whose Fiscal Year 1976 performance was determined to be satisfactory as recorded in the quarterly Program Status Summary (PSS) reports which are used to assess the grantees' performance in carrying out the objectives of the Act, and whose performance continues during the grant negotiation period to be at an acceptable level. (If prior to award of grant, a sponsor's performance is determined not to be acceptable, the Secretary may invite proposals for that area from other organizations and, with or without a panel review, negotiate a grant with one or more proposers pursuant to 29 CFR 92.217.) Satisfactory performance was determined after a review of "actual performance versus planned performance" on 11 factors:

1. Number of participants enrolled.
2. Number placed in jobs.
3. Number of direct job placements.
4. Number of indirect job placements.
5. Number of other positive terminations.
6. Number enrolled in classroom training.
7. Number enrolled in on-the-job training.
8. Number enrolled in work experience.
9. Number enrolled in other activities.
10. Accrued expenditures.
11. Level of nonpositive terminations.

Satisfactory performance for each factor was considered as obtaining at least 85 percent of the planned goal. (For factor 11—level of nonpositive terminations—the grantee had to be at or under the number of planned nonpositive terminations.) For each factor, each grantee was given a positive mark when they adequately met the goal. Grantees with eight or more positive marks were determined to be satisfactorily performing and were selected as grantees to be renewed without competition.

Grantees experiencing serious audit questioned costs or management difficulties were excluded from the noncompetitive list. Also, the new sponsors (selected in 1977) automatically compete since they did not have a full year's experience to rate their actual versus planned performance. Section 97.219 requires that no grant shall be operated in any State or area for a period of more than 2 years without recompetition. Consequently, all States or areas that did not recompete last year were also excluded from the noncompetitive list.

The following are the organizations which demonstrated satisfactory performance and will not compete for Fiscal Year 1978 sponsor status:

States	Sponsors	Areas
Alabama	Alabama Migrant and Seasonal Farmworker Council.	Statewide.
California	County of Los Angeles	Los Angeles.
Iowa	Migrant Action Program	Statewide.
Louisiana	Manpower, Education, and Training of Louisiana	Do.
Massachusetts	New England Farmworkers Council, Inc	Do.
Michigan	United Migrants for Opportunity, Inc	Do.
Minnesota	Minnesota Migrant Council	Do.
Nevada	State of Nevada	Do.
New Jersey	Farmworkers Corp. of New Jersey	Do.
New Mexico	Home Education Livelihood Program	Do.
Tennessee	Tennessee Opportunity Program	Do.
Texas	Community Action Council of South Texas	Starr and Zapata Counties.
	Economic Opportunities Development Corporation of San Antonio.	Counties of Atoscosa, Guadalupe, Bandera, Karnes, Bexar, Kendall, Comal, Kerr, Frio, Medina, Gillespie, Wilson, and McMullen.
	Manpower Education and Training	All remaining counties statewide, excluding the following counties, which will be open for competition: Hidalgo, Jim Hogg, Cameron, and Willacy.

Intra-State planning estimates for Texas and California will be published to enable applicants for funding in areas not closed to competition to prepare funding requests.

All programs to be renewed without competition are required to submit an updated comprehensive plan for Fiscal Year 1978 and, in addition, are subject to the requirements set forth in 29 CFR 97.217 covering negotiation of final grant which includes procedures in case of the failure of negotiations to result in an acceptable, negotiated grant.

3. *Areas Open for Competition.* (a) All areas, except those listed in Paragraph No. 2, above, are open for competition. Organizations interested in applying for these funds should consult the January 7, 1977, FEDERAL REGISTER for the procedures to be used. A notice of intent to apply, the Preapplication for Federal Assistance form, Part I (OMB No. 29–RO218), must be submitted by eligible organizations to the Department of Labor, Employment and Training Administration, Patrick Henry Building, Room 7122, 601 D Street, NW., Washington, D.C. 20213, by August 1, 1977. The Preapplication must be registered or certified by the Postal Service on or before August 1, 1977, or actually received in Room 7122 before 4 p.m. e.d.t. on August 2, 1977. In accordance with 29 CFR 97.212(b), no preapplication received after this time shall be considered for funding.

(b) In a State or area where no organization except the current 303 sponsor submits a Preapplication for a Fiscal Year 1978 grant, the Secretary may elect to negotiate a Fiscal Year 1978 grant without submitting the funding request for panel review.

All programs to be renewed are required to submit an updated comprehensive plan for Fiscal Year 1978 and, in addition, are subject to the requirements set forth in 29 CFR 97.217 covering negotiation of final grant which includes procedures in case of the failure of negotiations to result in an acceptable negotiated grant.

Signed at Washington, D.C. this 5th day of July, 1977.

ERNEST G. GREEN,
Assistant Secretary for Employment and Training.

[FR Doc.77-19528 Filed 7-7-77;8:45 am]

federal register

FRIDAY, JULY 8, 1977

PART VI



DEPARTMENT OF THE INTERIOR

Bureau of Land Management

■

RANGE MANAGEMENT AND TECHNICAL SERVICES

Grazing Administration and Trespass

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[43 CFR Parts 4100, 4700, 9230]

RANGE MANAGEMENT AND TECHNICAL SERVICES

Grazing Administration and Trespass

AGENCY: Bureau of Land Management, Interior.

ACTION: Proposed rulemaking.

SUMMARY: Rulemaking is proposed to update livestock grazing regulations for public lands and to add provisions required by the Federal Land Policy and Management Act of 1976. Changing and increasing land use demands and passage of the new Act necessitate new rulemaking. This proposal changes the grazing regulations to allow for management flexibility to achieve multiple use and environmental objectives.

DATE: Comment by September 6, 1977.

ADDRESS: Send comments to Director (210), Bureau of Land Management, 1800 C Street, NW., Washington, D.C. 20240. Comments will be available for public review in Room 5555 at the above address from 7:45 a.m.–4:15 p.m. on regular working days.

FOR FURTHER INFORMATION CONTACT:

Billy R. Templeton, 202–343–8735.

SUPPLEMENTARY INFORMATION: The principal author of this proposed rulemaking is Allan W. Strobel of the Bureau of Land Management, Washington Office, Division of Range Management, assisted by staff of the Division of Legislation and Regulatory Management and Gail L. Achterman of the Solicitor's Office, Department of the Interior.

Proposed rulemaking was published on pages 31504 through 31515 of the FEDERAL REGISTER of July 28, 1976, under authority of the Taylor Grazing Act of 1934 and other Acts. Comments were invited through January 31, 1977. The purpose of that proposed rulemaking was to modernize the rules for grazing on public lands and to conform with changing land use demands and the resulting need for management flexibility to achieve multiple use and environmental objectives.

The proposed rulemaking of July 28, 1976 was the first major proposed revision of the grazing regulations in decades. Following passage of the Taylor Grazing Act in 1934, regulations were adopted to control use of public rangelands and to adjudicate livestock use allowances to qualified ranch operations. The existing regulations have several deficiencies. First, they are divided into two repetitive sections, one covering grazing administration inside grazing districts and the other covering grazing administration outside grazing districts, making the regulations unnecessarily long and unclear. Second, nearly all of the administrative procedures, including those pertaining to base property and commensurability requirements and transfers of grazing preferences, are cumbersome and time consuming. Third, the existing regulations fail to recognize the multiple use values of the land and the need for management flexibility to achieve multiple use and environmental objectives. In addition, the primary objective of the existing regulations, allocating grazing preferences among ranch operations, was essentially accomplished by the mid-1960's.

The rules proposed last July responded to these deficiencies largely by simplifying the rules, and requiring grazing management to be consistent with land use plans. The key substantive change responded to the increasing and changing demand for public land use. Since the total public land area remains constant, demand can only be accommodated through land use planning for multiple use to minimize adverse impact on the land and its resources. Therefore, the proposed regulations based grazing allocation and management on land use plans incorporating environmental and other resource values. In addition, varying degrees of livestock grazing management intensity were recognized based on the resource evaluations made in land use plans.

Approximately 1,000 comments were received on the proposed rulemaking. During the comment period the Federal Land Policy and Management Act of 1976 was signed into law. The rulemaking process was delayed to determine the effect of the Act on the grazing rules. The Act amended the Taylor Grazing Act and provided for the following: Including a redistribution of grazing fee revenue, new provisions on permit and lease terms, and a new requirement for cancellation notice and compensation for range improvements. Most importantly, though, the Federal Land Policy and Management Act requires that livestock grazing management be carried out in accordance with multiple use land use plans. This statutory provision thus affirms previously adopted administrative policy. New provisions were added to the proposed rules in order to implement the new Act.

Many individuals and groups analyzed the initial proposal and submitted good thoughtful comments and suggestions. Since substantive changes were made in the proposed rulemaking because of the new Act, some comments are no longer appropriate. The proposed rulemaking was amended and clarifying language added in several places as a result of the suggestions received. Interested and affected persons and organizations should critically examine this current proposed rulemaking and comment again.

DISCUSSION OF COMMENTS RECEIVED ON THE PROPOSED RULEMAKING OF JULY 28, 1976

SHOULD ALLOCATION OF GRAZING USE BE BASED ON HISTORICAL USE OF THE PUBLIC LANDS BY DEPENDENT PRIVATE PROPERTY OWNERS IN ORDER TO MAINTAIN THE STABILITY OF THE LIVESTOCK INDUSTRY?

Many comments were received from ranchers, state and local governments and extension agents suggesting that maintaining the stability of the livestock industry be included as an objective of the regulations, as stated in the Taylor Grazing Act. This provision has been included in the new proposed rules. These commentators also feared that elimination of the commensurability requirement and much of the adjudication language in the old regulations indicated that grazing would no longer be allocated on the basis of historic use by dependent private property owners. The concept of commensurability, basing grazing preference on public lands on the productive capacity of private lands, has been included in the new proposed rules in modified form. Base property must be capable of producing crops or forage that can be used to support livestock, but the new proposed regulations do not require the crops or forage to actually be produced. Land base property must be owned or controlled and must be used in a livestock operation. Provision is also made for future adjudication, if necessary, in the sections on grazing preference and conflicting applications.

HOW MUCH CONTROL SHOULD THE BUREAU HAVE OVER PRIVATE LIVESTOCK OPERATIONS?

Many ranchers and their representatives criticized provisions in the proposed regulations which they believed interfered unjustifiably with the rancher's judgment on how to run livestock. They especially feared unilateral imposition of allotment management plans by the Bureau. The new proposed regulations require that allotment management plans be developed in consultation with the permittee or lessee. Only if agreement cannot be reached will the Bureau institute a grazing management plan by decision. The comments also criticized the provision allowing the Bureau to specify the breed of livestock in a permit or lease. This provision was clarified by limiting its use to community allotments where two or more operators graze their livestock in common. Comments also criticized prohibiting placing feed or mineral supplements on public lands without authorization. Many noted that salt placement is a necessary and proper part of livestock management which should not require prior authorization. We agree and the new proposed regulations have been changed accordingly.

HOW MUCH PUBLIC PARTICIPATION SHOULD OCCUR BEFORE CLOSING PUBLIC LANDS TO GRAZING?

Some comments criticized the provision allowing public lands to be closed to livestock by notifying livestock operators and the public. Greater opportunity for public comment was suggested. This provision was clarified to emphasize that it will only be used in exceptional circumstances to protect the soil, vegetative or other public land resources usually in cases such as droughts. These circumstances require quick action inconsistent with time-consuming public participation.

HOW MUCH NOTICE IS NECESSARY BEFORE GRANTING A LIVESTOCK OPERATOR A CHANGE OF USE?

The proposed rules required livestock operators to apply for a change in grazing use 30 days before the grazing season or year begins. Permittees or lessees must file their basic grazing schedules with the Bureau and they are billed for scheduled use unless a change in use is allowed in advance. Many comments suggested that changes be allowed up until the first day of the season or year. The suggestion was not adopted because 30 days is needed to evaluate the compatibility of the proposed change with existing operations and management objectives for the allotment and to complete necessary administrative requirements.

SHOULD WILLFUL AND NONWILLFUL TRESPASS BE DISTINGUISHED?

Many comments criticized the proposed rules for failing to treat willful and non-willful trespass differently. Ranchers believed the penalties were too severe in cases of non-willful trespass. Environmental groups and others believed they were too lenient in cases of willful trespass. The existing rules allow collection of twice the value of the forage consumed in cases of willful trespass, while the proposed rules did not. The new proposed rules distinguish between willful and non-willful trespass and reinsert the double damage provision in cases of willful trespass in order to provide a real disincentive to trespassers.

COORDINATING GRAZING USE WITH STATES AND PRIVATE LANDOWNERS WHERE THEIR LANDS ARE INTERMINGLED WITH PUBLIC LAND

Many States and ranchers owning land intermingled with public land commented on the inclusion of these lands in allotment management plans and the application of prescribed systems of livestock grazing on these lands. The new proposed rules explain that private and State land shall be considered if these lands are unfenced and intermingled with public lands in the allotment or with consent or request of the rancher. The exchange-of-use permit provision was not changed because in such cases the private owner voluntarily applies for the permit and subjects his private land to Bureau control in exchange for free use of the intermingled public land.

WHO IS THE AUTHORIZED OFFICER?

The existing grazing regulations refer to the State Director of the Bureau and the District Manager. Many comments criticized the shift to the term "authorized officer" in the proposed rules contending that no one knows who this person is. While we agree that the term causes some confusion, it would be even more confusing to state explicitly who has each particular authority since delegations of authority change frequently. The authorized officer is not a new concept or person. The term refers to any official of the Bureau of Land Management who has been delegated the authority, through specific Secretarial or Bureau delegations, to carry out the management responsibilities of the Secretary of Interior on a particular management area of the public land. The authorized officer may be an Area Manager, District Manager, State Director, or the Director of the Bureau of Land Management depending upon the location and the resource program involved. The authorized officer will most often be an Area Manager or a District Manager under these rules.

SHOULD CONSULTATION WITH ADVISORY BOARDS BE REQUIRED?

Several comments from both ranchers and environmental groups suggested that consultation with advisory boards should be mandatory in certain instances. Ranchers also sought reestablishment of grazing district advisory boards. This was done in a limited way by the Federal Land Policy and Management Act. Regulations governing the boards appear in 43 CFR Subpart 1784.

SHOULD VIOLATION OF STATE AND FEDERAL CONSERVATION LAWS BE GROUNDS FOR CANCELLING OR REDUCING A RANCHER'S GRAZING PREFERENCE?

The proposed rules made violation of a Federal or State law or regulation concerning the conservation or protection of natural or cultural resources or the environment a prohibited act punishable by cancellation or reduction of the violator's grazing preference. This provision was widely criticized. Ranchers contend that the provision is unfair because it punishes them twice, once under the conservation law or regulation violated and once under this provision. Conservation organizations contend that there should be no requirement for criminal conviction, rather that the Bureau should administratively determine whether such laws have been violated. Both arguments have been thoroughly reviewed. The rule proposed in July has not been changed. First, it should be noted that the Bald Eagle Protection Act and the Endangered Species Act both authorize reduction or cancellation of grazing permits or leases only following criminal conviction. This standard was adopted in the proposed rules in order to provide due process and because the Bureau cannot legally determine whether these other laws and regulations have been violated. This provision is necessary though because in some instances violation of these laws and regulations indicates that a permittee or lessee has insufficient regard for the public lands and their resources to warrant continuation of his preference.

SHOULD VEGETATIVE RESOURCES BE ALLOCATED TO WILDLIFE AND WILD HORSES AND BURROS BEFORE ALLOCATING FORAGE TO DOMESTIC LIVESTOCK?

Several conservation organizations, state governments and university professors commented on the needs of wildlife. The existing regulations explicitly recognize the need to set aside forage for wildlife while the rules proposed last July implied that this would be done through land use planning. The new proposed rules require in § 4110.2–2(a) that grazing preference be allocated to qualified applicants only following the allocation through land use planning of the forage between livestock grazing, wild horses and burros, wildlife and other forage needs. No priority is given to one forage use over another since this would not conform with multiple use land use planning objectives. It is also important to note that these regulations only cover domestic livestock grazing. Other regulations now being prepared by the Department will cover land use planning, the process in which vegetative resources are allocated between livestock, wildlife and wild and free-roaming horses and burros.

LIVESTOCK GRAZING CAPACITY

The regulations proposed in July used the term "livestock grazing capacity" without defining it. This omission and failure to explicitly condition grazing permits and leases on available forage were severely criticized. A definition is included in the new proposed rules. In addition, a general condition was added stating that authorized livestock grazing use shall not exceed the livestock grazing capacity. One comment suggested that grazing capacity should be reviewed annually to assure that use matches available forage. This procedure would be costly, cumbersome, and is unnecessary since a number of provisions allow for reductions in grazing if necessary for resource protection.

Accordingly, in line with the above discussion, the proposed rulemaking has been changed as appropriate in accordance with comments received on the July 28, 1976 publication and the applicable provisions of the Federal Land Policy and Management Act. The amended rulemaking is published as a proposed rulemaking and public comments and suggestions are invited.

MAJOR FEATURES

These regulations apply to livestock grazing on all lands administered by the Bureau of Land Management outside of Alaska. Regulations for the public lands within and outside grazing districts are consolidated and the issuance of grazing permits and leases will be treated in nearly identical fashion.

The allocation of grazing preference and the authorization of grazing use on the public lands through the issuance of grazing permits and leases will be accomplished in accordance with land use plans which provide for multiple use management and protection of the environment and other resource values. The regulations provide for issuing grazing permits and leases for a term of 10 years; however, if the public lands involved are pending disposal or will be devoted to a public purpose which precludes livestock grazing prior to the end of 10 years, the grazing permits or leases will be issued for a term coinciding with the anticipated date of disposal or anticipated date for devoting the lands to another public purpose. Grazing permits or leases will also be issued for less than 10 years in the interest of sound land management if necessary to achieve the objectives in the land use plans or if the land use plans have not been completed.

The proposed regulations provide for the application of the appropriate intensity of livestock grazing management, along with associated range improvement, needed to achieve the management objectives on specific areas of public land consistent with land use plans. Allotment management plans will be developed and implemented in consultation with the grazing permittees or lessees. Only if agreement cannot be reached will the Bureau institute a grazing management plan by decision.

While the commensurability and base property requirements are retained, they have been streamlined to reduce administrative requirements and to provide more livestock operator flexibility. Transfer procedures have been simplified.

No change is proposed in the grazing fee formula. This issue will be dealt with separately after the study required by the Federal Land Policy and Management Act is submitted to Congress. Until then the fee will remain the same. Grazing fees must be paid prior to using the public land for grazing unless a management permit or lease has been issued providing for billing and payment after use. If such a permit or lease has been issued, a fee notice based upon actual use reported will be issued after the grazing season. A $25 service charge will be made for each transfer of grazing preference and for each supplemental or revised billing made on the motion of the permittee or lessee. Unless provided otherwise in an allotment management plan, a request to change the grazing use authorized by a grazing permit or lease must be made in writing and approved by the authorized officer before the change is made.

The means of coping with livestock grazing trespass have been strengthened. Instead of using a $2 nonwillful and $4 willful trepass, fee, settlement for unauthorized grazing use will include a charge for the cash rental value of the forage consumed plus costs arising from damage to the public land and property. The proposed rulemaking provides for impoundment and sale of trespass livestock. The expenses incurred in gathering, impounding, caring for, and disposing of livestock may also be included in the settlement. Additionally, the authorized officer may suspend a grazing permit or lease in whole or in part or may cancel a grazing permit or grazing lease, and grazing preference in whole or in part for nonwillful trespass. The authorized officer is required, under these rules, to suspend a grazing permit or lease in whole or in part or cancel a grazing permit or grazing lease and grazing preference in whole or in part for trespass determined to be clearly willful or repeated.

The Department of the Interior has determined that this document does not contain a major proposal requiring preparation of an Economic Impact Analysis under Executive Order 11821 and OMB Circular A–107.

An environmental impact statement (EIS) for livestock grazing management on national resource lands, released on January 22, 1975, was prepared in accordance with section 102(2)(C) of the National Environmental Policy Act of 1969 (42 U.S.C. 4332(2)(C)). The revised regulations will facilitate implementation of the proposed grazing program discussed in this statement. Implementation of the proposed action will be completed through the preparation of EIS's which discuss livestock grazing activities on localized areas of public lands.

Under the authority of the Taylor Grazing Act of 1934, as amended, (43 U.S.C. 315, 315(a)–315(r)), section 4 of the Act of August 28, 1937 (43 U.S.C. 1181(d)), and the Federal Land Policy and Management Act of 1976 (43 U.S.C. 1701 et seq.), it is proposed to amend Group 4100, Subchapter D, Chapter II, Title 43 of the Code of Federal Regulations as set forth below.

1. Part 4100 is revised to read as follows:

PART 4100—GRAZING ADMINISTRATION—EXCLUSIVE OF ALASKA

Subpart 4100—Grazing Administration—Exclusive of Alaska; General

Sec.
4100.0–1 Purpose.
4100.0–2 Objectives.
4100.0–3 Authority.
4100.0–5 Definitions.
4100.0–7 Cross-references.

Subpart 4110—Allocation of Grazing Use

4110.1 Mandatory qualifications.
4110.2 Grazing preference.
4110.2–1 Base property.
4110.2–2 Grazing preference allocation.
4110.2–3 Transfer of grazing preference.
4110.2–4 Relinquishment of grazing preference.
4110.3 Changes in available forage.
4110.3–1 Additional forage.
4110.3–2 Decrease in forage.
4110.4 Changes in public land acreage.
4110.4–1 Additional land acreage.
4110.4–2 Decrease in land acreage.
4110.5 Conflicting applications.
4110.6 Interest of Member of Congress.

Subpart 4120—Grazing Management

4120.1 Allotments.
4120.2 Terms and conditions.
4120.2–1 General terms and conditions.
4120.2–2 Allotment management plans.
4120.3 Closure to livestock.
4120.4 Ownership and identification of livestock.
4120.5 State livestock requirements.
4120.6 Range improvements.
4120.6–1 Cooperative agreements.
4120.6–2 Range improvement permits.
4120.6–3 Standards and design.
4120.6–4 Assignment of range improvements.
4120.6–5 Removal and compensation for loss of range improvements.
4120.6–6 Contributions.
4120.7 Special rules.

Subpart 4130—Authorizing Grazing Use

Sec.
4130.1 Applications.
4130.2 Grazing permits or leases.
4130.2–1 Regular permits or leases.
4130.2–2 Management permits or leases.
4130.2–3 Custodial permits or leases.
4130.3 Free-use grazing permits.
4130.4 Other permits.
4130.4–1 Exchange-of-use grazing permits.
4130.4–2 Nonrenewable grazing permits.
4130.4–3 Crossing permits.
4130.5 Fees.
4130.5–1 Payment of fees.
4130.5–2 Refunds.
4130.5–3 Service charges.
4130.6 Changes in grazing use.
4130.7 Pledge of permit or lease as security for loan.

Subpart 4140—Prohibited Acts

4140.1 Acts prohibited on public lands.

Subpart 4150—Unauthorized Grazing Use

4150.1 Unauthorized grazing.
4150.2 Notice and order to remove.
4150.3 Settlement.
4150.4 Demand for payment.
4150.5 Impoundment and disposal.
4150.5–1 Notice of intent to impound.
4150.5–2 Notice of public sale.
4150.5–3 Redemption.
4150.5–4 Sale.

Subpart 4160—Administrative Remedies

4160.1 Proposed decisions.
4160.1–1 Proposed decisions on permits or leases.
4160.1–2 Proposed decisions on alleged violations.
4160.2 Protests.
4160.3 Final decisions.
4160.4 Appeals.

Subpart 4170—Penalties

4170.1 Penalty for violations.
4170.1–1 Failure to use.
4170.1–2 Federal and State law or regulation.
4170.2 Penal provisions.

AUTHORITY: 43 U.S.C. 315, 315a–315r, 1701 et seq., 1181d.

Subpart 4100—Grazing Administration—Exclusive of Alaska; General

§ 4100.0–1 Purpose.

The purpose of these regulations is to provide for the uniform administration and management of livestock grazing on the public lands, exclusive of Alaska.

§ 4100.0–2 Objectives.

The objectives of these regulations are to manage livestock grazing on public lands, to preserve the land and its resources from destruction or unnecessary injury, to stabilize the livestock industry dependent on the public lands, and to provide for the orderly use, improvement, and development of the public lands for livestock grazing consistent with multi-

ple-use, environmental, economic, and other objectives as stated in Subpart 1725 of this chapter and in Section 1.02 of the Federal Land Policy and Management Act of 1976, Pub. L. 94–579, 90 Stat. 2745 (43 U.S.C. 1701 et seq.).

§ 4100.0–3 Authority.

(a) The Taylor Grazing Act of June 28, 1934, as amended (43 U.S.C. 315, 315a–315r), authorizes the Secretary of the Interior to establish grazing districts and to make provisions for the protection, administration, regulation, and improvement of the public lands. It also authorizes the Secretary to lease lands outside of such districts for grazing purposes upon such terms and conditions as he may prescribe.

(b) The Federal Land Policy and Management Act of 1976, Pub. L. 94–579, 90 Stat. 2745 (43 U.S.C. 1701 et seq.), provides for the management, protection, development, and enhancement of the public lands and directs the Secretary to manage these lands under principles of multiple use and sustained yield in accordance with land use plans.

(c) Executive orders transferring land acquired under the Bankhead-Jones Farm Tenant Act of July 22, 1937, as amended (7 U.S.C. 1012), to the Secretary for administration under the Taylor Grazing Act.

(d) Section 4 of the O&C Act of August 28, 1937 (43 U.S.C. 1181d), which authorizes the Secretary, at his discretion, to lease for grazing purposes any revested Oregon and California Railroad or Reconveyed Coos Bay Wagon Road grant lands in the State of Oregon which may be so used without interfering with the production of timber or other purposes specified in the O&C Act.

(e) Public land orders, Executive orders, or agreements which authorize the Secretary to administer livestock grazing on specified lands in accordance with the Taylor Grazing Act or other authority as specified.

§ 4100.0–5 Definitions.

Whenever used in this part, unless the context otherwise requires, the following definitions apply:

(a) The "Act" means the Taylor Grazing Act of June 28, 1934, as amended (43 U.S.C. 315, 315a–315r).

(b) "Allotment" means an area of land designated and managed for grazing of livestock.

(c) "Allotment management plan (AMP)" means a documented program which applies to livestock operations on the public lands, which is prepared in consultation with the permittee(s) or lessee(s) involved, and which (1) prescribes the manner in and extent to which livestock operations will be conducted in order to meet the multiple-use, sustained-yield, economic, and other needs and objectives as determined for the public lands through land use planning; and (2) describes the type, location, ownership, and general specifications for the range improvements to be installed and maintained on the public lands to meet the livestock grazing and other objectives of land management; and (3) contains such other provisions relating to livestock grazing and other objectives as may be prescribed by the authorized officer consistent with applicable law.

(d) "Animal unit month (AUM)" means the amount of forage necessary for the sustenance of one cow or its equivalent for a period of 1 month. One horse, one burro, five sheep, or five goats shall be considered equivalent to one cow.

(e) "Authorized officer" means any person authorized by the Secretary to administer regulations in this part.

(f) "Base property" means (1) farm or ranch property (land and improvements) that serves as a base for a livestock operation and has the capability to produce crops or forage that can be used to support authorized livestock for a specified period of the year, or (2) water that is suitable for consumption by livestock and is available, accessible, and adequate for the authorized livestock when the public lands are used for livestock grazing.

(g) "Cancellation" means a permanent termination of a grazing permit or grazing lease and grazing preference in whole or in part.

(h) "Class of livestock" means age and/or sex groups of a kind of livestock.

(i) "Contiguous land" means land that borders upon or corners upon public land.

(j) "District" means the specific area of public lands administered by a District Manager.

(k) "Grazing district" means the specific area within which the public lands are administered under section 3 of the Act. Public lands outside grazing district boundaries are administered under Section 15 of the Act.

(l) "Grazing fee year" means the year March 1 to the last day of February which is used for billing purposes.

(m) "Grazing lease" means a document authorizing use of the public lands outside grazing districts under section 15 of the Act for the purpose of grazing livestock.

(n) "Grazing permit" means a document authorizing use of the public lands within grazing districts under section 3 of the Act for the purpose of grazing livestock.

(o) "Grazing preference" means the total number of animal unit months of livestock grazing on public lands apportioned and attached to base property owned or controlled by a permittee or lessee.

(p) "Livestock" or "kind of livestock" means species of domestic likestock—cattle, sheep, horses, burros, and goats.

(q) "Livestock grazing capacity" means the number of animal unit months of forage available for livestock grazing on a sustained yield basis on the public lands as determined through land use planning.

(r) "Modification" means a change or revision of the terms and conditions of an unexpired grazing permit or lease including changes in kind or class and number of livestock, season(s) of use, and area(s) of use.

(s) "Other lands under Bureau of Land Management control" means those State or private lands controlled by the Bureau of Land Management through lease, agreement, or otherwise.

(t) "Public lands" means any land and interest in land outside of Alaska owned by the United States and administered by the Secretary of the Interior through the Bureau of Land Management, except lands located on the Outer Continental Shelf and lands held for the benefit of Indians.

(u) "Range betterment" means the rehabilitation, protection, and improvement of the public lands to arrest range deterioration and to improve forage conditions, fish and wildlife habitat, watershed protection, and livestock production consistent with land use plans.

(v) "Range betterment fund" means the separate account in the Treasury established by Section 401(b)(1) of the Federal Land Policy and Management Act of 1976 consisting of 50 per centum of all moneys received by the United States as fees for grazing livestock on public lands.

(w) "Range improvement" means a structure, development, or treatment used to rehabilitate, protect, or improve the public lands to advance range betterment.

(x) "Secretary" means the Secretary of the Interior or his authorized officer.

(y) "Suspension" means temporarily withholding a grazing permit or lease in whole or in part.

§ 4100.0–7 Cross-references.

The regulations in Subpart 1784 of this chapter govern advisory boards and the regulations in Part 4 of this title govern appeals and hearings.

Subpart 4110—Allocation of Grazing Use

§ 4110.1 Mandatory qualifications.

Except as provided under §§ 4130.3 and 4130.4–3, to qualify for grazing use on the public lands an applicant must be engaged in the livestock business, must own or control land or water base property, and must be:

(a) A citizen of the United States or have properly filed a valid declaration of intention to become a citizen or a valid petition for naturalization; or

(b) A group or association authorized to conduct business in the State in which the grazing use is sought, all members of which are qualified under paragraph (a) of this section; or

(c) A corporation authorized to conduct business in the State in which the grazing use is sought, and in which the controlling interest is vested in persons qualified under paragraph (a) of this section.

§ 4110.2 Grazing preference.

§ 4110.2–1 Base property.

(a) The authorized officer shall find land or water owned or controlled by an applicant to be base property (see § 4110.0–5(f)) if:

(1) It is used in conjunction with a livestock operation which utilizes public lands within a grazing district; or

(2) It is contiguous land, and in certain cases non-contiguous land, used in conjunction with a livestock operation which utilizes public lands outside a grazing district.

(b) The authorized officer shall specify the lenth of time for which land base property shall be capable of supporting authorized livestock, during the year, taking into consideration the availability and customary use of base properties and the management requirements for the public lands.

(c) An applicant shall provide a legal description of his base property and shall certify to the authorized officer that this base property meets the requirements under paragraph (a) and (b) of this section and § 4110.0–5(f).

§ 4110.2–2 Grazing preference allocation.

(a) Grazing preference shall be allocated to qualified applicants following the allocation of the forage resources between livestock grazing, wild free-roaming horses and burros, wildlife, and other forage uses in the land use plans.

(b) Applicants who own or control base property contiguous to public land outside of a grazing district where such public land consists of an isolated or disconnected tract embracing 760 acres or less shall have a preference right for 90 days after the tract has been offered for lease to lease the whole tract.

(c) The animal unit months of grazing preference is attached to the acres of land base property on a pro rata basis.

§ 4110.2–3 Transfer of grazing preference.

(a) Transfers of grazing preference in whole or in part are subject to the following requirements:

(1) The transferee shall qualify for a grazing preference under the regulations of this part.

(2) The transfer shall not disrupt the stability of the livestock industry in the general area within which the public lands involved are located.

(3) The transfer document, under paragraph (b) of this section or the transfer application, under paragraph (c) of this section, shall evidence assignment of interest and obligation in range improvements authorized on public lands under § 4120.6 and used and maintained in conjunction with the transferred preference (see § 4120.6–4). The transferee shall accept the terms and conditions of the cooperative agreements and range improvement permits with such modifications deemed necessary by the authorized officer.

(4) The transferee shall accept the terms and conditions of the grazing permit or lease (see § 4130.2) with such modifications as he may request which are consistent with the land use plans and approved by the authorized officer.

(5) The transferee shall file an application for a grazing permit or lease to the extent of the transferred preference simultaneously with filing a transfer document or a transfer application under paragraph (b) or (c) of this section.

(b) If base property is sold or leased, the transferee shall file with the authorized officer a properly executed transfer document showing the base property and the amount of grazing preference being transferred, in animal unit months, within 60 days of the date of sale or lease. If the transfer document has been timely filed and the requirements under paragraph (a) of this section have been met, the authorized officer shall approve the transfer of the grazing preference attached to the affected base property, shall approve the assignment of interest and obligation in range improvements on the public lands, and shall issue a grazing permit or lease.

(c) If a grazing preference is being transferred from one base property to another base property, the transferee shall file with the authorized officer a properly competed transfer application in advance for approval. The transfer application shall (1) state the amount of grazing preference being transferred, in animal unit months, (2) include a legal description of the old and new base property, (3) contain the concurrence of any lien holder, and (4) contain the consent of the owner(s) of the base property from which the transfer is to be made, unless the transferee is a lessee of the base property without whose livestock operation a grazing preference would not have been established, in which case the consent of the owner of the base property is not required. If the transfer application has been properly filed and the requirements under paragraph (a) of this section have been met, the authorized officer may approve the transfer of grazing preference between the base properties, may approve the assignment of interest and obligation in range improvements on the public lands, and may issue a grazing permit or lease.

(d) As the date of approval of a transfer, the existing grazing permit or lease shall terminate automatically and without notice to the extent of the transfer.

(e) If an unqualified transferee acquires rights in base property through operation of law or testamentary deposition, such transfer will not affect the grazing preference or any outstanding grazing permit or lease, or preclude the issuance or renewal of a grazing permit or lease based on such property for a period of 2 years after the transfer. However, such a transferee shall qualify under paragraph (a) of this section within the 2-year period or the grazing preference shall be subject to cancellation. The authorized officer may grant extensions of the 2-year period where there are delays solely attributable to probate preceedings.

(f) Failure of the transferee to comply with the regulations of this section may result in the cancellation of the grazing preference.

§ 4110.2–4 Relinquishment of grazing preference.

Upon written request, the authorized officer shall accept the relinquishment of a grazing preference in whole or in part. No such relinquishment shall be accepted without the written concurrence of any lien holder and the written consent of the owner(s) of the base property to which the preference is attached, unless the applicant is a lessee of the base property without whose livestock operation a grazing preference would not have been established.

§ 4110.3 Changes in available forage.

§ 4110.3–1 Additional forage.

Additional forage may be allocated to qualified applicants for livestock grazing use at the discretion of the authorized officer if this use is consistent with the land use plans.

(a) Additional forage temporarily available, including forage which is temporarily available within an allotment because of a change in grazing use under § 4130.6, may be allocated on a nonrenewable basis.

(b) Additional forage permanently available for livestock grazing use shall first be allocated in satisfaction of grazing preferences to the permittee(s) or lessee(s) authorized to graze in the allotment in which the forage is available.

(c) Additional forage permanently available for livestock grazing use over and above the preference(s) of the permittee(s) or lessee(s) in an allotment may be allocated in the following priority to:

(1) Permittee(s) or lessee(s) in proportion to their preferences or in proportion to the permittee's or lessee's contirbution or efforts which resulted in increased forage production; or

(2) Other qualified applicants under § 4110.5.

§ 4110.3–2 Decrease in forage.

When authorized grazing use exceeds the amount of forage available for livestock grazing within an allotment or where reduced grazing use is necessary to facilitate achieving the objectives in the land use plans, grazing permits or grazing leases and grazing preferences shall be cancelled in whole or in part. The cancellation will be equitably apportioned by the authorized officer or as agreed to among permittees or lessees and the authorized officer. If consistent with resource management needs, the cancellations may be scheduled over a period not to exceed 3 years at the discretion of the authorized officer if necessary to ease the economic impacts on the affected permittees or lessees.

§ 4110.4 Changes in public land acreage.

§ 4110.4–1 Additional land acreage.

When land outside designated allotments becomes available for grazing administration by the Bureau of Land Management, the forage available for livestock grazing may be allocated to qualified applicants at the discretion of the authorized officer if this use is consistent with the land use plans. If there are applicants who were previously authorized to make grazing use of these lands, they shall have a preference to grazing use of the additional lands.

Otherwise, grazing use will be allocated under § 4110.5.

§ 4110.4–2 Decrease in land acreage.

(a) Where there is a decrease in public land acreage available for livestock grazing use within a allotment, grazing permits of grazing leases and grazing preferences shall be cancelled in whole or in part. The cancellations will be equitably apportioned by the authorized officer or as agreed to among authorized users and the authorized officer.

(b) When public lands are disposed of or devoted to a public purpose which precludes livestock grazing, the permittees and lessees shall be given two years' prior notification except in cases of emergency, before their grazing permit or grazing lease and grazing preference may be cancelled in whole. A permittee or lessee may unconditionally waive the two year prior notification. Such a waiver shall not prejudice the permittee's or lessee's right to reasonable compensation for the fair market value of his interest in authorized permanent range improvements located on these public lands (see § 4120.6–5).

§ 4110.5 Conflicting applications.

When more than one qualified applicant applies for livestock grazing use of the same public land and/or where additional forage or additional land acreage becomes available, the authorized officer may allocate grazing use of such land or forage consistent with the land use plans on the basis of any or all of the following factors:

(a) Historical use of the public land;

(b) Proper range management and use of water for livestock;

(c) General needs of the applicants' livestock operations;

(d) Public ingress and egress across privately owned or controlled land to public lands;

(e) Topography;

(f) Other land use requirements unique to the situation.

§ 4110.6 Interest of Member of Congress.

Title 18 U.S.C. 431–433 (1970) generally prohibits a Member of or Delegate to Congress from entering into any contract or agreement with the United States. Title 41 U.S.C. 22 (1970) generally provides that in every contract or agreement to be made or entered into, or accepted by or on behalf of the United States, there shall be inserted an express condition that no Member of or Delegate to Congress shall be admitted to any share or part of such contract or agreement, or to any benefit to arise thereupon. The provisions of these laws are incorporated herein by reference and apply to all permits, leases, and agreements issued under these regulations.

Subpart 4120—Grazing Management

§ 4120.1 Allotments.

As land use plans are prepared, the authorized officer shall designate allotments where the public lands and other lands under Bureau of Land Management control are suitable and available for livestock grazing.

§ 4120.2 Terms and conditions.

Livestock grazing permits and leases shall contain terms and conditions necessary to achieve the management objectives for the public lands and other lands under Bureau of Land Management control identified in land use plans.

§ 4120.2–1 General terms and conditions.

(a) The authorized officer shall specify the kind or class and number of livestock, the season(s) of use, the allotment(s) to be used, and the amount of use, in animal unit months, that can be made. The authorized livestock grazing use shall not exceed the livestock grazing capacity and shall be limited or excluded to the extent necessary to achieve the objectives established for the allotment.

(b) The authorized officer may:

(1) Specify breed of livestock in allotments within which 2 or more permittee(s) or lessee(s) are authorized to graze.

(2) Authorize and direct the placement of feed and mineral supplements for livestock on the public lands.

(3) Authorize grazing use by kinds of indigenous animals under specific terms and conditions.

(c) If allotment management plans have not been prepared or if it has been determined that allotment management plans are not necessary, the authorized officer shall incorporate terms and conditions under this section in grazing permits or leases. The authorized officer shall modify these terms and conditions if the condition of the range requires modification of grazing use and may cancel grazing permits or grazing leases and grazing preferences as conditions warrant under §§ 4110.3–2 and 4110.4–2. These modifications and cancellations may be made at anytime and shall be put into full force and effect on the date specified by the authorized officer.

§ 4120.2–2 Allotment management plans.

Grazing management may be applied on allotments through the preparation and implementation of allotment management plans.

(a) An allotment management plan shall be prepared in consultation with the affected permittee(s) or lessee(s), approved by the authorized officer and implemented (see § 4100.0–5(c)). The allotment management plan shall include appropriate terms and conditions under § 4120.2–1 and shall prescribe a system of grazing designed to meet specific management objectives. The plan shall include the limits of flexibility within which the permittee or lessee may adjust his operation without prior approval of the authorized officer. The plan shall provide for the collection of studies data that shall be used to evaluate the effectiveness of the system of grazing in achieving the specific objectives.

(b) Private and State lands shall be considered in the allotment management plan if these lands are unfenced and are intermingled with the public lands in the allotment or with the consent or at the request of the permittee or lessee.

(c) Allotment management plans may be revised in consultation with the affected permittee(s) or lessee(s).

(d) If allotment management plans have been prepared, the authorized officer shall incorporate these plans in grazing permits or leases when they are issued. If grazing permits or leases have been issued prior to the preparation of allotment management plans, the authorized officer shall incorporate the allotment management plans in the grazing permits or leases when these plans are completed.

(e) Decisions which specify that allotment management plans are incorporated as terms and conditions of grazing permits or leases may be protested and appealed under Subpart 4160.

§ 4120.3 Closure to livestock.

Where required for the protection of the soil, vegetative, or other resources on the public lands, the authorized officer may close allotments to grazing by any kind of livestock and for any period of time. The action taken by the authorized officer shall be specified in a notice of closure. The notice shall be published in a local newspaper and shall be posted at the county courthouse and at a post office near the public land area involved. Written notification shall be delivered personally or by certified mail to those who are authorized to graze livestock on the allotments affected. The notice of closure shall be issued as a final decision in full force and effect under § 4160.3(c) and shall require all owners of livestock affected thereby to remove such livestock in accordance with provisions of the notice. The authorized officer may proceed to impound, remove, and dispose of any livestock found in violation of the closing notice after the closure date specified in the notice in accordance with § 4150.5.

§ 4120.4 Ownersaip and identification of livestock.

(a) The permittee or lessee shall own or control and be responsible for the management of the livestock which graze the public lands under a grazing permit or lease. If the permittee or lessee does not own the livestock, he shall furnish the authorized officer a document specifying the kind and number of livestock, the brand or other marking the livestock are carrying, and the arrangements which in fact give him control of the livestock. This document shall be approved by the authorized officer prior to placing the livestock on the public lands.

(b) All cattle, horses, and burros over 6 months of age shall carry a brand which has been filed with the authorized officer. All sheep and goats over 6 months of age shall be identified with an earmark, paint brand, or other marking that has been filed with the authorized officer.

(c) The authorized officer may exempt certain livestock from the mini-

mum requirements under paragraph (b) of this section. An alternative method of identifying the livestock satisfactory to the authorized officer shall be used in such instances.

(d) The authorized officer may require additional or special marking or tagging of the authorized livestock in order to control trespass or in order to otherwise promote the orderly administration of the public lands.

§ 4120.5 State livestock requirements.

Authorized users shall comply with the requirements of the State in which the public lands are located relating to: branding of livestock; breed, grade, and number of bulls; and sanitary requirements.

§ 4120.6 Range improvements.

(a) When appropriated, one-half of the range betterment funds (see § 4130.5-1(d)) shall be available for use in the District from which the grazing fees were collected for the purpose of on-the-ground range rehabilitation, protection, and improvement of public lands after consultation with user representatives. The other one-half of the range betterment funds shall be used for on-the-ground range rehabilitation, protection, and improvement of public lands at the discretion of the authorized officer after consultation with user representatives. See § 4100.0-5 (u), (v), and (w).

(b) Range improvements shall be installed, used, maintained, and/or modified on the public lands in a manner consistent with the land use plans.

(c) Prior to installing, using, maintaining and/or modifying range improvements on the public lands permittees or lessees shall have entered into a cooperative agreement with the Bureau of Land Management or must have a range improvement permit.

§ 4120.6-1 Cooperative agreements.

Any permittee or lessee may enter into a cooperative agreement with the Bureau of Land Management for the installation, use, maintenance, and/or modification of range improvements needed to achieve management objectives within his designated allotment. Cost and/or labor shall be placed between United States and permittees or lessee. The United States shall have title to range improvements authorized under cooperative agreements.

§ 4120.6-2 Range improvement permits.

Any permittee or lessee may apply for a range improvement permit to install, use, maintain and/or modify range improvements that are needed to achieve management objectives within his designated allotment. The permittee or lessee shall agree to provide total funding. The range improvement permits are issued at the discretion of the authorized officer. The permittee or lessee shall have title to range improvements authorized under range improvement permits.

§ 4120.6-3 Standards and design.

Range improvement cooperative agreements and permits shall specify the standards and design for the range improvements and shall contain conditions and construction criteria deemed necessary by the authorized officer to facilitate achieving the objectives in the land use plans. Where an existing range improvement is significantly inconsistent with these objectives, the authorization for the improvement may be modified by the authorized officer to reflect needed changes. Upon failure of the permittee or lessee to comply with the standards and design specified by the authorized officer or failure to comply with the authorized officer's order to modify an existing range improvement, authorization for the improvement may be cancelled.

§ 4120.6-4 Assignment of range improvements.

The authorized officer shall not approve the transfer of a grazing preference under § 4110.2-3 nor approve use by the transferee of an existing range improvements, unless the transferee has agreed to compensate the transferor for fair market value of his interest in the authorized improvements within the allotment as of the date of transfer. If the parties are unable to agree as to the amount or manner of reasonable compensation, the matter shall be resolved by the authorized officer.

§ 4120.6-5 Removal and compensation for loss of range improvements.

(a) The authorized officer may require permittees or lessees to remove range improvements which they own on the public lands if these improvements are no longer serving the purpose for which they were installed or if they fail to meet the standards and design criteria under § 4120.6-3.

(b) If grazing permits or grazing leases and grazing preferences are cancelled in whole or in part because the public lands are being disposed of or devoted to a public purpose which precludes livestock grazing, the permittees or lessees shall receive fair market value from the United States for their interest in the authorized permanent range improvements located on the public lands (less salvage value) which will no longer be available for livestock grazing.

(c) Permittees or lessees may be allowed a period of 180 days from the date of cancellation of a range improvement permit to salvage material owned by them and to perform such rehabilitation measures as are deemed necessary by the authorized officer.

§ 4120.6-6 Contributions.

(a) The authorized officer may accept contributions of labor, material, equipment, or money for administration, protection, and improvement of the public lands necessary to achieve the objectives of this part.

(b) The authorized officer may require the permittee or lessee to finance individually, or to share proportionately with other permittees or lessees, the cost of installation and/or maintenance of range improvements if the permittee or lessee will benefit in substantial measure or should reasonably be responsible for such costs.

§ 4120.7 Special rules.

Whenever it appears to a State Director that local conditions within his administrative jurisdiction require a special rule to achieve improved administration consistent with the objectives of this part, he may recommend such a rule for approval by the Director. These recommendations shall be subject to public review and comment, as appropriate, and upon approval shall become effective when published in the FEDERAL REGISTER as final rules. Special rules shall be published in a newspaper within the local area. Copies of the rule shall be sent to those who are authorized to graze livestock in the area where the special rule is applicable.

Subpart 4130—Authorizing Grazing Use

§ 4130.1 Applications.

Applications for grazing permits or leases (active use and non-use), free-use grazing permits and other permits shall be filed with the authorized officer at the local Bureau of Land Management office.

§ 4130.2 Grazing permits or leases.

(a) Grazing permits or leases shall be issued to authorize livestock grazing on the public lands and other lands under Bureau of Land Management control. These grazing permits or leases shall specify the amount of active grazing use, nonuse, or combination of active grazing use and nonuse that is authorized and shall include appropriate terms and conditions under § 4120.2.

(b) A grazing permit or lease conveys no right, title, or interest in any lands or resource use authorized thereunder and is a privilege for the exclusive benefit of the permittee or lessee.

(c) Grazing permits or leases authorizing livestock grazing on the public lands, and other lands under Bureau of Land Management control, shall be issued for a term of ten years unless:

(1) The land is pending disposal; or

(2) The land will be devoted to another public purpose prior to the end of ten years; or

(3) It will be in the best interest of sound land management to specify a shorter term.

If the public lands involved are pending disposal or shall be devoted to a public purpose which precludes livestock grazing prior to the end of 10 years, the grazing permits or leases shall be issued for a term coinciding with the anticipated date of disposal or anticipated date for devoting the lands to another public purpose. Grazing permits or leases shall be issued for less than ten years in the interest of sound land management if necessary to achieve the objectives in the land use plans or if the land use plans have not been completed. The absence of details from allotment management plans shall not be the basis for establishing a term shorter than ten years.

(d) Permittees or lessees holding expiring grazing permits or leases shall be

given first priority for receipt of new permits or leases if:

(1) The lands remain available for livestock grazing in accordance with land use plans (see Subpart 4120).

(2) The permittee or lessee is in compliance with the regulations contained in this part and the terms and conditions of his grazing permit or lease; and

(3) The permittee or lessee accepts the terms and conditions to be included in the new permit or lease by the authorized officer.

§ 4130.2–1 Regular permits or leases.

Regular permits or leases shall be issued for terms of from 1 up to and including 10 years to authorize livestock grazing on allotments within areas where land use plans have not been completed. The term of the permits or leases shall coincide with the scheduled completion dates for the land use plans for the affected areas.

§ 4130.2–2 Management permits or leases.

Management permits or leases shall be issued for a term of not more than 10 years to authorize livestock grazing on allotments within areas where land use plans have been completed and where allotment management plans have been or will be incorporated into the permits or leases.

§ 4130.2–3 Custodial permits or leases.

Custodial permits or leases shall be issued for a term of not more than 10 years to authorize livestock grazing on allotments wthin areas where land use plans have been completed and where it has been determined that allotment management plans are not necessary.

§ 4130.3 Free-use grazing permits.

A free-use grazing permit shall be issued to any applicant whose residence is adjacent to public lands within grazing districts and who needs these public lands to support those domestic livestock owned by the applicant whose products or work are used directly and exclusively by the applicant and his family. The permit may be issued for a period of not more than 10 years.

§ 4130.4 Other permits.

Exchange-of-use grazing permits, nonrenewable grazing permits, and crossing permits have no priority for renewal and cannot be transferred or assigned.

§ 4130.4–1 Exchange-of-use grazing permits.

An exchange-of-use grazing permit may be issued to any permittee or lessee who owns or controls lands within the exterior boundaries of the allotment covered by his grazing permit or lease. An exchange-of-use permit may be issued to authorize use of public land within the allotment to the extent of the livestock grazing capacity of the permittee's or lessee's land within the allotment. No fee shall be charged for this grazing use. The exchange-of-use permit may be issued for a term of not more than 10 years. The expiration date of the exchange-of-use permit shall coincide with the expiration date of the grazing permit or lease issued on the allotment in which the land offered in exchange is located. During the term of the exchange-of-use permit, the Bureau of Land Management shall have management control of such private land for grazing purposes under the provisions of this part and may authorize grazing use as deemed appropriate.

§ 4130.4–2 Nonrenewable grazing permits.

Nonrenewable grazing permits may be issued to qualified applicants when forage is temporarily available, provided this use does not interfere with existing livestock operations on the public lands and it is consistent with the land use plans. This use shall be authorized on a seasonal or annual basis only. Nonrenewable grazing use may be included in a regular grazing permit or lease issued for 1 year under § 4130.2–1.

§ 4130.4–3 Crossing permits.

Any applicant showing the necessity for crossing the public land with livestock for proper and lawful purposes may be issued a crossing permit upon such terms and conditions deemed necessary by the authorized officer to achieve the objectives of this part.

§ 4130.5 Fees.

§ 4130.5–1 Payment of fees.

(a) The fees for each grazing fee year shall be published annually in the FEDERAL REGISTER.

(b) Fees shall be charged for livestock grazing upon or crossing the public lands and other lands under Bureau of Land Management control at a specified rate per animal unit month. A minimum annual charge of $10 will be made for livestock grazing upon or crossing the public lands. No fee shall be charged for livestock grazing authorized under free-use grazing or exchange-of-use grazing permits.

(c) Fees shall be established by the Secretary in equal annual increments effective with the grazing fee year beginning March 1, 1978, to attain fair market value of range forage beginning March 1 of the 1980 grazing fee year. Fair market value is that value established by the Western Livestock Grazing Survey of 1966 or as determined by any study which may be conducted to update the fee base. Annual adjustments shall also be made for any of the 1978–80 grazing fee years and thereafter to reflect changes in the current market value as determined by an adequate index(es).

(d) Fifty percent of the grazing fees collected for grazing livestock on public lands (other than ceded Indian lands) under the Act shall be deposited in a separate account in the United States Treasury for the range betterment program (see § 4120.6).

(e) Fees are due upon issuance of the billing notice and must be paid in full prior to grazing use except where an allotment management plan has been incorporated in a management permit or lease, in which case a billing notice based on actual use may be issued at the end of the grazing season or year or a billing notice based on the normal operation may be issued prior to the grazing season or year followed by an adjusted billing notice based on actual use after grazing use has been completed. Each permittee or lessee operating under a management permit or lease incorporating an allotment management plan shall submit within 15 days after the end of his authorized grazing period, or as otherwise specified in the permit or lease, a report of the actual livestock grazing use made. Upon failure or refusal to submit an actual use report, a billing notice, or adjusted billing notice, reflecting charges for grazing use at the upper limit of flexibility as specified in the allotment management plan, shall be issued and is immediately due and payable.

(f) The full fee shall be charged for all weaned livestock which are not the natural increase of livestock upon which fees are paid and for animals that shall become 12 months of age during the period of use. No charge shall be made for animals under 6 months of age at the time of entering public lands and other lands under Bureau of Land Management control, which are the natural increase of the livestock upon which fees are paid or for those born during the season for which the permit or lease authorizes use, and until they are 12 months of age.

§ 4130.5–2 Refunds.

(a) Grazing fees may be refunded at the discretion of the authorized officer where applications for change in grazing use and related refund are filed prior to the period of use for which the refund is requested.

(b) No refunds shall be made for failure to make grazing use, except during periods or range depletion due to severe drought, fire, or other natural causes or general epidemic of disease that occurs during the term of a permit or lease. During these periods of range depletion the authorized officer may credit or refund fees in whole or in part, or fee payment may be postponed for as long as the emergency exists.

§ 4130.5–3 Service charge.

Except for actions initiated by the authorized officer, a service charge of $25 shall be made for each transfer of a preference and for each supplemental or revised billing issued under § 4130.6.

§ 4130.6 Changes in grazing use.

(a) Permittees and lessees shall have on file with the authorized officer a basic grazing schedule which outlines their annual livestock grazing use on the public lands, including the kind or class and number of livestock, the season(s) of use, the allotment(s) to be used, and the amount of use, in animal unit months. Permittees and lessees shall be billed in accordance with the basic grazing schedule unless a change in use has been requested.

(b) Requests for grazing use different than the basic grazing schedule should

be filed with the authorized officer no later than 30 days before the grazing season or year. Requests for change in use filed later than 30 days before the grazing season or year, or after the start of the grazing season or year, shall be subject to a service charge under § 4130.5–3.

(c) A request for change in use may be granted at the discretion of the authorized officer if the request is compatible with existing operations and consistent with the objectives for the allotment.

§ 4130.7 Pledge of permit or lease as security for loan.

The authorized officer shall renew a grazing permit or lease that has been pledged as security for a loan from a lending agency for a period of not to exceed 10 years if the loan is for the purpose of furthering the permittee's or lessee's livestock operation, *Provided*, That the permittee or lessee has complied with the rules and regulations of this part and that such renewal will be in accordance with other applicable laws and regulation.

Subpart 4140—Prohibited Acts

§ 4140.1 Acts prohibited on public lands.

The following acts by permittees and lessees are prohibited on public lands and other lands under Bureau of Land Management control:

(a) Allowing livestock on or driving livestock across these lands in violation of the terms and conditions of a permit or lease, either by exceeding the number of livestock authorized, or by allowing livestock to be on these lands in an area or at a time different from that designated;

(b) Failing to make substantial grazing use as authorized for 2 consecutive fee years;

(c) Placing feed or mineral supplements, other than salt, for livestock on these lands without authorization;

(d) Failing to comply with the terms of a range improvement cooperative agreement or range improvement permit;

(e) Refusing to finance individually, or to share proportionately with other permittees or leasees, the cost of installation, maintenance and/or modification of range improvements when so directed by the authorized officer if the permittee or lessee will benefit in substantial measure or should reasonably be responsible for such costs.

(f) Installing, using, maintaining, and/or modifying range improvements on these public lands without authorization;

(g) Cutting, burning, spraying, destroying, or removing vegetation without authorization;

(h) Damaging or removing United States property without authorization;

(i) Molesting livestock lawfully grazing on these lands;

(j) Littering;

(k) Violating any provision of Part 4700 of this subchapter concerning the protection and management of wild free-roaming horses and burros;

(l) Violating any Federal or State law or regulation concerning conservation or protection of natural and cultural resources or the environment including, but not limited to, those relating to air and water quality, protection of fish and wildlife, plants, and the use of chemical toxicants;

(m) Interfering with lawfully uses or users;

(n) Knowingly or willfully making a false statement or representation in grazing applications, range improvement permit applications, and/or amendments thereto.

Subpart 4150—Unauthorized Grazing Use

§ 4150.1 Unauthorized grazing.

Allowing livestock on or driving livestock across public lands and other lands under Bureau of Land Management control without proper authorization is prohibited and constitutes unauthorized grazing use. See § 4140.1(a). Violators shall be liable in damages to the United States for the forage consumed by their livestock, for injury to Federal property caused by their unauthorized grazing use, and for expenses incurred in impoundment and disposal, and may be subject to civil penalties or criminal sanction for such unlawful acts.

§ 4150.2 Notice and order to remove.

(a) Whenever it appears that a violation exists and the owner of the unauthorized livestock is known, written notice shall be served upon the alleged violator or his agent by certified mail or personal delivery and a copy of the notice shall be sent to any known lien holder. The notice shall set forth the act or omission constituting the violation and refer to the specific terms, conditions, or regulatory provisions, alleged to have been violated. It shall also order the alleged violator to remove the livestock within a specified time. The notice shall allow a specified time from receipt of notice for the alleged violator to show that there has been no violation or to make settlement under § 4150.3. If the alleged violator fails to comply with the notice, the authorized officer may proceed to impound the livestock under § 4150.5.

(b) When neither the owner of the unauthorized livestock nor his representative is known, the authorized officer may proceed to impound the livestock under § 4150.5.

(c) A notice alleging unauthorized horse or burro use in areas with wild free-roaming horses and burros shall specify that the unauthorized horses or burros can be claimed and gathered only in accordance with the procedures of Part 4700 of this subchapter.

§ 4150.3 Settlement.

The authorized officer shall weigh the facts and circumstances of the case and shall determine if the violation is nonwillful or willful and whether it is a repeated violation. When violations are determined to be nonwillful, settlement shall be made under paragraphs (a)(1) and (a)(3) of this section. When violations are determined to be willful, and/or repeated, settlement shall be made under paragraphs (a) (2), (3), and (4) of this section and the authorized officer shall take action under § 4170.1.

(a) The amount due the United States in settlement for unauthorized grazing use shall be determined by the authorized officer as follows:

(1) "Nonwillful violations." The value of forage consumed as determined by the average monthly rate for pasturing livestock on privately owned land for the 11 Western States as published annually by the Department of Agriculture.

(2) "Willful, and/or repeated violations." Twice the value of the forage consumed as determined in paragraph (a)(1) of this section.

(3) The full value for all damages to the public lands and other property of the United States.

(4) All expenses incurred by the United States including those incurred in gathering, impounding, caring for, and disposing of livestock in cases which necessitate impoundment under § 4150.5.

(b) Payment made under this section does not relieve the alleged violator of any criminal liability under Federal or State law.

§ 4150.4 Demand for payment.

Where the livestock have been removed, but satisfactory settlement has not been made within the time allowed under § 4150.2, a certified letter demanding payment will be sent or personally delivered to the owner or his agent and a copy of the letter shall be sent to any known lien holder. This letter shall allow not more than 15 days from date of receipt to settle the obligation.

§ 4150.5 Impoundment and disposal.

Unauthorized livestock remaining on the public lands after the date set forth in the notice and order to remove sent under § 4150.2 may be impounded and disposed of by the authorized officer as provided herein.

§ 4150.5–1 Notice of intent to impound.

(a) A written notice of intent to impound shall be sent by certified mail or personally delivered to the owner, or his agent, and a copy of the notice shall be sent to any known lien holder. Any time after five days of delivery of the notice the unauthorized livestock may be impounded.

(b) Where the owner or agent is unknown, or a known owner or agent refuses to accept delivery, a notice of intent to impound shall be published in a local newspaper and posted at the county courthouse and a post office near the public land involved. Any time after 5 days of the posting of the notice, the unauthorized livestock may be impounded.

(c) Unauthorized livestock may be impounded without further notice any time within the 12-month period following the effective date of a notice given under this provision.

§ 4150.5–2 Notice of public sale.

Following the impoundment of livestock under this subpart the livestock may be disposed of by the authorized officer or, if a suitable agreement is in effect, they may be turned over to the State for disposal. If the authorized officer disposes of the livestock, he shall publish a notice of sale in a local newspaper and post this notice at the county courthouse and at a post office near the land involved. The notice shall describe the livestock and specify the date, time, and place of sale. The sale date shall be at least 5 days after the publication and posting of the notice. Any known owners or agents and known lien holders shall be notified in writing by certified mail or by personal delivery of the sale and the procedure by which the impounded livestock may be redeemed prior to the sale.

§ 4150.5–3 Redemption.

Any owner or known lien holder of the impounded livestock may redeem them in accordance with State law, prior to the time of sale upon settlement with the United States under § 4150.3 or adequate showing that there has been no violation.

§ 4150.5–4 Sale.

If the livestock are not redeemed on or before the date and time fixed for their sale, they shall be offered at public sale to the highest bidder either by the authorized officer or by the State. If a satisfactory bid is not received, the livestock may be reoffered for sale, condemned and destroyed, or otherwise disposed of in accordance with State law. When livestock are sold by the authorized officer pursuant to these regulations, he shall furnish the purchaser a bill of sale or other written instrument evidencing the sale. If sold by the State, the Bureau of Land Managament shall be reimbursed for the amount due under § 4150.3 up to the amount received for sale of the livestock.

Subpart 4160—Administrative Remedies

§ 4160.1 Proposed decisions.

§ 4160.1–1 Proposed decisions on permits or leases.

The authorized officer shall serve a proposed decision on any applicant, permittee, or lessee, or his agent, who is adversely affected by his proposed action on applications for permits or leases or by his proposed action related to terms and conditions of permits or leases, by certified mail or personal delivery, and shall notify any known lien holder of the proposed decision. The proposed decision shall state the reasons for the action, including reference to the pertinent terms, conditions, and/or regulating provisions, and shall provide for a period of 15 days after receipt for the filing of a protest.

§ 4160.1–2 Proposed decisions on alleged violations.

If the authorized officer determines that a permittee or lessee appears to have violated any provision of this part he shall serve a proposed decision on the permittee or lessee, or his agent, by certified mail or personal delivery, and shall notify any known lien holder of the proposed decision. The proposed decision shall state the alleged violation and refer to the specific terms, conditions, and/or regulatory provisions alleged to have been violated and the reasons for the proposed decision. As applicable, the proposed decision shall state the amount due under § 4150.3 and the action to be taken under § 4170.1. The proposed decision shall provide for a period of 15 days after receipt for the filing of a protest.

§ 4160.2 Protests.

Any applicant, permittee, lessee, or any other person adversely affected by a proposed decision of the authorized officer may protest the proposed decision in person or in writing to the authorized officer within 15 days after receipt of the proposed decision.

§ 4160.3 Final decisions.

(a) In the absence of a protest, the proposed decision shall become the final decision of the authorized officer without further notice.

(b) Upon the timely filing of a protest, the authorized officer shall reconsider his proposed decision in light of the protestant's statement of reasons for protest and in light of other information pertinent to the case. At the conclusion of his review of the protest, the authorized officer shall serve his final decision on the protestant, or his agent, and on any other known interested individual, and shall notify any known lien holder of the final decision.

(c) The final decision shall provide for a period of 30 days after receipt for filing of an appeal. An appeal shall suspend the effects of the final decision from which it is taken pending final action on the appeal unless the authorized officer provides in the final decision that it shall be in full force and effect pending decision on appeal thereform. Final decisions shall be in full force and effect only if required for the orderly administration of the range or for the protection of other resource values. See § 4.477 of this title.

§ 4160.4 Appeals.

Any applicant, permittee, lessee, or any other person whose interest is adversely affected by a final decision of the authorized officer may appeal the decision for the purpose of a hearing before an administrative law judge under § 4.470 of this title by filing his notice of appeal in the office of the authorized officer within 30 days after the receipt of the decision.

Subpart 4170—Penalties

§ 4170.1 Penalty for violations.

The authorized officer may suspend the grazing use authorized under a grazing permit or grazing lease in whole or in part or may cancel a grazing permit or grazing lease and grazing preference in whole or in part under Subpart 4160 for violation by a permittee or lessee of any of the provisions of this part. However, the authorized officer shall suspend the grazing use authorized under a grazing permit or grazing lease in whole or in part or shall cancel a grazing permit or grazing lease and grazing preference in whole or in part under Subpart 4160 for willful or repeated violation by a permittee or lessee of § 41.40.1(a). Whenever a nonpermittee or nonlessee violates § 4140.1(a) and has not made satisfactory settlement under § 4150.3, the authorized officer shall refer the matter to proper authorities for appropriate legal action by the United States against the violator.

§ 4170.1–1 Failure to use.

Failing to make substantial grazing use as authorized for 2 consecutive fee years may result in the cancellation of the grazing preference only to the extent of failure to use (see § 4140.1(b)).

§ 4170.1–2 Conservation and protection of resources.

Violation of § 4140.1(1) may result in suspension, reduction, or revocation of a permit, lease, or grazing preference where:

(a) Public land administered by the Bureau of Land Management is involved or affected;

(b) Such violation is related to grazing use authorized by permit or lease; and

(c) The permittee or lessee has been convicted of violating any such laws by a court.

§ 4170.2 Penal provisions.

Under section 2 of the Act and under section 303(a) of the Federal Land Policy and Management Act of 1976, any person who willfully violates the provisions of these Acts or of this part or of approved special rules and regulations may be brought before a designated United States magistrate and is punishable by a fine of not more than $1,000 or imprisonment for no more than twelve months, or both.

PART 4700—WILD FREE-ROAMING HORSE AND BURRO PROTECTION, MANAGEMENT, AND CONTROL

2. Part 4700 is amended by changing references in §§ 4720.3, 4730.3, and 4730.4. These sections are revised to read as follows:

§ 4720.3 Trespass animals.

Unauthorized horses or burros which have been claimed and have been determined to be privately owned in accordance with the provisions of this section will be considered to have been in trespass and may not be released until a proper trespass charge has been determined by the authorized officer in accordance with the provisions of Subpart 4150 of this subchapter.

§ 4730.3 Habitat reservation and allocation.

The biological requirements of wild free-roaming horses and burros will be determined based upon appropriate studies or other available information. The needs for soil and watershed pro-

tection, domestic livestock, maintenance of environment quality, wildlife, and other factors will be considered along with wild free-roaming horse and burro requirements. After determining the optimum number of such horses and burros to be maintained on an area, the authorized officer shall reserve adequate forage and satisfy other biological requirements of such horses and burros and, when necessary, adjust or exclude domestic livestock use accordingly. See §§ 4110.2–2 and 4110.3–2 of this subchapter.

§ 4730.4 Closure to livestock grazing.

The authorized officer may close public lands to use by all or a particular class of domestic livestock where it is necessary to allocate all available forage to, or to satisfy other biological requirements of wild free-roaming horses or burros. Such closures may be made only after appropriate public notice and in accordance with the procedures for reduction or cancellation of grazing privileges provided for under provisions in this subchapter. See §§ 4110.2–2 and 4110.3–2 of this subchapter.

PART 9230—TRESPASS

3. Part 9230 is amended by deleting §§ 9239.3, 9239.3–1, and 9239.3–2 and redesignating "§ 9239.3–3 Alaska." as "§ 9239.3 Grazing, Alaska." as follows:

§§ 9239.3—9239.3–2 [Deleted]

§ 9239.3 Grazing, Alaska. [Redesignated from § 9239.3–3]

GUY R. MARTIN,
Assistant Secretary of the Interior.

JULY 6, 1977.

[FR Doc.77–19608 Filed 7–7–77;8:45 am]



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FRIDAY, JULY 8, 1977

PART VII

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Products

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 343]

[Docket No. 77N-0094]

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Products

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: This is a proposal to establish conditions under which over-the-counter (OTC) internal analgesic, antipyretic and antirheumatic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products.

DATES: Comments by October 6, 1977, and reply comments by November 7, 1977.

ADDRESSES: Written comments to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Division of OTC Drug Evaluation (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857 (301-443-4960).

SUPPLEMENTARY INFORMATION: Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on April 5, 1977, a report of the Advisory Review Panel on Over-The-Counter (OTC) Internal Analgesic and Antirheumatic Products. In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC internal analgesic, antipyretic and antirheumatic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The summary minutes of the Panel meetings are on public display in the office of the Hearings Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC internal analgesic, antipyretic and antirheumatic drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before August 8, 1977, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to FDA, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD-510), 5600 Fishers Lane, Rockville, MD 20857.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

(1) That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for not longer than 3 years (for the specific conditions specified in this document) after the date of publication of the final monograph in the FEDERAL REGISTER, if the Food and Drug Administration (FDA) receives notification in accordance with § 330.10(a)(13) (21 CFR 330.10(a)(13)) that tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel will be conducted. The period of time within which studies must be completed will be carefully reviewed by the Commissioner after receipt of comments on this document.

The Commissioner recognizes that new additional data or information not previously available to the Panel regarding Category III conditions may become available prior to publication of the tentative final monograph in the FEDERAL REGISTER pursuant to § 330.10(a)(7) of the OTC drug review regulations. The Commissioner concludes that it is in the best interest of all parties if additional time is provided for the submission of such data to the FDA. Therefore, the Commissioner shall accept new data or information regarding Category III conditions until January 9, 1978.

Any changes justified by the new data and information will be included in the tentative final monograph. Full opportunity for comment on both the changes and the new data and information will be provided by the opportunity to file objections to the tentative final monograph pursuant to § 330.10(a)(7).

The Commissioner has not yet fully evaluated the report, but has concluded that it should first be issued as a formal proposal to obtain full public comment before any decision is made on the recommendations of the Panel. The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report of the Panel represents the best scientific judgment of the members. The report has been prepared independently of FDA and does not necessarily reflect the agency position on any particular matter contained therein.

The Commissioner recognizes that major changes will result in the current marketing practices of these products if the recommendations of the Panel are fully implemented. The Panel's recommendations include many revisions in labeling, particularly limitations of indications for use, and additional warnings against unsafe use. In addition, revised dosage schedules are proposed with major changes in the labeling for pediatric use.

In the final order for antacid products published in the FEDERAL REGISTER of June 4, 1974 (39 FR 19862), the antacid monograph provides that any safe and effective analgesic, as determined by the internal analgesic monograph, may be used in combination with an antacid for concurrent analgesic and antacid symptoms. The Commissioner determined that the issue of the safety, effectiveness, and appropriate labeling of the analgesic component of an antacid/analgesic combination would be addressed in the course of reviewing the recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products. The Commissioner is aware of the Panel's recommendation that (1) combinations of nonsalicylate ingredients that meet the standard for Category I combination products may be combined with antacid ingredients which meet the requirements of § 331.10 of the OTC antacid monograph provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for acid indigestion" and (2) aspirin may be combined with antacid active ingredients identified in § 331.11 of the OTC antacid monograph such that the finished product meets certain specifications regarding neutralizing capacity

and pH and the product is identified as highly buffered aspirin for solution with labeling only as an analgesic and/or antipyretic.

At this time, the Commissioner seeks comment on these recommendations before any final determination is made. After review of the comments and data submitted, the Commissioner will address this issue in the publication of the internal analgesic, antipyretic and antirheumatic tentative final monograph. At that time the Commissioner will also address any related modifications that may be required in the antacid monograph (21 CFR Part 331).

The Commissioner notes that the Panel's recommendation concerning the dosage of acetaminophen exceeds that set forth in § 310.201(a)(1) (21 CFR 310.201(a)(1)). The Commissioner's final acceptance of the Panel's recommendation regarding acetaminophen, including its dosage and labeling, would necessitate withdrawal of NDA's for acetaminophen drugs and revocation of § 310.201(a)(1).

The Commissioner invites full public comment on all of the Panel's recommendations. After careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC internal analgesic, antipyretic and antirheumatic drug products.

The Commissioner has reviewed the potential environmental impact of the recommendations and proposed monograph for OTC internal analgesic, antipyretic and antirheumatic products of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products and has concluded that the Panel's recommendations and proposed monograph will not significantly affect the quality of the human environment and that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

The conclusions and recommendations in the report of the Advisory Review Panel on OTC Internal Analgesic, Antipyretic and Antirheumatic Products follow:

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness and labeling of all OTC drugs by independent advisory review panels. On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review under § 330.10 (formerly § 130.301) published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), which were made effective immediately. Pursuant to these regulations, the Commissioner issued in the FEDERAL REGISTER of July 21, 1972 (37 FR 14633) a request for data and information on all internal analgesic and antirheumatic active ingredients in drug products.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC internal analgesic and antirheumatic ingredients pursuant to § 330.10(a)(1):

Henry W. Elliott, M.D., Ph.D., Chairman, deceased August, 1976
J. Weldon Bellville, M.D., Chairman from August, 1976
William H. Barr, Ph.D.
Julius M. Coon, M.D., Ph.D.
Ninfa I. Redmond, Ph. D., resigned January, 1977
Naomi F. Rothfield, M.D.
George Sharpe, M.D.

The Panel was first convened on October 24, 1972 in an organizational meeting. Working meetings were held on November 21 and 22, 1972; January 22 and 23, February 26 and 27, April 12 and 13, June 11 and 12, July 30 and 31, September 25 and 26, October 22 and 23, November 19 and 20, and December 17 and 18, 1973; March 11 and 12, April 10 and 11, May 8 and 9, July 8, 9 and 10, September 25 and 26, November 11 and 12, and December 9 and 10, 1974; March 17, 18 and 19, June 25, 26 and 27, August 14 and 15, October 6 and 7, and November 18 and 19, 1975; April 8 and 9, May 20 and 21, August 21, 22 and 23, October 15 (telephone conference) and November 22, 23, and 24, 1976.

Two nonvoting liaison representatives served on the Panel. Ms. Kathryn Eilers Van Flue, nominated by the Consumer Federation of America, served as the consumer liaison and Joseph M. Pisani, M.D., nominated by the Proprietary Association, served as the industry liaison.

The following FDA employees served: Brigitta Dassler, M.D., served as Executive Secretary until August 1975 followed by Lee Geismar who also served as Panel Administrator. Lee Quon, R.Ph., served as Drug Information Analyst until August 1973, followed by Thomas H. Gingrich, R.Ph., until May 1975, followed by Timothy T. Clark, R.Ph. until June 1976, followed by Victor H. Lindmark, Pharm.D.

The following individuals were given an opportunity to appear before the Panel to express their views:

Clealand Baker
Dorothy L. Carter-Staples, M.D.
Robert B. Choate
John M. Clayton, Ph.D.
Allan R. Cooke, M.D.
Alan K. Done, M.D.
Constantine J. Falliers, M.D.
Edward E. Fischel, M.D.
George S. Goldstein, M.D.
Arthur Grollman, M.D.
Robert John, M.D.
Daniel R. Johnson, Esq.
Charles Jolly, Esq.
Edward H. Kass, M.D.
David Katz, M.D.
Priscilla Kincaid-Smith, M.D. (Australia)
Jan Kock-Weser, M.D.
Irving Kushner, M.D.
Ben Marr Lanman, M.D.
Louis Lasagna, M.D.
Jack R. Leonards, M.D., Ph.D.
Robert Levine, M.D.
Dietrich Lorke, M.D. (Germany)
William Madison, Ph.D.
Arnold D. Marcus, M.D.
F. Gilbert McMahon, M.D.
Bernard L. Mirkin, M.D.
Fred Mueller
Ranjit S. Nanra, M.D. (Australia)
William M. O'Brien, M.D.
Peter D. Orahovats, M.D.
W. K. Poole, M.D.
Laurie Prescott, M.D. (Scotland)
Adrien L. Ringuette, Esq.
Mervyn A. Sahud, M.D.
George Schreiner, M.D.
Cecil Slome, M.D., C.H.B., D.P.H.
J. Edward Smiley, M.D.
Hale Sweeney, Ph.D.
Garrett W. Swenson, Esq., R.Ph.
Monroe E. Trout, M.D.
Walter Tucker, Jr., Ph.D.
Ralph Vinegar, Ph.D.
Ralph O. Wallerstein, M.D.
T. E. Watson
Richard M. Welch, Ph.D.
Harvey Weiss, M.D.
Sidney Wolfe, M.D.
Sumner J. Yaffe, M.D.

The following individuals were given an opportunity to present their views at the Panel's request:

John Baum, M.D.
William T. Beaver, M.D.
Gordon Benson, M.D.
Owen M. Edwards, M.D.
Henry M. Gault, M.D.
Thomas Haley, M.D.
Raymond Houde, M.D.
L. W. Hoyer, M.D.
Harold Mielke, M.D.
Ronald F. Miller, M.D.
S. I. Rapaport, M.D.
Jane Schaller, M.D.

No other person requested an opportunity to appear before the Panel. No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through November 22, 1976 in arriving at its conclusions and recommendations. Because the charge to the Panel required the review of three classes of OTC drugs, i.e., analgesics, antipyretics and antirheumatics, the Panel has presented its conclusions and recommendations in three separate parts. (See part III. below—ANALGESIC AGENTS, part IV. below—ANTIPYRETIC AGENTS, and part V. below—ANTIRHEUMATIC AGENTS.) Each part covers the submission of data and information discussed below. (See part I. below—SUBMISSION OF DATA AND INFORMATION.)

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to these classes of drugs are set out in three categories:

Category I. Conditions under which internal analgesic, antipyretic and antirheumatic products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which internal analgesic, antipyretic and antirheumatic products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel recommends the following for each class of drugs:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded or as Category II—not being generally recognized as safe and effective or would result in misbranding (Category III) be permitted to remain in use for 3 years after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to answer the questions raised by the Panel with respect to the particular condition.

I. SUBMISSION OF DATA AND INFORMATION

Pursuant to the notice published in the FEDERAL REGISTER of July 21, 1972 (37 FR 14633) requesting the submission of data and information on OTC internal analgesic and antirheumatic drugs, the following firms made submissions relating to the indicated products:

A. SUBMISSIONS BY FIRMS

Firm:	*Marketed products*
Abbott Laboratories, North Chicago, Ill. 60064	Children's Chewable Aluminum Aspirin.
Berry & Withington Co., Cambridge, Mass. 02140	Aspirin, Aspirin Compound No. 2, Buffered Aspirin, Sodium Salicylate.
Block Drug Co., Inc., Jersey City, N.J. 07302	BC Powder, BC Tablet.
Boericke & Tafel, Philadelphia, Pa. 19107	B & R Tablet No. 171-A, Boericke & Runyon Tablets No. 200.
Bristol-Myers Co., New York, N.Y. 10022	Arthritis Strength Bufferin, Bufferin, Dissolve, Excedrin, Excedrin P.M., Neolin.
Cooper Laboratories, Inc., Wayne, N.J. 07470	Persistin.
Curtis Drug Co., Decatur, Ill. 62521	Curtis A-R Pain Relief.
Dorsey Laboratories, Lincoln, Nebr. 68501	Calurin, Cama Inlay Tablets, Chexit, Pabirin, Triaminicin, Tussagesic Tablets/Suspension, Ursinus Inlay Tablets.
The Dow Chemical Co., Research Center, Zionsville, Ind. 46077.	Phensal, Tenlap.
Eli Lilly and Co., Indianapolis, Ind. 46206	Aspirin Suppositories.
Endo Laboratories, Inc., Garden City, N.Y. 11530	Percogesic, Dilone.
Eneglotaria Medicine Co. of Puerto Rico, Santurce, P.R. 00907.	Pediascirin.
L. W. Estes Co., Inc., Washington, D.C. 20010	Estes Nu-Ral.
Fountain Laboratories, Inc., Fountain Inn, S.C. 29644.	Pano.
R. L. Gaddy, Pharmacist, Tallahassee, Fla. 32302	EZ-IT APC.
Goody's Manufacturing Corp., Winston-Salem, N.C. 27102.	Goody's Headache Powders.
Edgar Larsen, Lafayette, Calif. 94549	Hoover Powders.
Lewis Manufacturing Co., Pierpont, Ohio 44082	Dr. Lewis' Preparation for Rheumatism.
McNeil Laboratories, Inc., Fort Washington, Pa. 19034.	Tylenol Chewable Tablets, Tylenol Drops, Tylenol Elixir, Tylenol Tablets.
Mead Johnson Labs., Evansville, Ind. 47721	Tempra Drops, Tempra Syrup, Tempra Tablets.
Miles Laboratories, Inc., Elkhart, Ind. 46514	Alka-Seltzer.
Norwich Pharmacal Co., Norwich, N.Y. 13815	Norwich Aspirin, Nebs Elixir, Nebs Tablets.
Plough, Inc., Memphis, Tenn. 38101	Aspergum, St. Joseph Aspirin, St. Joseph Aspirin for Children.
Purdue Frederick Co., Yonkers, N.Y. 10701	Arthropan Liquid.
Republic Drug Co., Inc., Buffalo, N.Y. 14207	A.P.C. with Codeine, A.P.C., Aspirin, Buffered Aspirin, Tapanol, Superin.
Rilox Co., New Orleans, La. 70122	Baltar's Medicine.
A. H. Robins Co., Richmond, Va. 23220	Arthralgen, Pabalate.
William H. Rorer, Inc., Fort Washington, Pa. 19034.	Ascriptin.

Sandoz Pharmaceuticals, East Hanover, N.J. 07936.	Flogesic.
Smith, Kline & French Laboratories, Philadelphia, Pa. 19101.	Ecotrin.
E. R. Squibb & Sons, Inc., New Brunswick, N.J. 08903.	Aspirin, Trigesic, Valadol Chewable Tablets, Valadol Liquid, Valadol Tablets.
Sterling Drug, Inc., New York, N.Y. 10016	Bayer Aspirin, Bayer Children's Aspirin, Bayer Timed-Release Aspirin, Cafenol, Cafiaspirina, Cope, Cortal, Fizrin, Measurin, Mejoral, Midol, Vanquish.
Templetons, Inc., Buffalo, N.Y. 14223	Templetons T-R-C's.
Upjohn Co., Kalamazoo, Mich. 49001	Acetonyl, Aspirin, P-A-C Compound, Salicionyl.
USV Pharmaceutical Corp., Tuckahoe, N.Y. 10707	Comeback, Femicin, Liquiprin.
Warner-Chilcott Laboratories, Morris Plains, N.J. 07950.	Sinutab, Sinutab II.
Warner Lambert Co., Morris Plains, N.J. 07950	Bromo Seltzer.
Warren-Teed Pharmaceutical, Inc., Columbus, Ohio 43215.	Magan.
T. E. Watson Co., Sarasota, Fla. 33578	Felsol.
Whitehall Laboratories, Inc., New York, N.Y. 10017.	Anacin, Arthritic Pain Formula, Duplexin, Saloxium.

In addition, the following firms made related submissions:

Firm:	*Submission*
Monsanto Industrial Chemicals Co., St. Louis, Mo. 63166.	Aspirin, Phenacetin, Salicylamide.

B. LABELED INGREDIENTS CONTAINED IN MARKETED PRODUCTS SUBMITTED TO THE PANEL

Acetaminophen (N-acetyl p-aminophenol; paracetamol)
Acetanilid
Aluminum aspirin
Aminoacetic acid (glycine, glycocoll)
Aminobenzoic acid (para-aminobenzoic acid (PABA))
Antipyrine
Ascorbic acid (vitamin C)
Aspirin (acetylsalicylic acid)
Bryonin
Caffeine
Calcium carbaspirin
Calcium carbonate
Calcium phosphate dibasic (monocalcium phosphate)
Calomel
Cascara sagrada
Choline salicylate
Cinnamedrine hydrochloride
Citrated caffeine
Citric acid
Codeine phosphate
Dextromethorphan hydrobromide
Dihydroxyaluminum aminoacetate (aluminum glycinate)
Dihydroxyaluminum sodium carbonate
Dried alumimum hydroxide gel
Homatropine methylbromide
Iodopyrine
Iris versicolor
Macrotin
Magnesium carbonate
Magnesium hydroxide
Magnesium salicylate
Methapyrilene fumarate
Nux vomica
Phenacetin (acetophenetidin)
Pheniramine maleate
Phenyltoloxamine dihydrogen citrate
Phenylpropanolamine hydrochloride
Potassium bromide
Potassium iodide
Pyrilamine maleate
Quinine
Riboflavin (vitamin B_2)
Salicylamide
Salsalate (Salicylsalicylic acid)
Sodium bicarbonate
Sodium carbonate
Sodium para aminobenzoate
Sodium salicylate
Terpin hydrate
Thiamine hydrochloride (vitamin B_1)

C. CLASSIFICATION OF INGREDIENTS

1. *Active ingredients.* The Panel has classified the following as analgesic, antipyretic, and antirheumatic agents:

Acetaminophen
Acetanilid
Aluminum aspirin
Antipyrine
Aspirin
Calcium carbaspirin
Choline salicylate
Codeine phosphate
Iodopyrine
Magnesium salicylate
Phenacetin
Quinine
Salicylamide
Salsalate (salicylsalicylic acid)
Sodium salicylate

These active ingredients may be further identified chemically into two groups. One group represents the "salicylates" (SA) in which all of the ingredients are chemically related to salicylic acid. The other group represents the "nonsalicylates" (NSA) in which the ingredients are not chemically related to salicylic acid. The most commonly used salicylate is aspirin or acetylsalicylic acid (ASA). Throughout this document the Panel has used the term aspirin which is the official adopted name for acetylsalicylic acid (ASA).

The Panel has included the following table in which the active ingredients have been categorized:

Categorization of active ingredients considered by the panel for safety and effectiveness as analgesics, antipyretics or antirheumatics

Active ingredient	Analgesic	Antipyretic	Antirheumatic [1]
Acetaminophen (NSA)[2]	I	I	II (E)
Acetanilid (NSA)	II (S)[3]	II(S)	II (S, E)
Aluminum aspirin (SA)[4]	III (E)[5]	III (E)	III (E)
Antipyrine (NSA)	III (S, E)	III (S, E)	III (S, E)
Aspirin (SA)	I	I	I
Calcium carbaspirin (SA)	I	I	I
Choline salicylate (SA)	I	I	I
Codeine (NSA)	II (S, E)	II (S, E)	II (S, E)
Iodopyrine (NDA)	II (S)	II (S)	II (S)
Magnesium salicylate (SA)	I	I	I
Phenacetin (NSA)	II (S)	II (S)	II (S, E)
Quinine (NSA)	II (S)	II (S)	II (S, E)
Salicylamide (NSA)	III (S, E)	III (S, E)	II (E)
Salsalate (SA)	III (E)	III (E)	III (E)
Sodium salicylate (SA)	I	I	I

[1] Antirheumatic active ingredients are limited to professional labeling.
[2] The term "(NSA)" refers to a nonsalicylate active ingredient.
[3] The term "(S)" refers to safety considerations.
[4] The term "(SA)" refers to a salicylate active ingredient.
[5] The term "(E)" refers to effectiveness considerations.

The Panel reviewed aminobenzoic acid, caffeine and phenyltoloxamine (and other antihistamines submitted) as possible analgesic, antipyretic and/or antirheumatic active ingredients and concludes that they cannot be properly included in these classes of internal analgesic ingredients. However, the Panel concludes that they may be considered adjuvants, categorized in the table as follows:

Categorization of ingredients considered by the panel for safety and effectiveness as analgesic, antipyretic or antirheumatic adjuvants

Adjuvant	Analgesic	Antipyretic	Antirheumatic
Aminobenzoic acid	II (S, E)	II (S, E)	II (S, E)
Sodium para-aminobenzoate	II (S, E)	II (S, E)	II (S, E)
Caffeine	III (E)	III (E)	III (E)
Methapyrilene fumarate	III (E)	III (E)	III (E)
Pheniramine maleate	III (E)	III (E)	III (E)
Phenyltoloxamine	III (E)	III (E)	III (E)
Pyrilamine maleate	III (E)	III (E)	III (E)
Salicylamide	III (S, E)	III (S, E)	III (S, E)

2. *Adjuvant agents.* The Panel has discussed adjuvants and their classification elsewhere in this document. (See part VI. below—ADJUVANTS AND CORRECTIVE AGENTS.) The agents identified below are included as active ingredients because they were submitted as such pursuant to the notice published in the FEDERAL REGISTER of July 21, 1972 (37 FR 14633) and the Panel considered that these agents (adjuvants) when combined with active ingredients could affect the activity or safety of the active component(s) of the submitted preparation(s):

(a) *Corrective (antacid or buffering) adjuvant agents.*

Aminoacetic acid (glycine, glycocoll)
Calcium carbonate
Calcium phosphate dibasic (monocalcium phosphate)
Citric acid
Dihydroxyaluminum aminoacetate (aluminum glycinate)
Dihydroxyaluminum sodium carbonate
Dried aluminum hydroxide gel
Magnesium carbonate
Magnesium hydroxide
Sodium bicarbonate
Sodium carbonate

(b) *Direct acting adjuvant agents.*
(1) *Caffeine-containing ingredients.*

Caffeine Citrated caffeine

(2) *Antihistamine-containing ingredients.*

Methapyrilene fumarate
Pheniramine maleate
Phenyltoloxamine
Pyrilamine maleate

(c) *Indirect acting adjuvant agents.*
(1) *Benzoic acid-containing ingredients.*

Aminobenzoic acid (para-aminobenzoic acid (PABA))
Sodium para-aminobenzoate
(2) Salicylamide

3. *Ingredients deferred to other OTC advisory review panels or other experts.* Agents deferred to other OTC panels are considered by this Panel not to have analgesic activity and it is not known whether they affect the safety or effectiveness of the analgesics listed above. (See part I. paragraph C.1. above—Active ingredients.)

a. The following agents were deferred for review to the Advisory Review Panel on OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products:

Ascorbic acid (vitamin C)
Dextromethorphan hydrobromide
Homatropine methylbromide
Methapyrilene fumarate (for uses other than as an analgesic adjuvant)
Pheniramine maleate (for uses other than as an analgesic adjuvant)
Phenylpropanolamine hydrochloride
Potassium iodide
Pyrilamine maleate (for uses other than as an analgesic adjuvant)
Terpin hydrate

b. The following agents were deferred for review to the Advisory Review Panel on OTC sedative, tranquilizer, sleep-aid and stimulant drug products:

Methapyrilene fumarate (for uses other than as an analgesic adjuvant)
Pheniramine maleate (for uses other than as an analgesic adjuvant)
Phenyltoloxamine (for uses other than as an analgesic adjuvant)
Potassium bromide
Pyrilamine maleate (for uses other than as an analgesic adjuvant)
Nux vomica

c. The following agents were deferred for review to the Advisory Review Panel on OTC laxative, antidiarrheal, antiemetic and emetic drug products:

Calomel
Cascara sagrada

d. The following agents were deferred for review to the Advisory Review Panel on OTC vitamin, mineral and hematinic drug products:

Ascorbic acid
Riboflavin
Thiamin hydrochloride

e. The following agent was deferred for review to the Advisory Review Panel on OTC internal miscellaneous drug products:

Cinnamedrine hydrochloride

f. The following agents were deferred and recommended for review to experts on homeopathy:

Bryonin
Iris Versicolor
Macrotin
Nux vomica

D. REFERENCED OTC VOLUME SUBMISSIONS

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of July 21, 1972 (37 FR 14633). The volumes shall be put on public display on or before August 8, 1977, in the office of the Hearing Clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, MD 20857.

II. GENERAL STATEMENTS AND RECOMMENDATIONS

A. INTRODUCTION

1. *Pain.* Pain is the most common symptom for which man seeks relief. While it is best to determine the cause of the pain and treat the underlying disease process, mild to moderate pain that is self-limited may often be treated symptomatically by self-medication. If pain persists more than 10 days or is severe, medical advice should be sought.

Many definitions of pain have been formulated. There is no doubt that everyone has experienced it. Beecher (Ref. 1), a recognized authority, has defined the symptom as follows:

> Unfortunately pain is a universal experience of mankind and everybody knows what is meant by it; so this discussion will concern itself only briefly with past unsatisfactory attempts to define pain. Pain is, it must be admitted, uncommonly difficult to define. But attempts at definition are useful in that they throw light on the process and on the nature of the difficulties encountered.

Pain is a subjective matter clearly "known to us by experience and described by illustration" [Ref. 609]. There seems little point for the present purposes to labor a definition of what all understand. Lexicographers, philosophers, and scientists have none of

them succeeded in defining pain. Having said that it is the opposite of pleasure, or that it is different from other sensations (touch, pressure, heat, cold) or how it is mediated (through separate nerve structures), or what the kinds of it are (bright, dull, aching, pricking, cutting, burning), or what kinds of things will produce it (trauma to nerve endings, or to nerves, electric shocks, intense stimulation of the sensations of touch, pressure, heat, cold), or what it comes from (injury, bodily derangements, or disease), or that certain types of mild stimulation can probably be stepped up to a painful level through conditioning or what some reaction patterns to it are (escape or avoidance), none of these individual statements, nor indeed their sum total, provides a definition of pain.

The Panel concludes that OTC analgesics are both safe and effective for use in the treatment of the symptoms of occasional minor aches and pains. Minor pain, for the purpose of self-medication, may be defined as pain that is self-limited and which requires no special treatment or prior diagnosis by a physician. The pain is usually described as of mild to moderate intensity as opposed to sharp, severe and/or protracted pain. Even though no medical treatment is required for minor aches and pains, analgesics may be desirable to reduce their intensity and provide relief and comfort to the sufferer. Individuals who must work or maintain normal daily activities, or those seeking comfort at home, may find these agents particularly useful. The role of these agents in the treatment of headache is discussed below. (See part II. paragraph A.7. below—Headache (cephalalgia).)

The Panel concludes that the most appropriate indications for pain for all OTC analgesic agents should state, "For the temporary relief of occasional minor aches, pains and headache".

The Panel has included the term "occasional" because recurrent or chronic pain, even of minor intensity may require a physician's diagnosis of its cause. For example, frequent headaches, joint pain which flares up periodically or lower back pain which undergoes exacerbations and remissions may indicate pathologic conditions and should not be treated with OTC analgesics except under the advice and supervision of a physician. Regardless of the type of pain, these agents should not be used in adults for more than 10 days. If symptoms persist beyond this period, become more severe, or new ones occur, a physician should be consulted. The Panel has concluded elsewhere in this document that the duration of use of all analgesic products should be limited to 5 days for children under 12 years of age rather than 10 days as recommended for adults. (See part II. paragraph F.3. below—Statement on children's dosage.) The Panel concludes that the most appropriate warning for all OTC analgesic agents should state for adults, "Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician", and for children under 12 years, "Do not take this product for more than 5 days. If symptoms persist, or new ones occur, consult your physician".

2. *Mechanism of action of an analgesic agent.* The Panel has defined an OTC analgesic drug as an agent useful to alleviate the symptoms of mild to moderate pain.

The analgesics alleviate pain principally by a peripheral effect (blockade of pain impulse generation) rather than by a central effect. The best evidence for this is based on the studies of Lim, who in 1967, induced experimental pain in animals and human volunteers and showed that the actions of aspirin and acetaminophen were predominantly on the peripheral nervous system rather than on the brain (Ref. 2).

In addition, there is evidence that a portion of the pain relief provided by analgesics that also have anti-inflammatory activity is due to a peripheral effect of decreasing the inflammation which removes one source of stimulation of pain receptors (Ref. 3). The basic mechanisms of action of the analgesics are further discussed in the analgesic section below. (See part III. below—ANALGESIC AGENTS.)

3. *Fever.* The ordinary individual has a normal body temperature of 98.6° F (37° C). Although most individuals have a 0.5° C variation during a 24-hour period or over several days, this is still considered by the Panel within the normal range. Fever is defined as a body temperature above the normal of 98.6° F (37° C) (Ref. 4) and is a common sign that may or may not be accompanied by pain. Many of the analgesics are also effective antipyretics (fever reducers) and may be safely used for self-medication when fever is due to the common cold or flu. However, fever also may indicate a serious illness and good medical practice dictates its cause, when not known, be determined immediately especially if it is marked, over 103° F (39.5° C) persists for more than 72 hours, or recurs. The Panel recommends that labeling of antipyretic products include the warning: "If fever persists for more than 3 days (72 hours), or recurs, consult your physician".

The Panel notes one author who states that the use of antipyretics has been abandoned, as fever is recognized as only a symptom which sometimes is beneficial (Ref. 5). Another author indicates that currently antipyretics are seldom used for the purpose implied by their name because efforts previously devoted to reducing fever are now turned more profitably to removing its cause (Ref. 6). The Panel concurs with the authors' views that modern use of antipyretics is limited to relief of fever, which is symptomatic of an underlying illness. The fact that fever is most often a symptom of disease rather than a disease itself is in stark contrast to broadly held medical views of 50 or more years ago when reduction of fever was the end, not the means. In fact, it was often the only way in which the physician could distinguish among the myriad of untreatable diseases confronting him. With the introduction of antibiotics, antipyretics are not as important as they once were (Ref. 6). Today, in some instances, fever or its absence can be used as a sign to aid in treatment and diagnosis. Once the cause of the fever is ascertained, that cause is treated, and treatment of fever, per se, becomes secondary to removal of the underlying cause.

Nevertheless, the Panel believes the availability of OTC antipyretics fulfills a need of a significant target population.

The Panel concludes that an acceptable labeling claim for an OTC antipyretic is, "For the reduction of fever".

4. *Mechanism of action of an antipyretic agent.* The Panel has defined an OTC antipyretic drug as "an agent used to reduce fever" and antipyresis as "symptomatic treatment of fever rather than of the underlying disease."

The salicylates and other antipyretics, e.g., acetaminophen, lower the temperature in patients with fever but have no effect on the body temperature when it is normal. The hypothalmic nuclei in the brain stem play a primary role in the regulation of body temperature. In fever, the balance between heat production and heat loss is still regulated by the hypothalamus but the latter sets the body temperature at a higher than normal level. The antipyretics are said to act to "reset" the "thermostat" (hypothalamus) so that the body temperature will decrease toward normal 98.6° F (37° C). Heat production is not changed but heat loss is increased by increased peripheral blood flow and sweating. The perspiration is not due to a direct effect of the antipyretics on peripheral blood flow or the sweating mechanism but rather to a central action on the hypothalamus.

Elevation in body temperature can occur following infection and inflammation. The causative agents of fever are referred to as pyrogens. Pyrogens may be differentiated into two basic categories: Those pyrogenic substances which are external to the body such as those produced by infectious agents and referred to as exogenous pyrogens and those pyrogenic substances which are produced by the body referred to as endogenous pyrogens. In a recent article by Milton (Ref. 7), a modern view on the pathogenesis of fever and the mode of action of antipyretic drugs is discussed. He notes that it is now generally accepted that the cells capable of producing endogenous pyrogens are activated either by exogenous pyrogens or by endogenous factors. These endogenous factors include inflammation, tissue damage, etc. which release endogenous pyrogens and it is this circulating material which is the common mediator of fever. Endogenous pyrogen is found to be a protein with a molecular weight of approximately 10,000 to 20,000.

These pyrogens which mediate fever induce changes in the central nervous system presumably in the region of the anterior hypothalamus to decrease heat loss and increase heat production resulting in the increase in deep body temperature. Milton notes that there is considerable evidence that both exogenous and endogenous pyrogens, when injected di-

rectly into the central nervous system, produced fever in a majority of the animal species studied, and that the fevers produced are similar to those resulting from peripheral administration of these pyrogens. However, he points out that there is a lack of evidence to demonstrate that pyrogens can enter the central nervous system from the periphery.

The role of pyrogens and their effect on the anterior hypothalamus to produce a rise in deep body temperature and the mechanism by which antipyretic drugs reduce fever may be related to the role of the prostaglandins. Prostaglandins are naturally occurring substances found in the body and consist basically of the fatty acid, prostanoic acid. These agents are known to be released from various tissues following nervous or chemical stimulation and to have numerous pharmacologic effects. Milton notes that the first evidence that prostaglandins might be involved in the pathogenesis of fever was reported in 1970 when a specific prostaglandin identified as E_1 (PGE_1) injected directly into the third cerebral ventricle of a cat's brain, resulted in a rapid rise in deep body temperature. In 1971 other workers (Ref. 8) confirmed these hyperthermic effects of PGE, not only in the cat but also in the rabbit and rat. More importantly, these studies showed that the hyperthermia produced was sustained only as long as the infusion lasted and the site of action was found to be in the preoptic area of the anterior hypothalamus.

Furthermore, Milton (Ref. 7) describes studies in which cerebrospinal fluid from the third ventricle of the brain of the cat was assayed for contractile activity which in turn could be related to prostaglandin activity. It was found that in the absence of fever, contractile activity was very low or absent in contrast to the considerably greater activity in the presence of fever, produced by injecting pyrogen directly into the third ventricle. Following the administration of the antipyretic drug acetaminophen, the fever abated and the contractile activity of the cerebrospinal fluid was again low. In subsequent studies in the cat, in which a microorganism was used to produce fever, it was found that the prostaglandin-like activity of the cerebrospinal fluid increased in all cases during the febrile response and that following the admininstration of three antipyretic drugs, i.e., aspirin, acetaminophen and indomethacin, fever was abolished in all cases and at the same time the prostaglandin content of the cerebrospinal fluid decreased.

Milton found that acetaminophen, but not salicylates, generally, may produce a fall in deep body temperature when administered to both man and animals in the absence of fever, particularly when given in large doses. In addition, in the presence of fever the reduction in temperature may be found to fall below that found in the afebrile state. Milton studied this phenomenon to determine whether the fall in body temperature in the absence of fever could be attributed to the inhibition of prostaglandin synthesis and its release. Indomethacin and acetaminophen both produced a fall in deep body temperature when administered to the conscious cat. When prostaglandin was infused, deep body temperature rose. When the temperature had reached a plateau, the infusion of the drugs produced vasodilation and panting but had no effect on the shivering and deep body temperature which fell slightly, reaching a new plateau level that was sustained until the infusion was stopped. From these studies, the author concluded that the effects of the antipyretic drugs were not mediated through inhibition of prostaglandin synthesis but were due to an action of the two drugs (indomethacin and acetaminophen) on the heat loss mechanisms concerned. Aspirin did not affect deep body temperature in either the afebrile state or during prostaglandin infusion. He concluded that the results could be regarded as further evidence that the prostaglandins are not involved in normal thermal regulation.

5. *Inflammation.* Inflammation and many rheumatic diseases usually are accompanied by pain and sometimes fever. In many rheumatic conditions the object of the therapy is to stop the disease process. This usually requires doses of drug higher than those recommended for OTC use. Furthermore, symptomatic self-medication with relief of accompanying pain may still allow permanent degenerative processes to continue. In certain inflammatory conditions, specific antibiotic therapy is indicated, e.g., inflammation of the joint or skin due to a bacterial infection, and if it is not provided early in the course of the disease, infection of the blood stream or spread of infection may occur. Therefore, the Panel concludes that these OTC drugs for the treatment of inflammatory conditions and rheumatic disease should be used only under the advice and supervision of a physician. For these reasons, which are explained more fully below in the antirheumatic ingredient section, the Panel further concludes that such OTC drugs should not contain OTC labeling for treating inflammatory or rheumatic conditions. (See part V. below—ANTIRHEUMATIC AGENTS.)

6. *Mechanism of action of an antirheumatic agent.* The Panel has defined an OTC antirheumatic drug as an agent which reduces joint or muscle tenderness or swelling.

Despite their long history of use, the precise mechanism(s) whereby salicylates exert anti-inflammatory actions remains unclear; numerous mechanisms of action have been proposed. They may interfere with cellular metabolism (Refs. 9, 10, and 11), inhibit the release of some inflammatory material from plasma protein (Ref. 12), interfere with the movements of ions such as sodium and potassium across cell membranes (Ref. 13), stabilize the membranes of lysosomes which are intracellular structures that may leak materials that cause inflammation and tissue injury (Refs. 14, 15, 16), or inhibit or compete with the actions of chemical mediators of inflammation (Refs. 16 through 22). However, all these possible mechanisms are controversial (Refs. 16 through 26). Recently, prostaglandins, complex molecules found in all cells, have been shown to be capable of producing inflammation and it has been proposed that aspirin and possibly other anti-inflammatory drugs inhibit the synthesis of prostaglandins (Refs. 27 through 38). Presently, this is thought to be a key mechanism whereby aspirin exerts its anti-inflammatory effects. This mechanism of action is discussed further in the antirheumatic section. (See part V. below—ANTIRHEUMATIC AGENTS.)

7. *Headache (cephalalgia).* OTC analgesic products are commonly used for the treatment of headache. A brief survey of the OTC analgesic market will readily indicate the extensive use of claims for "headache", "simple headache", "common headache", "occasional headache", and in many combination drug products containing additional nonanalgesic active ingredients terms such as "sinus headache" or "nervous tension headache". Regardless of the descriptive terminology used, the Panel finds headache to be a very common term for a pain affecting almost everyone.

Headache is a unique symptom. Unfortunately, it is an ambiguous term for pain having many different etiologies which can originate in almost any part of the body. Most headaches are transient usually lasting less than 1 day. However, some types are chronic and may recur over months or years. The occasional headache may be secondary to many factors including fatigue, tension, eyestrain, fever, or even alcohol ingestion. The chronic or recurrent headaches may be caused by more serious underlying diseases such as vascular disturbances, brain tumor or abscess, intracranial lesions, or lesions of the eye, nose, ear, or throat.

Wolff (Ref. 39) has differentiated headaches into two major categories based upon their origin, i.e., those that arise mainly as a result of stimulation of intracranial structures and those that occur on stimulation of tissues outside the head or adjacent to the skull. He describes 11 major types of headaches. In most cases each type could be further classified into distinct subgroups. He found that most of the tissues covering the cranium are sensitive to pain, particularly the arteries.

Diamond and Dalessio (Ref. 40) have separated headaches into three main groups, based upon their probable etiology, to include vascular, psychogenic and traction-inflammatory headaches. Vascular headaches include the classical and common migraine headache, whereas psychogenic headaches are usually attributed to anxiety or depression. Traction and inflammatory headaches include those attributed to organic diseases of the brain and associated structures, arteries, veins, eyes, ears, teeth, nose and paranasal sinuses.

A common feature of all vascular headaches are physiological changes in cranial blood vessels. In a majority of cases there is a tendency for vasodilation which provokes the headache. When cranial vessels are distended there is a

reduced ability of the vessel walls to accommodate changes in blood pressure. This results in a more direct transmission of pressure variation to sensory receptors in vessel walls and the subarachnoid space of the brain and is interpreted as pain.

One type of vascular headache, the hypertensive headache, is related to elevation in the systemic arterial blood pressure. A sudden rise in arterial blood pressure in either normal or hypertensive individuals causes headache by virtue of a sudden dilation of the pain-sensitive intracranial blood vessels. Another type of vascular headache is the common migraine. It has been estimated that nearly 12 million people in the U.S. suffer from migraine and 8 percent of all headaches seen by the physician are attributable to migraine. A common feature of the migraine headache is a recurrent, throbbing, unilateral head pain. OTC analgesics are usually not appropriate for the treatment of hypertensive or migraine headaches which require diagnosis of the disease by a physician and usually treatment with drugs available only by prescription.

Next to migraine, the most common vascular headache is the toxic vascular headache produced by fever for which OTC analgesics may be indicated. Diamond and Dalessio (Ref. 40) note that generalized vasodilation may occur as a consequence of any significant fever, the vasodilation usually becoming more intense as the fever rises. It has even been suggested that alcohol can produce a toxic vascular headache which is commonly referred to as a hangover headache. Another common form of toxic vascular headache occurs after withdrawal of caffeine. This caffeine withdrawal headache is common in heavy coffee drinkers and is discussed in the caffeine statement later in this document. (See part VI. paragraph B.3. below—Caffeine (citrated caffeine).)

The second major type of headache is the psychogenic headache which is considered one of the most common forms of headache. Apprehension, anxiety, posttraumatic experiences, and depression can precipitate the symptoms. This form of headache is usually accompanied by persistent contraction of the muscles of the head, neck and face. In some individuals, it is described as a sense of pressure rather than a true pain. Wolff notes that "the intensity of the headache is likely to be unaffected by the simple analgesics, whereas agents such as opiates or barbiturates that alter reaction to pain may grant significant, though transient, relief" (Ref. 39). The Panel concurs and finds the use of OTC analgesics for the persistent psychogenic headaches undesirable.

The terms "muscle contraction" and "tension" headache have been used synonymously for almost 40 years. These headaches are not vascular in nature or associated with traction or inflammation. Psychogenic headaches, which may account for up to 90 percent of the chronic headaches seen by the physician, are more common in those aged 30 years and over, but can occur at any age, even in childhood. The symptoms are usually described as a generalized pain not localized on one side of the head. The headache is diffuse in nature and usually difficult to describe. Various factors which may cause a psychogenic headache include the individual's marital relations, occupation, social relationships, life stresses, and habits.

The third major group of headache includes the traction and inflammatory headache evoked by organic disease. The term traction headache has been defined "to describe the often nonspecific headache seen with mass lesions of the brain, including tumors, hematomas, abscesses, or brain edema from whatever cause" (Ref. 37). Traction and inflammatory headaches are associated with inflammatory disease of the meninges, and intracranial or extracranial arteritis or phlebitis. The sinus inflammatory headache is related to sinus disease. The symptoms include localized pain within the frontal sinus of a deep, dull, aching, nonpulsatile quality. With proper diagnosis of a precise paranasal disease by a physician the underlying cause of such a sinusitis or allergic rhinitis can be properly treated.

The frequency, duration, location, and severity of the headache may be useful in determining its cause. The diagnosis of the occasional headache can usually be related by the individual to a direct, causative factor, e.g., fatigue, acute febrile episodes or alcohol ingestion. However, the cause of chronic and recurrent headaches require diagnosis by a physician. With regard to children, the large majority complaining of headache do not have organic disease (Ref. 37) but vascular, psychogenic and traction-inflammatory headaches are found among children as well as adults.

The Panel concludes that the occasional headache is self-limited and requires no definitive medical treatment. However, the Panel recognizes that OTC analgesics are useful for symptomatic treatment. For example, in many situations an OTC analgesic may be desirable to reduce the intensity and duration of the headache providing relief to the sufferer enabling him to return more readily to normal activity. The Panel has found the Category I analgesics discussed later in this document safe and effective for use for the occasional headache. (See part III. paragraph B.1. below—Category I Conditions under which analgesic agents are generally recognized as safe and effective and are not misbranded.) As in adults, the Panel finds the use of OTC analgesics appropriate for the treatment of occasional headache in children. However, the treatment of the psychogenic headache as, for example caused by stress situations at school or disturbed family relationships at home, should stress counseling rather than use of drugs.

The Panel has limited labeling claims for analgesics to the statement "For the temporary relief of occasional minor aches, pains and headache". The Panel has found other labeling claims for analgesic products unacceptable for reasons discussed later in this document and they are therefore classified as Category II. (See part III. paragraph B.2. below—Category II Labeling.) The Panel has specifically included the term "headache" as an acceptable labeling claim because of the wide acceptance and usage of OTC analgesics by the general population for headaches as caused by muscle fatigue from occasional overexertion for example, as opposed to the more complex migraine headache. The Panel believes that the consumer can usually distinguish the symptoms of this form of headache from other forms of headache or pain. In addition, whereas the etiology of some headaches, such as migraine, require prior diagnosis of a disease by a physician, the pain of occasional minor headache can be suitably relieved by self-medication with an appropriate OTC analgesic.

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B. GUIDELINES FOR DETERMINATION OF EFFECTIVENESS AND SAFETY

In arriving at its conclusions and recommendations regarding the effectiveness and safety of all active ingredients, the Panel considered all pertinent data and information submitted and adopted the following general guidelines:

1. *Effectiveness.* The Panel's determination of analgesic, antipyretic and antirheumatic effectiveness was based on published and unpublished studies considered to be scientifically valid and pertinent to the pharmacologic effect(s) evaluated. Clinical criteria for proof of analgesic effectiveness of single agents or combinations were essentially those described in the review by Beaver (Ref. 1) and will be discussed elsewhere in this document. (See part III. paragraph C. below—Data Required for Evaluation.)

Criteria for proof of antipyretic effectiveness were obtained from clinical studies which showed that the agent or combination studied, significantly lowered disease-induced fever. These will be discussed elsewhere in this document. (See part IV. paragraph C. below—Data Required for Evaluation.)

Criteria for antirheumatic effectiveness were obtained from clinical studies which showed that the agent or combination studied significantly decreased signs of certain rheumatic diseases. These criteria will be discussed elsewhere in this document. (See part V. paragraph C. below—Data Required for Evaluation.)

2. *Safety.* The Panel's determination of the safety for single agents and combinations of agents was based on the following criteria:

a. The incidence and risk of adverse reactions and significant side effects when the agent is used according to adequate directions and instructions on the label.

b. The potential for harm that might result from abuse or misuse under conditions of widespread OTC availability.

c. Assessment of the benefit to risk ratio.

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C. LABELING OF ANALGESIC, ANTIPYRETIC AND ANTIRHEUMATIC DRUG PRODUCTS

The Panel reviewed the general labeling requirements previously adopted by the Food and Drug Administration for OTC (analgesic, antipyretic and antirheumatic) products (21 CFR Part 201). These requirements provide for labeling information on the principal display panel of the packaging form, the identity of ingredients, directions for use and general and specific warnings. The Panel concurs that these general requirements are appropriate for such OTC preparations. The labeling of individual active ingredients will be discussed later in this document.

After reviewing all submitted labels of OTC analgesic, antipyretic, and antirheumatic preparations, the Panel recommends the following additional requirements:

1. *Ingredients.* The Panel concludes that analgesic, antipyretic, and antirheumatic products should contain only active ingredient(s) plus such inactive ingredients (pharmaceutical necessities) as may be necessary for product formulation. All such drug products should identify the active and inactive ingredients in the labeling. Active ingredients should be listed by the established name. Since the United States is converting to the metric system, the label should state the quantity of active ingredient in the recommended dosage in metric units, e.g., 325 mg per teaspoonful, 325 mg per tablet, etc. Secondarily, the quantity of the more widely used drugs aspirin and acetaminophen in the recommended dosage should also be stated in apothecary units, e.g., 325 mg (5 gr) per teaspoonful, 325 mg (5 gr) per tablet, etc., until the metric system becomes official.

The Panel reviewed the labeling requirements adopted by the Food and Drug Administration for OTC antacid products containing sodium and magnesium salts (21 CFR Part 331). The Panel concurs with these requirements and for reasons stated later in this document concludes that they be adopted for OTC internal analgesic, antipyretic and antirheumatic products containing sodium and magnesium salts. (See part III. paragraph B.1.f.(2) below—Safety and part III. paragraph B.1.e.(2) below—Safety.) Therefore, the Panel recommends that the labeling of products should contain the sodium content per dosage unit, e.g., tablet, teaspoonful, if it is 0.2 mEq (5 mg) or higher. For products containing more than 5 mEq (125 mg) sodium in the maximum recommended daily dose, the labeling should contain the warning "Do not take this product if you are on a sodium restricted diet except under the advice and supervision of a physician". For products containing magnesium salts with more than 50 mEq of magnesium in the recommended daily dosage, the labeling should contain the warning "Do not take this product if you have kidney disease except under the advice and supervision of a physician".

2. *Indications and directions for use.* The indications for use should be simply and clearly stated, provide the user with enough information for effective and safe use of the preparation and include the statement that the preparation is for the temporary relief of symptoms applicable to the ingredient(s) of the

preparation. For analgesic-antipyretic drugs, the Panel believes that the general indications statement "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever" answers these needs. This general statement covers the many slightly different claims found on the labeling of presently marketed OTC preparations and discourages the implication that these drugs are to be used for the self-treatment of diseases.

An important area of the Panel's responsibility is concerned with the labeling of OTC analgesic-antipyretic products. In years past it was believed that the greater the number of claims, the better the product. Often the claims would be vague, not easily understood or ambiguous. Even in today's OTC analgesic market there has been some carryover of this philosophy by industry and government. Specific analgesic studies have been cited to support claims for particular types of pain. However, a plethora of claims may be confusing, and misleading to the consumer.

The Panel recognizes that well-controlled studies have been done with various analgesic-antipyretic agents in patients with specific types of pain such as postpartum pain, pain due to cancer, pain following tooth extraction, etc. It is the Panel's opinion, however, that "pain" is sufficiently broad to encompass all the studies in populations with pain of specific etiology and therefore it is in the public's best interest to emphasize the use for pain generally rather than list on the labeling all the specific types of pain that have been shown to be effectively treated in well-controlled clinical studies.

Some of the claims for alleviation of pain found on the labeling of presently marketed OTC analgesics include: "muscle aches"; "stiffness"; "pain of toothaches", "teething", "dental procedures and dental work"; "muscle soreness"; "body aches"; "simple headache"; "nervous headache"; "tension headache", "pain due to head colds"; "simple pain of inoculations and immunizations"; etc. Rather than list all the numerous conditions all basically describing the common problem of pain, the Panel believes the term "minor pain" is sufficiently broad to encompass the specific types of pain effectively treated by this group of ingredients.

Another frequent problem with a variety of claims for alleviation of pain is their vagueness and lack of clarity. Often the consumer does not know what is meant by such claims and is misled when similar products have different claims. For example, if the labeling of one manufacturer's product omitted claims found on the labeling of another identical product, the consumer would be misled into believing the two preparations are different or are for different indications. Also, the same claim can have a meaning for one consumer that is exactly opposite to its meaning for another consumer. Furthermore, some claims are not even recognized by the medical community. For example, the Panel does not understand what is meant by "jumpy nerves", "fretfulness", "nighttime pain and its tension", or "under the weather". Since the Panel does not comprehend such claims, it anticipates that the consumer would have similar difficulty.

The Panel further notes that this current labeling of some OTC products lists claims for conditions for which they are clearly ineffective such as "depression", "nervous tension", etc. The Panel believes that such claims are inappropriate.

To protect the consumer from unfounded, misleading, and possibly hazardous claims, the Panel decided that the best labeling is one which states indications for use in simple, clear and easily understood language. The consumer would benefit greatly from such labeling. Therefore, the Panel recommends the restriction of the claims that may be made for analgesic-antipyretic products and has concluded that the general indications statement "For the temporary relief of occasional minor aches, pains and headaches, and for the reduction of fever", is the most appropriate.

Since OTC drugs are meant to be used only for the temporary relief of symptoms, the labeling should not indicate or imply that the preparation is for the treatment of disease entities, such as arthritis. This is especially important for preparations containing antirheumatic drugs, which if taken without medical supervision, may prevent or delay definitive treatment of arthritis which requires prior diagnosis by a physician, establishment of a proper antirheumatic dosage and concomitant or alternate therapy. Self-medication may lead to irreversible joint damage if taken in inadequate dosage intermittently for pain relief over prolonged periods by individuals with some forms of arthritis. Since the most common forms of arthritis, rheumatoid arthritis and osteoarthritis, are chronic diseases, "temporary" relief by OTC analgesic doses is inappropriate therapy for these diseases. Therefore, the labeling for preparations containing salicylates should include the statement, "Take this product for the treatment of arthritis only under the advice and supervision of a physician". For preparations containing the nonsalicylate, acetaminophen, labeling should include the statement, "Do not take this product for the treatment of arthritis except under the advice and supervision of a physician".

The Panel has further determined that some of the current claims for specific conditions recognized by the medical community and found on OTC labeling and in product names are not amenable to self-diagnosis or treatment. Consumers with these conditions, such as several types of arthritis, gout, and acute rheumatic fever, should be under the care of a physician. The Panel believes that any labeling for diseases such as these which require medical intervention may mislead the consumer who attempts to self-diagnose and self-treat serious diseases. Therefore, the Panel strongly recommends that product names or labeling that imply or suggest the use of these products for specific diseases requiring prior diagnosis by a physician should not be allowed. Any reference to "arthritis", "arthritic strength", "arthritis pain formula", "rheumatism preparation", etc., in product names or labeling is unacceptable to the Panel. As will be noted later in this document, the Panel concurs with the Arthritis Foundation's opposition to the term "arthritis" in aspirin brand names and also concurs with their recommendation that sufferers of the disease would be best served if the term "arthritis" were banned from the labeling and advertising of these products, leaving the choice of drug treatment to the physician. (See part V. below—ANTIRHEUMATIC AGENTS). The only terms acceptable to this Panel are those included in the general OTC indication statement for all analgesic-antipyretics, i.e., "For the temporary relief of occasional minor aches, pains and headaches, and for the reduction of fever".

3. *General and specific warnings.* The Panel decided additional statements need to be included on the labeling of analgesic-antipyretic products for proper use and adequate consumer protection. These statements should come under the general headings of warnings and cautionary statements.

The Panel agrees with the current regulation (21 CFR 330.1(g)) containing the general warning statement "Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately", and considers it reasonable and proper for all OTC medications. In regard to specific warnings or cautions the Panel recommends that potential users be alerted to possible serious side effects of therapeutic doses and especially serious consequences of overdose.

Because OTC products can be purchased by anyone, it is the view of the Panel that the public generally does not regard these products as medicines which, if used improperly, can result in injurious or potentially serious consequences. The public needs to be continually alerted to the idea that these products like all medicines carry some risk and should be treated with respect. The Panel, therefore, concurs with the Food and Drug Administration and considers it prudent to include the general warning statements now required under § 330.1(g).

The consumer should be informed of any possible signs of known toxicity or any indication requiring discontinuation of the use of the drug so that appropriate steps may be taken before more severe symptoms become apparent. For example, one of the first symptoms of salicylate intoxication, or overdose, is tinnitus or "ringing in the ears" which is discussed later in this document. (See part III. paragraph B.1.a. below—Aspirin.) It is very important for the consumer to recognize this symptom. With continued dosing, serious intoxication may occur due to the mode of salicylate metabolism.

For example, a small increase in the salicylate dose ingested may cause a disproportionate increase in the salicylate blood level and could result in serious consequences.

Unfortunately, acetaminophen has no similar sign of toxicity or "safety valve" to alert the consumer. Further, some advertising for acetaminophen gives the impression that it is much safer than aspirin and implies that the toxic effects of the drug are less than those encountered with aspirin. Actually, a large overdose of acetaminophen can result in serious liver damage which is not as amenable to therapy as salicylate intoxication. This is discussed later in this document. (See part III, paragraph B.1.b. below—Acetaminophen.)

Therefore, the Panel decided to include the warning, "Stop taking this product if ringing in the ears or other symptoms occur", on all products containing salicylates, and the warning, "Do not exceed recommended dosage because severe liver damage may occur", on all products containing acetaminophen, a nonsalicylate.

Likewise, consumers should be alerted to possible serious side effects from therapeutic doses of these products. Some evidence suggests that aspirin might be contraindicated in pregnancy. (See part III, paragraph B.1.a.(2)(iv) below—Adverse effects during pregnancy.) Therefore, the Panel concludes that it is necessary to include the labeling warning statement on all aspirin-containing products, "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

The labeling of several currently marketed aspirin products contains the advice that the product should be taken with a full glass of water. Baum (Ref. 1) also states that aspirin should be taken with large amounts of fluids. *The Medical Letter* (Ref. 2) also advises that "to minimize gastrointestinal irritation, any aspirin tablet should be taken with a full glass of water."

The Panel could not find any controlled studies to support the contention that the quantity of water used to administer the drug has any effect relative to safety or efficacy. However, it is the opinion of the Panel that this advice is sound, since the water would be expected to facilitate dissolution of the drug and reduce the irritation of the mucosa of the stomach from aspirin particles as discussed elsewhere in this document. (See part III, paragraph B.1.a.(2)(ii) below—Adverse effects on the gastrointestinal tract.) The Panel believes that this recommendation should apply to all salicylates. Therefore, the Panel concludes that the labeling for products containing salicylates intended for oral administration as a solid dosage form, e.g., tablets, state for adults, "Adults: Drink a full glass of water with each dose" and for children under 12 years, "Children under 12 years: Drink water with each dose".

In summary, the Panel concludes that the purpose of OTC preparations is to provide for the temporary relief of self-limited symptoms and not for the self-treatment of disease entities. If OTC products are used for a long period of time to treat symptoms which indicate a potentially serious problem, a disease requiring medical supervision could be masked until irreparable damage has occurred. This is especially important for those drugs with antirheumatic properties. As previously noted, if such drugs are taken there could be a delay in proper treatment of rheumatic disease which could lead to irreversible joint damage when inadequate dosage is taken intermittently for prolonged periods by patients with some rheumatic diseases such as rheumatoid arthritis. The Panel also decided that if an individual needs to take these products for a long period of time, i.e., more than 10 days in an adult, or more than 5 days in a child, he or she is sufficiently ill to require the consultation of a physician. Therefore, the Panel added the word "temporary" to the general indications statement making it read: "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever", and has added a general warnings statement for adults, "Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician", and for children under 12 years, "Do not take this product for more than 5 days. If symptoms persist, or new ones occur, consult your physician". Such warnings or cautions will be included in the proposed labeling for individual preparations presented later in this document.

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(1) Baum, J., "Rheumatoid Arthritis," in "Current Therapy," Edited by Conn, H. F. and W. B. Saunders, Philadelphia, 1973.

(2) Anonymous, "Is All Aspirin Alike?," *The Medical Letter*, 16:57-59, 1974.

D. LABELING WARNINGS, ADVERTISING AND THE MEDIA

Because the consumer needs to be correctly and fully informed, the Panel recommends that the advertising in any medium for these drugs that in any way uses the labeling, package or container not be inconsistent, even on subtle implication through mood, focus or innuendo, with the applicable labeling in the OTC internal analgesic monograph.

The Panel has noted, with concern, certain aspects of commercial advertising of OTC medicines that urge the consumption of these drugs without directing attention to adequate warnings regarding the possible immediate hazards of the use of these products or the potential hazards from their long-term use.

This concern was shared by representatives of consumer and children's advocacy groups, by representatives of pharmaceutical associations and manufacturers, the broadcast media, and researchers from the academic world at a 2-day conference on televised OTC drug advertising that was sponsored by the Federal Communications Commission and the Federal Trade Commission on May 20 and 21, 1976. At the three Panels comprising the conference the status of research, industry self-regulation, and government regulation was discussed and alternatives suggested; governmental policy decisions were not formulated (Ref. 1).

As was pointed out to the Panel, based upon common sources of advertising information, the advertising expenditures for internal analgesic drugs are greater than for other OTC drug categories (Ref. 2). It was noted that analgesic promotion in this country has reached a new level of sophistication with advertising references to whole new ailments such as "file cabinet backaches" or "camper noise tension." While the National Association of Broadcasters and the Proprietary Association representing many OTC drug manufacturers have been active in developing codes for the advertising of nonprescription or OTC medicines, the Panel believes that government requirements for the inclusion of warnings and cautionary language are inadequate, particularly as to possible effects of this advertising upon children (Ref. 2).

The Panel notes that the Food and Drug Administration does not regulate the advertising of OTC drug products. Therefore, the Panel asks that the proper authority, i.e., the Federal Trade Commission, with the full support and active cooperation of the Food and Drug Administration, more effectively regulate commercial advertising of internal analgesic, antipyretic and antirheumatic preparations on the basis of the labeling recommendations contained in this document. Further, the Panel strongly urges the Federal Trade Commission to require that the cautionary language and warnings developed by the Panel be given emphasis in commercial advertising more so than is currently being done, and that special attention be given to the regulation of OTC drug advertising on those television programs watched most often by children or whose viewing audience includes large numbers of children.

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(1) Transcript of Proceedings, Federal Communications Commission/Federal Trade Commission Conference, May 20 and 21, 1976.

(2) Choate, Robert B., Presentation before the FDA OTC Review Panel on Internal Analgesics, March 17, 1975, copy of unpublished paper is included in OTC Volume 030150.

E. STANDARD DOSAGE UNIT AND ANALGESIC EQUIVALENCE VALUE

1. *Background.* The Panel recognizes that currently the OTC drug market provides for many different products containing a large variety of analgesic, antipyretic and/or antirheumatic drugs. These products are marketed containing either single ingredients or combinations of active ingredients. A majority of these products contain aspirin with variation from product to product in the amount of aspirin per dosage unit. Likewise, there are many marketed products containing nonaspirin ingredients, e.g., acetaminophen, or derivatives of salicylic acid other than aspirin, e.g., sodium salicylate, which in most cases contain labeling

similar to that found for products containing aspirin. The Panel is concerned with the confusion that may arise when a consumer purchases such products.

To more fully inform the consumer as to the contents and therapeutic capabilities of these products as well as to minimize the hazard of confusion, the Panel recommends for these reasons and for reasons of safety described below, that products containing aspirin be clearly labeled on the principal display panel to indicate the presence of aspirin, that a standard amount of aspirin per dosage unit be established of 325 mg (5 gr) for all marketed products containing aspirin alone, as the single OTC analgesic-antipyretic active ingredient, and that labeling clearly indicate that the product contains the standard or a nonstandard amount of aspirin per dosage unit. The Panel has further determined that a standard dosage unit of 325 mg (5 gr) also be established for acetaminophen and sodium salicylate. It is the Panel's opinion that it is rational to establish standards, not only for aspirin, but for all three commonly used ingredients, thus enabling the consumer to more fully compare marketed OTC products.

2. *Standard dosage unit.* Aspirin is the most commonly used OTC drug in the United States. The majority of products marketed are labeled 325 mg or 5 gr aspirin. However, there are products marketed with less than 325 mg and some with 300 mg aspirin labeled as 5 gr. To most individuals these dosages are assumed to be equivalent but on a weight basis they are actually not equivalent. Confusion arises because there are two systems of weight measurement commonly used. One system, which has been historically used in pharmacy is the apothecary system of weights based on the "grain" (gr) and the other being the more universal metric system based on the "gram" (g). The apothecary weight of 1 gr is equivalent to the metric system measurement of 64.8 mg but is often approximated as equal to 60 mg. Therefore, a 5 gr aspirin dosage unit should actually contain 324 mg aspirin but is sometimes equated to 300 mg of active ingredient, thus making for a difference of 24 mg of aspirin.

A further factor contributing to a wide range in the amount of available aspirin is the provision of the *United States Pharmacopeia XIX* to provide for a variation of ±5 percent of the labeled amount of aspirin per dosage unit (Ref. 1). The Panel recognizes this as an understandable requirement necessary for manufacturing purposes but is concerned with the potentially wide variation in the currently allowable content of aspirin which, because of different interpretations of the "grain", varies for a labeled "5 gr product" between 285 mg and 340.2 mg aspirin from one marketed brand product to another brand. This could represent a possible difference of 55.2 mg or almost 1 gr aspirin between two different marketed products. To avoid the confusion that presently exists in the conversion between the two systems of weight measurement, i.e., between the apothecary system (gr) and the metric system (mg), the Panel recommends that the amount of aspirin in a 325 mg (5 gr) standard dosage unit be established on the basis of the apothecary weight of 1 gr being equivalent to the metric system measurement of 65 mg.

The Panel also recommends that this equivalence between the apothecary and metric systems be used for all ingredients. The following table illustrates equivalent values for the two systems as used throughout this document:

EQUIVALENT VALUES FOR APOTHECARY AND METRIC SYSTEMS

Apothecary (gr)	*Metric (mg)*
1.0	65
1.23	80
5.0	325
10.0	650
61.54	4,000

The Panel has evaluated the amounts of aspirin contained in the submissions for marketed products submitted to the review. (See part I, paragraph A, above—Submissions by Firms.) For example, of the submissions reviewed by the Panel, 32 pertained to dosage forms containing aspirin as a "single" ingredient. In 16 of these single ingredient products (50 percent), the amount of aspirin differed from the standard 325 mg (5 gr). The range was from a low of 227 mg for a chewable gum to a high of 650 mg in a single tablet. This represents a variation of 70 to 200 percent of the standard 325 mg (5 gr) aspirin dosage unit available as a single ingredient in such marketed products.

The Panel has provided the following table to illustrate the variations in the amount of aspirin contained in submitted products:

AMOUNT OF ASPIRIN CONTAINED IN SUBMITTED PRODUCTS WHERE ASPIRIN WAS THE SINGLE ANALGESIC INGREDIENT

Grains of aspirin	*Number of submissions*
3.5	1
4.5	2
5.0	16
6.0	2
7.5	7
10.0	4
Total	32

The Panel is aware of the widespread and common belief that the usual amount of aspirin an adult should ingest is "two tablets." The Panel believes that this can cause a problem if a person accustomed to buying and properly taking a particular analgesic product containing 325 mg aspirin per tablet changes to another analgesic product such as those currently marketed containing 295 mg or even 650 mg aspirin per tablet. If this same individual follows the usual custom of ingesting "two tablets" every 4 hours, he may receive as little as 590 mg or as much as 1,300 mg aspirin. The Panel is concerned that the 1,300 mg dosage will achieve the desired effect but with the potential hazard of toxic overdose. Since aspirin is the most common drug used in the United States, the latter situation is critically important. If a person takes 1,300 mg aspirin every 4 hours for several dosing intervals, serious aspirin intoxication may result. This is due to both the absolute quantity of aspirin taken and the kinetics of aspirin metabolism which is discussed later in this document. (See part III, paragraph B.1.a.(2) below—Safety.)

As an example, a 20 percent increase in dosage can cause a 40 to 60 percent increase in blood salicylate level over a period of time, which can produce a therapeutic response in patients who had not responded to a lower dose, or more importantly, result in an increase of dose-related systemic toxic effects (Refs. 2 and 3). Even those aspirin tablets commonly marketed in 300 mg or 325 mg dosage units, which usually permit variation of ±5 percent active ingredient per tablet as described above, when calculated to each extreme (a low of 285 mg for the 300 mg tablet to a high of 340 mg for the 325 mg tablet), represent a 20 percent variation in dosage.

This could be a problem in the area of pediatric overdosing. If a pediatrician instructs a parent to give a child half or quarter of an aspirin tablet, the child could, depending upon the strength of the tablet, be exposed to a potentially serious aspirin overdose. In the case of antipyresis (fever reduction) for an infant or small child this is especially hazardous because the young child cannot complain of tinnitus (ringing of the ears), one of the early symptoms of aspirin overdose. Further, the symptoms could progress to include fever, one of the later signs of salicylate intoxication (Ref. 4). The parent, noting that the fever has not subsided, may continue to give excessive amounts of aspirin, continuing a vicious cycle.

The Panel believes that the current availability of so many different amounts of aspirin per dosage unit is very confusing to the consumer. It is the opinion of the Panel that this availability has encouraged the myriad of claims such as "higher levels of pain reliever" or "arthritis strength" that are currently used. Of even more concern to the Panel is the fact that wide ranges in the amount of aspirin per dosage unit can result in either subtherapeutic or even toxic aspirin blood levels.

The Panel strongly recommends, based upon considerations of safety and effectiveness, that all products containing aspirin, acetaminophen, or sodium salicylate be standardized to contain and labeled to indicate either 325 mg (5 gr) per dosage unit for adults or 80 mg (1.23 gr) per dosage unit for children under 12 years of age.

The Panel recommends an adult oral dosage of 325 mg (5 gr) to 650 mg (10 gr) aspirin, acetaminophen or sodium salicylate every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours. The Panel finds this dosage regimen safe and effective for the treatment of occasional minor aches and pains, headache, and fever indicated later in this document. The Panel believes that

a standardized dosage unit of 325 mg (5 gr) is safe and effective when used as directed. More importantly, the adult oral dosage of 650 mg (10 gr) is the amount consumers believe they are ingesting, i.e., two 325 mg (5 gr) tablets.

However, the Panel recognizes the current availability of products containing an amount different than 325 mg (5 gr) per dosage unit. If the Food and Drug Administration is unable to implement the Panel's advice that products contain only 325 mg (5 gr) aspirin, acetaminophen or sodium salicylate per dosage unit, the Panel recommends that products contain not less than 325 mg (5 gr) per dosage unit since this is the minimum effective dosage for adults. Since a single dosage greater than 650 mg (10 gr) is not commonly required by the general population, the Panel believes it rational to establish 650 mg (10 gr) as the upper limit for the quantity of drug to be included in a single dosage unit. Therefore, the Panel has defined nonstandard dosage units as dosage units containing not less than 325 mg (5 gr) and not greater than 650 mg (10 gr) aspirin, acetaminophen or sodium salicylate. In addition, the Panel concludes that only nonstandard dosage units of 500 mg (7.69 gr) be recognized for acetaminophen in addition to the standard unit of 325 mg (5 gr) since the Panel is unaware of any other nonstandard dosage units currently available in marketed adult strength products containing acetaminophen as the single active ingredient.

The Panel recommends that any product containing an amount different from 325 mg (5 gr) per dosage unit be clearly labeled as to the amount of active ingredient the product contains and any product containing more than 325 mg (5 gr) per dosage unit shall be labeled appropriately "Contains nonstandard strength of X mg (X gr) aspirin per dosage unit compared to the established standard of 325 mg (5 gr) aspirin per dosage unit", "Contains nonstandard strength of 500 mg (7.69 gr) acetaminophen per dosage unit compared to the established standard of 325 mg (5 gr) acetaminophen per dosage unit", or "Contains nonstandard strength of X mg sodium salicylate per dosage unit compared to the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" for the specific product shall be used.

3. *Analgesic-antipyretic recommended dosage.* The Panel has defined the components of a dosage schedule below. The basis of the Panel's recommendation and conclusions are discussed elsewhere in this document. (See part II. paragraph F. below—Statement on Recommended Dosage Schedules.)

a. *Dosage range.* The Panel has examined the data submitted and finds for purposes of clarity that it is necessary to define the components of a dosage schedule which include a minimum effective dosage, a usual single dosage, a usual effective dosage range, a maximum single dosage, and a maximum daily (24 hours) dosage. These components of a dosage schedule are defined by the Panel in relation to a general OTC target population seeking relief of symptoms, such as occasional minor aches, pains and headache, and the reduction of fever.

(1) *Minimum effective dosage.* The minimum effective dosage is the amount of drug necessary to achieve the intended effect in some individuals in the general OTC target population.

(2) *Usual single dosage.* The usual single dosage is the amount of drug necessary to achieve the intended effect in most individuals in the general OTC target population.

(3) *Usual effective dosage range.* The usual effective dosage range is the range between the minimum effective dosage and the usual single dosage.

(4) *Maximum single dosage.* The Panel finds that there may be circumstances when more than the usual single dosage may be needed to provide an adequate effect. An increase in the usual single dosage may be needed, for example, by individuals who because of their large body size (unusual height) or overweight (obesity) require a higher dosage. To meet this contingency, the Panel defines the maximum single dosage as the maximum amount of drug that is safe and effective for use in a 4-hour period. The Panel has established 1,000 mg as the maximum single safe and effective dosage for the standard drugs (aspirin, acetaminophen and sodium salicylate). The Panel does not believe that this maximum single dosage should be encouraged on OTC labeling, except as an initial dosage, as it may be subsequently used routinely even when it may not be necessary and may potentially lead to toxic side effects.

(5) *Maximum daily dosage.* The maximum daily dosage is the maximum amount of drug that is safe and effective for use in a 24-hour period. The Panel has established 4,000 mg as the maximum daily dosage for the standard drugs (aspirin, acetaminophen and sodium salicylate).

The Panel considers the adherence to a maximum daily dosage of not greater than 4,000 mg necessary in the interest of safety. The clinical evaluation of aspirin clearly shows that higher daily dosages produce more side effects on the central nervous system, the blood clotting system, the gastrointestinal tract, etc. (See part III. paragraph B.1.a. (2) below—Safety.)

b. *Recommended dosage for products containing standard dosage units.* For products containing the standard dosage unit of 325 mg (5 gr) aspirin, acetaminophen or sodium salicylate, the minimum effective dosage for adults is 325 mg (5 gr), the usual single dosage is 650 mg (10 gr), the usual effective dosage range is 325 mg (5 gr) to 650 mg (10 gr), the maximum single dosage is 1,000 mg (15.38 gr) but should not be provided for in OTC drug labeling, and the maximum daily dosage is 4,000 mg (61.54 gr). The Panel notes that it is convenient to relate the standard dosage unit of 325 mg (5 gr) to a maximum single dosage of 975 mg (15 gr) and to a maximum daily dosage of 3,900 mg (60 gr) rather than to the established maximum single dosage of 1,000 mg and the established maximum daily dosage of 4,000 mg as defined above by the Panel. The recommended dosage schedules are described in section d. below.

c. *Recommended dosage for products containing nonstandard dosage units.* The Panel has defined nonstandard dosage units as dosage units containing not less than 325 mg (5 gr) and not more than 650 mg (10 gr) aspirin, acetaminophen or sodium salicylate. In addition, the Panel concludes that only nonstandard dosage units of 500 mg (7.69 gr) be recognized for acetaminophen in addition to the standard unit of 325 mg (5 gr) since the Panel is unaware of any other nonstandard dosage unit currently available in marketed adult strength products containing acetaminophen as the single active ingredient. The recommended dosage schedules are described in section d. below.

d. *Recommended adult dosage schedules.* Besides the establishment of standard and nonstandard dosage units, the Panel has also established standard and nonstandard dosage schedules for their use. The Panel strongly recommends that the standard dosage schedule be utilized but recognizes the current availability of nonstandard schedules. Therefore, the Panel recommends the following dosage schedules:

Recommended adult dosage schedules for standard and nonstandard aspirin, acetaminophen or sodium salicylate dosage units

Dosage unit [1] (milligram (grain))	Initial dosage units [2] (milligram)	Frequency [3] (tablets/hours)	Dosage units/day [4] (tablets (milligram))
Standard dosage schedule under: 325 (5)	2	2 after 4	12 (3,900)
Nonstandard dosage schedule under:			
325 (5)	2 to 3 (650 to 975)	do	12 (3,900)
400 (6.15)[5]	1 to 2 (400 to 800)	1 after 3	9 (3,600)
421 (6.48)[5]	1 to 2 (421 to 842)	do	9 (3,780)
485 (7.46)[5]	1 to 2 (485 to 970)	1 after 4 or 2 after 6	8 (3,880)
			8 (3,880)
500 (7.69)	1 to 2 (500 to 1,000)	1 after 3 or 2 after 6	8 (4,000)
			8 (4,000)
650 (10)[5]	1 (650)	1 after 4	6 (3,900)

[1] The amount of drug contained in a single dosage unit.
[2] The maximum number of dosage units that cannot be exceeded when dosing is initiated.
[3] The number of dosage units per time interval.
[4] The maximum total number of dosage units that cannot be exceeded in 24 hours regardless of the initial number of dosage units taken or the frequency of repeated dosing.
[5] This nonstandard dosage schedule does not apply to acetaminophen since only the 500 mg (7.69 gr) nonstandard dosage unit is recognized by the panel.

4. *Analgesic equivalence value.* Consumers may be perplexed not only by the variation in the available amounts of an active ingredient per dosage unit, but also by any attempt to compare the relative potency of an active ingredient with other active ingredients. For example, if an individual normally takes a product containing 325 mg sodium salicylate and compares its label with the label of a product containing choline salicylate, the directions may instruct the user to take a total of 650 mg sodium salicylate but 870 mg choline salicylate. This may result in the mistaken notion that because more choline salicylate is taken there will be more of a therapeutic benefit, although 650 mg sodium salicylate is chemically equivalent in salicylate content to 870 mg choline salicylate.

The Panel reviewed the submissions for marketed "combination" products containing aspirin. The Panel found that of the submissions containing "combination" analgesic-antipyretic products, the amount of aspirin contained in the products varied from 194.4 mg to 650 mg per dosage unit with the total amount of analgesic ingredients ranging from 360 mg to 842.4 mg per tablet.

It is most difficult to equate the total amount of analgesic effectiveness for such combination products. While these submissions are not necessarily a representative sample of the dosage variation in all of the currently marketed OTC analgesic products, they represent the major products in this market and do in fact give some concept of the range of aspirin dosages currently available to consumers. This represents a confusing and potentially harmful situation, since consumers may substitute one brand of analgesic product for another containing different active ingredients, ignorant of the fact that there are differences in potency between brands, and inadvertently ingest either too much or too little of the product.

The Panel is concerned that current labeling for some products extols the virtues of different quantities of analgesics for pain relief with such claims as "adult pain formula", "extra added ingredients", or "arthritis formula". The consumer, faced with such different claims has no ready source to consult to determine the validity of these claims. Consequently, an analgesic product may be purchased with the mistaken notion, "if one ingredient is good, two or more are better."

In addition to the current confusion, i.e., variable aspirin dosages, availability of many combinations of ingredients with and without aspirin, and many labeling claims, there is still another area of concern which involves the clinical evaluation of analgesics in general, i.e., increased blood levels of analgesic-antipyretics do not demonstrate an equivalent increase in the desired effect. The problem of trying to correlate analgesia with blood levels is discussed elsewhere in this document. (See part II. paragraph J. below—Effects of Product Formulations on Drug Absorption and Pharmacologic Effectiveness.)

Therefore, the Panel recommends that standard drugs (aspirin, acetaminophen and sodium salicylate) and standard dosage units of 325 mg (5 gr) be established. The analgesic equivalence to other drugs can then be compared as follows:

OTC Analgesic Equivalence Drugs

Standard 325 mg (5 gr)/dosage unit drugs:	*Comparison drugs*
Aspirin	Aluminum aspirin.
	Calcium carbaspirin.
Acetaminophen	None (comparisons only to standard dosage unit).
Sodium salicylate	Choline salicylate.
	Magnesium salicylate.
	Salsalate.

The Panel believes that the current availability of so many different products containing derivatives of salicylic acid other than aspirin or nonsalicylate active ingredients with labeling claims similar to products containing aspirin is confusing and recommends that an analgesic equivalence value be established. This value would inform the purchaser as to the contents and therapeutic capabilities of these products and thereby benefit the consumer. The labeling should clearly describe the strength of the product as compared to the standard applicable dosage unit.

5. *Labeling of products.* Because of the many common side effects observed with the use of aspirin as discussed later in this document, the Panel recommends that all products containing aspirin be clearly labeled as containing aspirin on the principal display panel. Such labeling will not only benefit all consumers but will alert those individuals having a sensitivity to aspirin.

a. *Products containing a standard drug in the standard dosage unit.* (1) *Aspirin.* The Panel recommends that products containing 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) aspirin per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event that the Food and Drug Administration cannot implement this recommendation under the current Federal Food, Drug, and Cosmetic Act, the labeling shall state "Contains standard strength of aspirin per dosage unit".

(2) *Acetaminophen.* The Panel recommends that products containing 325 mg (5 gr) acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event that the Food and Drug Administration cannot implement this recommendation under the current Federal Food, Drug, and Cosmetic Act, the labeling shall state "Contains standard strength of acetaminophen per dosage unit".

(3) *Sodium salicylate.* The Panel recommends that products containing 325 mg sodium salicylate per dosage unit be clearly labeled on the prinicpal display panel: "Contains the standard strength of 325 mg sodium salicylate per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event that the Food and Drug Administration cannot implement this recommendation under the current Federal Food, Drug, and Cosmetic Act, the labeling shall state "Contains standard strength of sodium salicylate per dosage unit".

b. *Products containing a standard drug in an amount different from the standard dosage unit.* (1) *Aspirin.* If the Food and Drug Administration is unable to implement the Panel's advice that products contain only 325 mg (5 gr) aspirin per dosage unit, the Panel recommends that products containing an amount of aspirin other than 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg (X gr) aspirin per dosage unit compared to the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount "X" of aspirin for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event the Food and Drug Administration cannot implement this recommendation, the labeling shall state "Contains nonstandard strength aspirin".

(2) *Acetaminophen.* If the Food and Drug Administration is unable to implement the Panel's advice that products contain only 325 mg (5 gr) acetaminophen per dosage unit, the Panel recommends that products containing 500 mg (7.69 gr) acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of 500 mg (7.69 gr) acetaminophen per dosage unit compared to the established standard of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event the Food and Drug Administration cannot implement this recommendation, the labeling shall state "Contains nonstandard strength acetaminophen".

(3) *Sodium salicylate.* If the Food and Drug Administration is unable to implement the Panel's advice that products contain only 325 mg sodium salicylate per dosage unit, the Panel recommends that products containing an amount of sodium salicylate other than 325 mg sodium salicylate per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg sodium salicylate per dosage unit compared to the established standard of 325 mg sodium salicylate per dosage unit". The actual amount "X" of sodium salicylate for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. In the event the Food and Drug Administration cannot implement this recommendation, the labeling shall state "Contains nonstandard strength sodium salicylate".

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F. STATEMENT ON RECOMMENDED DOSAGE SCHEDULES

1. *Statement on standard and nonstandard salicylate dosage schedules.* The Panel has defined the components of a dosage schedule elsewhere in this document. (See part II. paragraph E.3. above — Analgesic-antipyretic recommended dosage.) The basis of the Panel's conclusions regarding recommended dosage schedules is discussed below.

a. *Factors in selection of optimal dosage schedules.* The Panel recognizes that one of the most important and critical factors in maximizing the safe and effective use of any therapeutic agent is the choice of optimal dosage regimens. The need to carefully define and promote adherence to a safe dosage regimen is particularly important for aspirin and other salicylates for several reasons.

First is the alarming fact that a significant proportion of the serious salicylate toxicities including deaths are caused by inappropriate multiple dosing during therapeutic use rather than accidental or suicidal ingestion of large single dosages of salicylates (Refs. 1 through 4). Toxicities that result from overzealous multiple dosing during therapy are claimed to be more serious (Refs. 3 and 4) and said to occur at lower plasma salicylate levels compared to toxicities resulting from large single doses (Ref. 1).

Secondly, the propensity for serious toxicities during multiple dosing can now be explained by the recent discovery that the salicylates have very unusual and complex pharmacokinetic characteristics. They are metabolized by processes which can be saturated by doses within the usual therapeutic range. As a result relatively small increases in the dose may exceed the capacity of the metabolizing systems and cause inordinate increases in salicylate plasma levels during multiple dosing.

A third problem in defining the dosage regimens is that aspirin is used extensively for several effects which may have different dosage schedules, e.g., antipyretic effect or antirheumatic effect. Furthermore, these schedules must be adapted to several age groups in which the metabolic capacity may vary greatly. Different dosage regimens for each type of therapy will also be required as a function of age, weight and other possible relevant variables.

Finally, the problem is further compounded by the large number of dosage forms and chemical derivatives which vary appreciably in the strength of the dosage form and recommended dosage schedules for different purposes. The multitude of strengths in currently marketed aspirin products presents a critical problem in the case of salicylates which have the potential for serious toxic effects when the wrong dosage is used. This can be partially overcome by designating a standard strength and standard dosage regimen which will provide the basis for assuring that each patient will be better informed.

In addition to the above considerations, the Panel received several opinions and recommendations regarding its proposed dosage schedules in response to the Panel's various public statements. The Panel's response to these opinions and recommendations are incorporated into this document.

b. *Considerations of risk to benefit.* Ideally the evaluation of OTC drugs should be based upon benefit to risk considerations. The Panel finds, however, that there are no generally accepted protocols or procedures for the objective evaluation of the often cited but seldom quantitated given "risk to benefit ratio." Unfortunately this phrase is usually employed to describe a subjective assessment rather than a real value, i.e., a number based on reproducibly quantifiable measurements.

The absence of a reasonable procedure that can be used to objectively compare the relative effectiveness and safety of different dosage forms, tablet strengths, dosage regimens or different therapeutic indications, e.g., headache or rheumatoid arthritis, is particularly disadvantageous in the case of OTC salicylates. This is due partly because of the toxicity potential related to the dose dependent saturation kinetics of the salicylates and partly to the multiplicity of products which contain different amounts of aspirin, at different doses and dosage intervals.

There is also no established procedure to address the fundamental question regarding appropriate criteria to determine if the potential risk exceeds the benefit when a product is used for self-medication, rather than under the supervision of a physician or other health professional. The Panel has attempted to address this question in terms of the need for additional types of specific monitoring of drug therapy that is required for safe use and whether this monitoring must be carried out by an individual with training beyond that which can be conveyed to the average individual through labeling instructions.

The Panel used the following guidelines in an attempt to establish a systematic means for the evaluation of risk to benefit questions. Based upon certain assumptions discussed below semi-quantitative methods were used for benefit to risk considerations in salicylate dosing.

In response to the Panel's various public statements, the Panel received submissions, some of which represented conflicting views on several of the recommendations of the Panel including the need for a standard dosage, the use of aspirin for arthritis, and alternative regimens for pediatric dosing and dosage regimens in which data to support the safety of larger dosages than those recommended by the Panel were presented. The Panel also received submissions supporting the recommendations of the Panel but suggesting that they should be more stringent. These submissions were considered by the Panel in the recommendations given in this document.

c. *Correlation of dose to blood levels.* (1) *Maximum safe salicylate blood levels.* A maximum salicylate blood concentration, termed the steady state blood level, is reached and maintained after several repeated dosages at periodic intervals (dosage interval during multiple dosing). This steady state or plateau salicylate blood concentration correlates quite well with early signs of dosage related salicylate toxicity. Tinnitus (ringing in the ears) and deafness which are early signs of dose related salicylate toxicity, occur above a salicylate concentration of 20 mg/100 ml of plasma.

The correlation of salicylate blood levels with early signs of salicylism provides the basis for using the steady state plasma levels as a quantifiable means to compare the toxic potential of different dosage regimens. Single dosage and multiple dosage regimens should result in plasma salicylate levels which are below 20 mg/100 ml for 95 percent of the population. The mean steady state blood levels are determined by both the total daily dosage and the hourly dosage rate.

The steady state salicylate blood level is a function of the total daily dosage and the average dosage rate throughout the day. Different dosage schedules, e.g., 650 mg every 4 hours or 975 mg every 6 hours can be adequately characterized and compared in terms of the total daily dosage and average hourly rate which is the usual maintenance dosage divided by the dosage interval.

(2) *Standard dosage.* The standard upper limit of the Panel's recommended dosage regimen for aspirin is 650 mg every 4 hours for six dosages which is within the upper limit of 4,000 mg maximum total daily dosage and 167 mg/hour average hourly dosage rate. The Panel considered this to be the maximum safe dosage for the general population. Dosage regimens exceeding either this total daily dosage or mean hourly rate provide a significantly greater risk without a compensating therapeutic benefit. A single dosage of 975 mg provides greater benefits to a few individuals without significant additional risk. Repeated dosing at this level can lead to plasma concentrations in the range where more than 5 percent of the population probably experiences tinnitus.

(3) *Nonstandard dosage.* Nonstandard single ingredient salicylate products containing nonstandard amounts per dosage unit should provide dosing instructions limiting the number and dosage intervals such that the total daily dosage and mean hourly dosage rate do not exceed the standard.

In the Panel's opinion, single active ingredient salicylate products which contain nonstandard amounts per dosage unit provide a greater potential for confusion and thus deviation from the standard dosage regimen. However, there have been no studies designed to evaluate this contention. The Panel concluded that the additional risk is probably minimal provided that the labeling provides adequate notice that such products contain nonstandard amounts per dosage unit and thus require dosage regimens that are suitably modified so as not to exceed maximum daily and hourly dosage rates specified by the Panel. Since the modified dosage schedules for nonstandard products would be expected to provide blood levels and total body salicylate levels comparable to those obtained with the standard strength products, any claims of greater strength, e.g., adult strength, 15 percent stronger than standard aspirin, would be misleading and incorrect.

d. *Criteria for determining optimal dosage regimens.* Wagner (Ref. 5) has summarized some useful criteria that have been used to evaluate comparative risk to benefit ratios for drugs. Listed below are those formulae that are applicable to the evaluation of an optimal dosage regimen for a given indication or relative risk to benefit ratio for different therapeutic indications, e.g., use for general analgesic effect compared to use for anti-inflammatory effect in rheumatoid arthritis. Equation (1), Ehrlich's Chemotherapeutic Index (ECI), is generally used for a single dosage in animals but it can be applied to multiple dosages in humans with the following definitions:

(1) $ECI = \frac{\text{minimal therapeutic dose}}{\text{maximal tolerated dose}}$

(2) Jardetzky's therapeutic characteristic (Te):

$$Te: \frac{Dt}{DE} = \frac{Qt - 2\ S.D.}{QE + 2\ S.D.}$$

$$= \frac{\text{Dosage rate producing toxicity to 2.5 pct of subjects}}{\text{Dose effective to 97.5 pct of subjects}}$$

Qt and QE are defined as the median dosage rate to produce a toxic and therapeutic effect, respectively, in 50 percent of subjects. Dt and DE could be a single dosage or multiple dosages where different dosages are given for a specific duration at fixed dosage intervals. This concept is extended in this document to include any multiple dosage rate (dosage/time) given for a sufficient time to reach steady state or the steady state salicylate plasma levels which correspond to toxic or therapeutic effects.

$$\frac{Dt}{DE} = \frac{Qt - 2\ St}{QE + 2\ SE}$$

Qt and *QE* are defined as the dosage to produce either a toxic effect or a therapeutic effect, respectively, in 50 percent of the subjects. *St* and *SE* represent the standard deviation of the distribution of the toxic or effective dosage respectively, which is usually considered to be log normally distributed. Thus *Qt*–2 St will represent the dosage that will produce toxic effects in 2.5 percent of the target population, and *QE*+2 *SE* represents the dosage to produce a desired therapeutic effect in 97.5 percent of the target population. The addition of the statistical estimates of the range of responses in the target population is a desirable approach to defining a general dosage for the total population. As discussed by Wagner (Ref. 5), the therapeutic indices of Chen and Jardetzky are useful for certain comparisons but do not provide a means of determining the optimal dosage to be used.

Wagner (Ref. 5) suggests the minimum loss function of Schneidermen et al. as a method to define the optimal dosage which minimizes a loss index (*L*) and is defined in terms of a "loss" due to the toxicity (q_t) and a loss due to failure to cure (q_s) in which q_t and q_s are equated using a weighing factor (λ) thus:

$$L = (1 - q_t)\ \lambda\ q_s$$

e. *Pharmacokinetic relationships.* (1) *A relationship between dosage and plasma concentrations.* Normally for most drugs there are linear relationships between the plasma concentration and the variables of the dosage regimen, mg, kg^{-1}, $hour^{-1}$. The complex nonlinear kinetics of the salicylates negate these usual assumptions, however, and care must be taken in extrapolating from one dosage regimen to another or using the same dosage regimen in individuals of different age or size. Because of the complex nonlinear pharacokinetic characteristics of the salicylates, comparison and adjustment of mutiple dosage regimens must be based upon substantial experimental data.

Unfortunately there are relatively few carefully controlled multiple dosage studies providing adequate blood level data at different dosage, dosage intervals or different body weights. In many studies, the dosage regimens are given in different units such as daily dosage/m^2 or mg/kg/4 hours without sufficient additional data on the patient characteristics to allow exact conversion to comparable units. Differences in the number of days the dosage regiment was administered and the types of patients (rheumatoid arthritics) compared to normal subjects also made some published data difficult to assess.

Nevertheless, there are data from pharmacokinetic and clinical studies which provide a firm basis for establishing a safe and effective dosage regimen recommendation consistent with the unusual pharmacokinetic characteristics of the salicylates.

On the basis of these studies reviewed below, the Panel established standard and nonstandard dosage schedules. The schedules shown below reflect the Panel's recommendations of a minimum initial and maintenance dosage of 325 mg (5 gr), a maximum initial single dosage of 975 mg (15 gr) to be used only once, and a maximum maintenance dosage of 650 mg (10 gr) every 4 hours (standard) or in the case of nonstandard dosage forms dosage instruction schedules designed so as not to exceed a maximum hourly rate of 167 mg/hour and a total maximum daily dosage of 4,000 mg. The dosage schedules are stated in terms of the initial starting number of dosage units, the number of dosage units per time interval and the maximum total dosage units per day (24 hours).

(i) *Hourly dosage rate.* Because of the unusual nonlinear kinetics of salicylates, some changes in dosage schedules which ordinarily would have little or no effect on steady state blood levels can result in clinically significant changes in the case of salicylates. For example, if salicylates behaved like most other drugs which have linear kinetics, the mean steady state blood level would essentially be the same for a total daily dosage regardless of whether it is given as four dosages taken every 4 hours only during the day (dosage rate is 1,000 mg every 4 hours) or every 6 hours day and night (dosage rate is 1,000 mg every 6 hours). In the case of salicylates, a change of the hourly dosage rate can lead to potentially toxic levels and it is necessary to put limits on the hourly dosage rate as well as the total daily dosage. On the basis of clinical data and pharmacokinetic calculations, the maximum critical hourly rate is 167 mg/hour for an adult.

This consideration is particularly important in the case of some currently marketed salicylate products containing 7½ gr aspirin per dosage unit with a recommended dosage schedule of 15 gr (975 mg) every 4 hours for four dosages during the day. Although the total daily dosage is within recommended limits, the hourly dosage rate is 244 mg/hour which is 50 percent greater than the recommended limit of 167 mg/hour.

The Panel's evaluation of the safety claims for this type of product involved the following considerations:

(*a*) Evaluation of the assumptions used in the submitted computer simulations to justify the safety of this dosage regimen (Ref. 6).

(*b*) Evaluation of blood level data from the literature in which the same or similar dosage regimens were used.

(*c*) Benefit to risk considerations regarding the use of this dosage schedule for analgesic, antipyretic and anti-inflammatory effects.

The Panel concludes that this dosage regimen would not provide any significant improvement in analgesic or antipyretic effectiveness, but may result in increased blood levels at the potentially toxic level. The increased blood levels may enhance the therapeutic effect in rheumatoid arthritis but will be inadequate to suppress inflammation in many arthritic patients in whom adequate plasma levels could have been attained under proper professional supervision.

The significance of small changes in the hourly dosage rate can be illustrated by consideration of a simplified model which assumes that drug elimination procedes by a constant rate regardless of the dosage input or plasma concentration. Although this assumption is not

strictly true, the apparent rate of elimination is quite constant at the dosages and corresponding plasma concentrations where toxicity begins to occur, i.e., above 20 mg/100 ml. The following simple model correlates quite well with the published data:

$$A = D/\gamma - M$$

where A is the rate of accumulation of drug in the body per unit time (hour or day); D/γ is the dosage rate per unit time (hour or day); and M is the maximum elimination rate per unit time.

The more detailed model of Levy (Refs. 7 through 10) was also used by the Panel in computer simulations.

Levy and coworkers have extensively studied the problem of saturable metabolism. They have explained many of the apparent discrepancies in the literature using computer simulations based upon the average values of kinetic parameters describing saturable metabolism obtained experimentally from healthy volunteers. These simulations indicate that simply by increasing the daily dosage by 50 percent from 2 to 4 g daily as four equal doses every 6 hours, the total amount of drug in the body at steady state will increase from 1.3 g to 5.3 g, a 400 percent increase (Ref. 7).

They also show that the time to reach the steady state plateau greatly increases with dosage levels in the OTC range. Their simulations show that a dose of 0.5 g (7½ gr) when given every 8 hours will reach a constant maximum level of salicylate in the body (plateau level) of less than 0.5 g after 2 days of dosing. However, if two tablets were taken every 8 hours, the amount in the body would continue to increase for at least 7 days reaching a total body load six times greater than that reached in the one tablet dosage.

After careful consideration of the variout risk factors discussed above, the Panel developed the following table for standard and nonstandard dosage units:

Relationship between dosage unit, frequency and hourly dosage rate

Dosage unit [1] (mg gr)	Initial dosage units [2] (mg)	Frequency [3] (tablets/hours)	Dosage units/day [4] (tablets mg)	Hourly dosage rate [5] (mg/hour)
325 (5)	2 to 3 (650 to 975)	2 after 4	12 (3,900)	163
400 (6.15)	1 to 2 (400 to 800)	1 after 3	9 (3,600)	133
421 (6.48)	1 to 2 (421 to 842)	do	9 (3,789)	140
485 (7.46)	1 to 2 (485 to 970)	1 after 4 or 2 after 6	8 (3,880)	122
			8 (3,800)	162
500 (7.69)	1 to 2 (500 to 1,000)	1 after 3 or 2 after 6	8 (4,000)	167
			8 (4,000)	167
650 (10)	1 (650)	1 after 4	6 (3,900)	163

[1] The amount of aspirin contained in a single dosage unit (tablet).
[2] The maximum number of dosage units (tablets) that cannot be exceeded when dosing is initiated.
[3] The number of dosage units (tablets) per time interval (number of tablets taken after each time interval (hours) for repeated dosing).
[4] The maximum total number of dosage units (tablets (mg)) that cannot be exceeded in 24 hours regardless of the initial number of tablets taken or the frequency of repeated dosing.
[5] The amount of aspirin (milligram) taken at each time interval divided by the number of hours in a time interval gives the hourly dosage rate.

(ii) *Other factors increasing risk.* It is emphasized that the upper dosage level of 4,000 mg aspirin daily for a limited period of time (7 to 10 days) may frequently be below the optimal adult daily dosage required for anti-inflammatory effects in patients with rheumatoid arthritis but above that needed by the vast majority of "normal" adults for occasional use as an analgesic and antipyretic agent. This upper dosage was selected by the Panel as the upper limit above which a significant risk of toxicity increases dramatically in the majority of the target population. Furthermore, in some individuals other factors may increase the risk of exceeding salicylate plasma concentrations that are considered safe.

Any factors, such as diet, diuretics or other drugs which may affect the acidity of urine will be greatly magnified at the 4,000 mg daily dosage level. Levy and Leonards (Ref. 11) found the average salicylate plasma concentration of 13 normal adults receiving 1 g aspirin four times daily (4,000 mg daily) for 7 days was 15.0 mg/100 ml plasma (standard deviation is 4.6) if urine pH was kept above 6.2 by administration of sodium bicarbonate. When urine pH was allowed to fall to the usual range below 6 (5.6 to 6.1), the average plasma salicylate levels increased to 27.0 mg/100 ml (standard deviation is 7.9) which is above the desired level to avoid ototoxicity.

It should be noted that the plasma salicylate level of 27 mg/100 ml but not the level of 15 mg/100 ml would usually be suitable for treatment of rheumatoid arthritis. Thus, subtherapeutic levels might occur in patients who were adjusted to a dosage satisfactory at normal pH levels but greatly reduced if the patient also was taking antacids which increase the urine pH. For this reason, Levy and Leonards (Ref. 11) recommend that in the treatment of rheumatoid arthritis the urine pH should be routinely monitored particularly if antacids are being taken.

The data of Brewer (Ref. 12) illustrates several points which form the basis of the Panel's recommended dosage schedule. In this study, 32 children ranging in age from 2 to 15 years with rheumatoid arthritis (mean age 9.4 years) were given a dosage of aspirin based upon the body surface area. A dose of 800 mg/m² aspirin was given every 4 hours for four doses and no drug was administered during the night. During the first 12 hours this hourly dosage rate (200 mg/hour/m²) resulted in a mean increase in the steady state plasma concentration from 35 mg/100 ml at 8 a.m. to 48 mg/100 ml at 8 p.m. Thus, the net plasma concentration accumulation rate (A) was +10 mg/L/hour during a dosage input of 200 mg/hour/m², and −10 mg/L/hour during zero input. Therefore, during dosing the values of the equation, $(dC/dt)\,Vd = D/\gamma/m^2 - Vm$, are (10 mg/$L$/hour) $Vd = 200$ mg/hour/m² − Vm, and during the second 12 hour period of zero input (−10 mg/L/hour) $Vd = -Vm$. The apparent volume of distribution (Vd) can be calculated from the equation 2(10 mg/L/hour) $Vd = 200$ mg/hour/m². Therefore, $Vm = 100$ mg/hour/m². If the mean dosing rate exceeds 100 mg/hour/m², the plasma concentration will not reach a plateau but will continue to increase during dosing for the entire 10-day dosing period.

It is important to note that the maximum safe rate determined in this study for an average adult of 1.73 m² surface area is 173 mg/hour which is only slightly higher than the upper hourly rate recommended by the Panel.

The Brewer study also illustrates the effect of using a dosage regimen in which the hourly rate exceeds the maximum elimination rate for part of the day even though the total dosage is below the critical daily dosage. The hourly rate was 200 mg/hour/m² for 12 hours during the day and during the second 12 hours, the rate was zero. Although the mean hourly rate was 100 mg/hour/m², the daily dosage is also just below the maximum rate. The increased hourly rate in the first 12 hours results in a plasma accumulation from 36 mg/100 ml, the upper desired therapeutic level for rheumatoid arthritis, to 48 mg/100 ml which is in the potentially toxic range because the dosage used by Brewer was on the average just equal to the mean maximum elimination rate for this group

It would be expected therefore that the maximum individual elimination rates will be just above and below this standard dosage input rate and therefore the range multiple dose plasma concentration will be very large. This is in fact the case. The plasma levels range from 14 mg/100 ml to 62 mg/100 ml at 8 a.m. and 27 mg/100 ml to 77 mg/100 ml at 8 p.m. for this dosage regimen.

For these children, the mean dosage calculation from body weight was 33.8 mg/kg (standard deviation is 5.3), and therefore, the ratio of body weight to surface area was 23.7 kg/m² (standard deviation is 5.3). Therefore, the mean maximum dosage per kg of body weight for this group would be·

$$\frac{100 \text{ mg/hour/m}^2}{23.7 \text{ kg/m}^2} = 4.2 \text{ mg/hour/kg or } \frac{33.8 \text{ mg/kg}}{(2)(4 \text{ hours})}$$

$$= \frac{8.45}{(2)} = 4.2 \text{ mg/hour/kg or } 101.4 \text{ mg/kg/day.}$$

From the study of Makela et al. (Ref. 13), it is clear that use of body weight to determine the dosage in children can be misleading and lead to toxicity because the ratio of body weight to surface area changes with different age groups. The average kg/m² ratio for this group of children was 23.7 kg/m² but would be about 40 kg/m² for an adult. When surface area is used to calculate the equivalent dosage for adults a maximum hourly input rate for a 70 kg adult (1.73 m²) would be 173 mg/hour which is in good agreement with the maximum hourly rate (167 mg/hour) recommended by the Panel. If body weight is used to calculate the adult dosage, the corresponding dosage would be 7,000 mg/day or 280 mg/hour.

Dosage forms which contain more than 10 gr must be taken at intervals which will generally not sustain blood levels unless the plasma levels are above 20 mg/100 ml (Ref. 14). They are therefore justified only for treatment of rheumatoid conditions under the direction of a physician. Most of the sustained release type microspherules do not significantly prolong the release of the drug. The plasma sustained levels are more a result of the prolonged duration in the body rather than delayed release during absorption (Ref. 15).

(iii) *Change of dosage interval with constant daily and hourly dosage rates.* Because of limited published data, the Panel used analog and digital computer simulations to study the effect of increasing the dosage interval when the daily and hourly dosage rates were maintained constant at the recommended level of 4,000 mg daily and 167 mg hourly. The total amount of salicylate in the body at steady state was similar at clinically realistic dosage intervals of 3 to 8 hours. The maximum amounts of drug in the body and plasma concentrations just after dosing and the minimum concentrations just before dosing at steady state that were obtained using the model and average values given by Levy and Tsuchiya (Ref. 7) are shown below:

Relationship between dosage and dosage interval (with constant daily and hourly dosage rates) to steady state concentration

Dosage interval (hours)	Average dosage rate (milligram/hour)	Total daily dosage (milligram) and number of dosage units per day	Steady state: Total body load after 5 days	
			Maximum amount in body (milligram)	Minimum amount in body (milligram)
Dosage (milligram):				
167	1	167 4,000/24	4,282	
500	3	167 4,000/8	4,472	4,133
650	4	167 4,000/6		
1,000	6	167 4,000/4	4,718	3,882
1,300	8	167 4,000/3	4,866	3,702
4,000	24	167 4,000/1	5,303	2,156

From these simulations, it appears that as long as the total daily dose and the mean hourly dosage regimen are kept constant, reasonable increases in the dosage interval of 3 to 8 hours will not greatly increase the total maximum and minimum body load of salicylates at steady state. As the dosage interval is increased from 3 to 8 hours, the difference between the total maximum and minimum amounts of salicylate in the body is less than 10 percent providing the dosage per dosage interval is also adjusted to maintain the same average dosage rate every hour.

(iv) *Maximum safe single dosage.* The Panel concludes that a large adult dosage of 975 to 1,000 mg may provide increased therapeutic benefit in some cases without significantly increasing the probability of toxicity provided that the dosage is administered only once as a single dosage or as the initial dosage in a multiple dosage regimen. The use of an initial (loading) dosage is a common practice in designing multiple dosage regimens for many drugs. The multiple dosage regimen results in an accumulated amount of drug in the body at steady state which is greater than the amount produced by a single maintenance dosage.

For most drugs which follow linear kinetics, the use of a higher initial (loading) dosage permits the desired steady state drug level in the body to be reached more quickly without changing the ultimate steady state drug level that is reached for a given maintenance dosage. For drugs such as the salicylates, which follow nonlinear kinetics, the amount of the loading dosage is more critical. If the dosage is too large or given repetitively, it may actually increase the final amount of drug in the body at steady state that is reached with a given multiple dosage level. The maximum initial dosage recommended by the Panel is only for use as a single nonrepeated dosage or as the initial dosage used only to initiate a multiple dosage schedule. The recommended maximum initial dosage is recommended, therefore, on the assumption that it will be used only once as a margin of safety for inadvertent or noncompliant use. Repetitive use of the 975 to 1,000 mg maximum single dosage at the usual dosage intervals would significantly increase the dosage rate and, therefore significantly increase the risk relative to any possible increase in analgesic or antipyretic effect.

The maximum single dosage was selected as the single dosage which produces salicylate plasma levels (6 mg/100 ml to 10 mg/100 ml) comparable to those achieved by the minimum dosage (325 mg) in a standard multiple dosage regimen known to be effective and free of major side effects. Thus, the maximum single dosage will produce rapid increase in plasma levels in multiple dosing which can be maintained by smaller dosages of 325 to 650 mg given every 4 hours.

Leonards (Ref. 15) found that comparable plasma salicylate levels of less than 10 mg/100 ml were produced by administration of 1,300 mg (20 gr) aspirin in three different ways. A total of 1,300 mg was given as a single dosage of one 1,300 "sustained release" capsule, a single dosage of four 325 mg tablets and two dosages of two 325 mg tablets (650 mg) given 4 hours apart.

The maximum plasma concentration time curves following one 1,300 mg dosage were similar for the sustained-release product and the large dosage of regular aspirin. Thus, the microsphere aspirin product did not produce a sustained plasma level due to a prolonged release or decreased absorption rate but simply because of saturated elimination which occurs independent of the product used.

The larger single dosage resulted in a greater total area under the plasma time curve than the divided dosage. The increase in the total area under the plasma time curves even though these regimens have the same total dosage and hourly dosages illustrates the effect of saturable metabolism which augments plasma levels from a large single dosage compared to the usual 650 mg (10 gr). The plasma concentrations were essentially the same, 8 hours after the initial dosing in both cases. Eight hours after the initial dosing, both dosage schedules resulted in essentially identical plasma levels of about 5 mg/100 ml. This may indicate that a dosage schedule of one 1,300 mg (20 gr) capsule every 8 hours could possibly produce blood levels that would be probably equivalent to blood levels produced by a standard dosage regimen of 650 mg (10 gr) dosage every 4 hours since the hourly rate is the same 167 mg/hr. Although the final plasma concentrations are similar, the increased area under the curve for the higher dosage may indicate potential differences in the two regimens, however. Additional data on the mean plasma levels and variability about the mean after several days of multiple dosing are required before the 1,300 mg (20 gr) capsule can be considered a safe dosage form for OTC analgesic and antipyretic use. The Panel is concerned that while this dosage form may be appropriate for treatment of conditions requiring high dosages such as arthritis, it offers no advantage in the treatment of pain or fever. It lacks flexibility when adjusting dosages.

(2) *Relationship between plasma concentration (and dosage) and toxicity.* Although it has not been possible to establish the plasma levels of aspirin or salicylic acid required for analgesic effects, estimates are available on the blood levels associated with several types of toxic effects.

The levels of aspirin following usual dosages of 600 mg are relatively low (2 mg/100 ml) and decline rapidly (half-life about 20 to 40 minutes). Aspirin levels have not been correlated with toxicity. Plasma levels of salicylic acid, however, correlate well with probability of toxicities.

Tinnitus is the most frequent and reliable symptom of salicylism which occurs at salicylate levels of about 20 mg/100 ml. Other early symptoms of salicylism include deafness, headache, vertigo, vomiting and hyperventilation. Above 30 mg/100 ml, irritability and psychosis may occur (Ref. 16). A target concentration of 20 mg/100 ml for the treatment of rheumatoid arthritis is usually sought in the treatment of adults while children can often tolerate higher doses (30 mg/100 ml) in the treatment of rheumatoid arthritis, but monitoring for toxicity is essential (Refs. 17 and 18). Children often develop other symptoms (nausea, hyperventilation) before experiencing tinnitus (Refs. 13 and 17).

Done found a very poor correlation between serum salicylate concentrations at the time of admission and the severity of salicylate intoxication (Ref. 19). The serum salicylate concentrations were extrapolated back to the time of ingestion (S_o), assuming a half-life value of 20 hours (k=0.03465 hour), and a much better correlation was observed. Of additional significance was the fact that the correlations were similar for both children and adults indicating that serum salicylate concentrations may provide a reasonable basis for comparing the potential of different dosage regimens to produce toxicities in adults and children.

The reversible effects of salicylates on hearing function appear to be the earliest and most useful indicators of toxic salicylate serum levels. Although permanent hearing loss has occurred with the use of salicylates (Ref. 20), this is relatively uncommon. Since the great majority of effects are rapidly reversible and correlate quite well with individual plasma levels except for patients who are already deaf, the incidence of tinnitus and common reversible hearing loss are the most reliable and earliest indicators of potentially toxic doses.

Salicylates can produce two effects on hearing function, tinnitus which is a ringing sensation, and deafness which involves a reversible loss of pure tone sensitivity affecting all frequencies. Both effects correlate with individual serum salicylate concentrations.

Progressive loss of the sensitivity to hear pure tones was demonstrated in volunteers receiving doses of three tablets (975 mg) every 4 hours (244 mg/hour) for 4 days (Ref. 21).

Similar effects of increasing aspirin dosage on actual hearing loss were studied by Myers et al. (Ref. 22). Audiometric measurements were made before and after administration of aspirin to 25 patients.

Myers et al. found that a dosage of 5,000 to 8,000 mg of drug was usually necessary to produce tinnitus and subject hearing loss (Ref. 22). In patients with normal hearing, high salicylate concentrations produced a bilateral hearing loss of 20 to 40 decibels for all frequencies which were reversible in all patients within 3 to 10 days.

Hearing loss did not occur below salicylate plasma concentrations of 20 mg/100 ml. Seventeen of 21 patients experienced hearing loss of more than 10 decibels (30 to 40 decibels in most) when salicylate concentrations were above 20 mg/100 ml. The hearing loss increased as plasma levels increased. Usually, hearing loss reached a maximum at 40 mg/100 ml.

The median dose at which tinnitus occurs was 4.5 g daily with a range of 2.4 to 6.0 g in a study by Ropes (Ref. 23) and at 5.3 g in the study by Mongan et al. (Ref. 24). Neither tinnitus nor deafness occurs at salicylate levels below 20 mg/100 ml which is greater than required for analgesia and antipyresis for 95 percent of patients.

(3) *Relationship between analgesic effects, dosage and salicylate plasma concentrations.* Although it has not been possible to relate analgesic effect with plasma salicylate concentrations, a relationship between oral dose and analgesic effect has been well-established for several different types of clinical pain.

In almost all well-controlled studies, analgesic effect cannot be distinguished from placebo at dosages below 325 mg. However, higher dosages of 650, 975 and 1,300 mg have been shown to be significantly different from placebo. (See Part III. paragraph B.1.a.(1) below—Effectiveness.) Dosages above 650 mg do not result in a significantly greater incidence or degree of pain relief in most studies. In some studies, however, dosages of 975 mg (three 325 mg tablets) to 1,300 mg (four 325 mg tablets) appeared to have a greater analgesic effect based on dose-response curves which appear to be increasing above 650 mg. The difference between the larger dosages compared with 650 mg generally could not be shown to be statistically significant but the apparent increase in the dose-response curve above 650 mg dosages suggests that greater pain relief may be obtained in some individuals with some types of pain with single dosages of 975 to 1,300 mg.

Although the dose-response curves in a few studies suggest that larger dosages may produce a slightly greater incidence of analgesia than a 650 mg dosage, there are important limitations in this assumption.

First, the relationship of increased analgesia to increased dosage is not linear but, like many drugs, the effect is proportional to the logarithm of the dosage. Second, the increase in response is generally relatively small because the dose-response curve is relatively flat requiring large increases in the dosage to obtain a relatively small increase in analgesic response.

A third consideration is that most studies of analgesic effects have involved only single dosages. There is relatively little information on the dose-response curves after multiple dosages.

Although limited, current data appeared to justify that an initial dosage of 975 mg may prove more beneficial than 650 mg for alleviating pain in a few individuals. For reasons discussed below, an increase in dosage above 650 mg would probably not greatly increase the potential of systemic toxicity if taken only once or twice. If the larger dosage is taken according to the usual multiple dosage schedule, significantly increased potential for toxicity will occur. Furthermore, there are no data available to show that multiple dosages greater than 650 mg will provide any greater clinical benefit for analgesic and antipyretic effects.

Although it is not possible at this time to correlate analgesic effect with the plasma salicylate concentrations, it is possible to determine the plasma salicylate concentrations that are attained with the dosages known to produce analgesia. Since toxicity correlates with plasma salicylate concentrations much better than with the dosage of salicylates, it is appropriate to determine and compare the toxicity potential of dosages and dosage regimens required for a certain therapeutic effect, e.g., analgesic or antirheumatic effects, by comparing the corresponding plasma salicylate concentrations.

The maximum salicylate plasma levels which are achieved with recommended multiple dosages with all different types of salicylates are less than 15 mg/100 ml (Refs. 15, 25, 26, and 27). Even the highest possible effective single dosage, 1300 mg (20 gr), doesn't usually result in plasma levels which exceed 15 mg/100 ml (Ref. 15). Thus, 20 mg/100 ml is both the lower toxic limit and also the concentration which should not be exceeded with multiple dosing of 650 mg every 4 hours or the equivalent. However, repeated administration of dosages above 650 mg at the usual dosage interval will accumulate in the body to produce higher concentrations that can be expected to produce toxic symptoms in a significant number of the population, i.e., greater than 5 percent of the population.

(4) *Relationship between plasma concentrations and anti-inflammatory effect in rheumatoid arthritis.* In contrast to analgesic and antipyretic efforts, the suppression of inflammation increases with the dosage of salicylates even beyond the point of toxicity (Ref. 28). Mills states that the therapeutic objective is to employ as large a dosage as possible short of toxicity and the most common reason for therapeutic failure is use of inadequate doses.

The usual target concentration tolerated by most patients is the range of 20.0 to 25.0 mg/100 ml. This is the region where small increases in dosing can result in very large increases in plasma levels. Special directions must be given

to the patient and, depending on the dosage and condition, special monitoring for adverse effects may be required and therapeutic doses must be determined for each patient.

Fremont-Smith and Bayles (Ref. 29) gave increasing dosages of salicylates to 11 hospitalized patients with rheumatoid arthiritis over a period of 5 days until the largest tolerated dose was reached. In most cases, the dosage increase was stopped because of auditory effects, either tinnitus or deafness, which occurred at an average daily dosage of 5.2 g. Fremont-Smith and Bayles established that salicylates produced an important anti-inflammatory effect in rheumatoid arthritis which was in addition to the analgesic effect. This effect, which could be quantitated by decreased joint size, measured by standard jewelers rings, or grip strength, was rapidly reversed when subtherapeutic doses were administered. These authors concluded that all patients with active rheumatoid arthritis, whether mild or severe, should receive salicylates regularly in the largest tolerated dosages. The average maximum tolerated dosage was 5.2 g.

Boardman and Hart (Ref. 30) compared placebo with prednisone, paracetamol, high dosages of salicylate (5.3 g daily), and low dosages of salicylate (2.6 g daily) administered in multiples of 10 gr (660 mg) tablets given in four equal doses daily for 7 days followed by 7 days rest. Therapeutic response was objectively measured by the occurrence of predefined significant changes in joint size, grip strength and also subjectively by patient preference. A significant change in joint size (4 mm or more over 7 days) was produced by high doses of salicylates but not by low doses of salicylate, paracetamol or placebo. Changes in joint size, compared sequentially with placebo, proved the most objective means of assessing the anti-inflammatory effect of salicylates and also prednisone, a drug known to have anti-inflammatory effects but no significant direct analgesic effects. It is significant that the drug therapies with analgesic, but not anti-inflammatory effects, such as paracetamol and low aspirin doses, produced slight improvements in grip strength and patient preference compared to placebo, presumably due to the analgesic effects, but had no effect on joint swelling.

With the high dosage of aspirin (5.3 g/day) improvement of joint size occurred in 5 of 7 patients (71 percent) in the first trial and 7 of 11 in the second trial in which the drug was given in the first or second week of a crossover study with a placebo. The mean decrease in joint size was 5 mm and 4 mm for the two studies. In a study in which a low dosage of salicylate (2.6 g) was compared with a high dosage of salicylate, improvement was noted in 1 of 11 patients in one trial when the low dosage was given first and 2 of 7 patients when the high dosage was given first indicating a possible residual effect of the high dosage of salicylate. Tinnitus occurred in 4 of 18 patients at the higher dosage and in none of 33 patients receiving the low dosage.

The authors conclude that their study confirms earlier reports that according to their criteria of objective clinical response, anti-inflammatory effects are essentially nonexistent with the lower dosage of salicylates used.

Boardman and Hart (Ref. 30) concluded that "These findings confirm the importance of administering high doses of salicylates in rheumatoid arthritis irrespective of symptoms and their severity if the aim of the treatment is the promotion of nonspecific anti-inflammatory actions."

Graham and coworkers (Ref. 31) state that inadequate suppression of inflammation of rheumatoid arthritis commonly occurs where salicylate plasma levels fall below 15 mg/100 ml. In a study of 12 hospitalized patients with rheumatoid arthritis in which a 4.8 g daily dosage was given and patient compliance and drug bioavailability carefully supervised, assured therapeutic plasma levels (greater than 15 mg/100 ml) were not reached in eight patients (67 percent). The maximum average midday plasma concentration after several days dosing was 12.6 mg/ml with a range of 5.5 to 27.6 mg/100 ml. Low levels of salicylate in these patients were stated to be due to rapid elimination, large volume of distribution or both. Concomitant administration of corticosteroids was also identified as a factor which might be involved in inadequate therapeutic plasma levels on long term therapy even though high dosages were given (3.6 to 4.8 g daily).

In summary, on the basis of pharmacokinetic considerations, the Panel concludes there is an abundance of published literature which clearly establishes that self-medication of even minor symptoms of rheumatoid arthritis constitutes irrational therapy. There is a greatly increased risk relative to benefit that would result from any attempts of untrained laity to determine and monitor an individual dosage regimen required to maximize the great potential benefit from dosages adequate to suppress inflammation and minimize the great potential risk from only slightly higher dosages which can cause serious toxicity.

The available literature clearly shows that in the case of rheumatoid arthritis, aspirin should not be used simply to relieve symptoms but rather to actively treat the disease by giving individualized dosages adequate to suppress inflammation. Because of the unusual pharmacokinetic characteristics of the salicylates only recently recognized, the determination of the appropriate dosage for rheumatoid arthritis requires skilled professional assistance. Furthermore, dosages and duration of therapy required for adequate therapeutic treatment are greater than those considered safe for unsupervised OTC dosing. Many factors must be considered beyond the capability of the general population and indeed requiring skilled clinical judgment and assessment.

In some cases, careful monitoring is required involving clinical laboratory tests, such as determination of plasma salicylate concentration, liver function tests and urine pH, which are not accessible to or interpretable by the untrained general population.

The Panel, therefore, believes that any labeling which encourages unsupervised treatment of rheumatoid arthritis even for relief of "minor symptoms" constitutes an unacceptable risk. The Panel recognizes that because of the large dosages required over a long period of time, it would create an unnecessary economic hardship to require a prescription status for the use of salicylates in the treatment of rheumatoid arthritis. By analogy, insulin can be purchased by diabetics without a prescription for medically supervised use. It would be irrational, however, to suggest that the labeling directions or promotional material should encourage the target population to determine the dosage to relieve their symptoms or attempt to monitor the effects of their drug treatment or their disease progress without laboratory testing and supervision by a physician.

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2. *Statement on standard and nonstandard nonsalicylate dosage schedules.* The components of a salicylate dosage schedule also apply to a nonsalicylate dosage schedule. (See part II. paragraph E.3. above—Analgesic-antipyretic recommended dosage.) Dosage schedules for the use of aspirin, a salicylate, in standard and nonstandard dosage units, were discussed above by the panel. The Panel also considered dosage schedules for the use of acetaminophen, a nonsalicylate, in standard and nonstandard dosage units.

There was much less information available to the Panel on the pharmacokinetics of acetaminophen in animals and man than of aspirin. However, there is good evidence that the pharmacokinetics of this drug are simpler than those for aspirin, and acetaminophen probably shows linear kinetics. However, the Panel finds it reasonable to recommend the use of acetaminophen in the same dosages as those recommended for the use of standard aspirin dosage units, i.e., 325 and 650 mg. (See part II. paragraph E.3.b. above—Recommended dosage for products containing standard dosage units.)

Of particular concern to the Panel in considering the possibility of increasing the dosages of acetaminophen was the paucity of data regarding the toxic effect of acetaminophen from single dosages that exceed the dosages recommended for chronic use of the drug for longer than the 5-day interval in children or the 10-day interval in adults, or from dosages that exceed the maximum adult daily dosage of 4,000 mg. Elsewhere in this document the Panel has discussed the toxicity of acetaminophen and its relationship to dosage level. (See part III. paragraph. B.1.b.(2) below—Safety.)

Until data based on clinical efficacy studies and appropriate toxicological studies are available to justify an increase in the dosage of acetaminophen, the Panel believes it unwarranted to introduce dosages that exceed those recommended for aspirin. Also, the Panel concludes that only nonstandard dosage units of 500 mg may be recognized for acetaminophen in addition to the standard dosage unit of 325 mg since the Panel is unaware of any other nonstandard dosage unit currently available in marketed adult strength products containing acetaminophen as the single active ingredient. Therefore, regarding the dosage schedule for acetaminophen in nonstandard dosage unit of 500 mg, the Panel concluded that the same dosage should apply to acetaminophen as that recommended for the use of nonstandard aspirin dosage unit of 500 mg. (See part II. paragraph E.3.c above—Recommended dosage for products containing nonstandard dosage units.)

3. *Statement on children's dosage.* a. *Introduction.* The Panel has reviewed OTC drug labeling for currently marketed products containing aspirin. The Panel finds that there is a lack of a single recognized pediatric dosage schedule. Initially, the Panel attempted to compile a pediatric dosage schedule based upon common features of dosage schedules presently found in the labeling of marketed pediatric products. This representative dosage schedule is given below in Pediatric Schedule A.

The Panel also sought comments from the drug industry, through the industry liaison Panel member, regarding a recommended pediatric dosage regimen for aspirin products. One drug manufacturer (Ref. 1) submitted data containing a review of the medical literature regarding pediatric dosages of aspirin, survey information on the aspirin dosages currently used by practicing pediatricians and data pertaining to the pharmacology and pharmacokinetics of aspirin dosages through consultation with pediatric clinical pharmacologists. In addition, a new regimen was proposed by the drug manufacturer discussed below as Pediatric Schedule B.

To support the submission, data and comments were presented that the currently labeled OTC pediatric dosage schedule (Pediatric Schedule A) is inadequate (Ref. 2). It was stated that the dosage in the labeling is too low particularly in the youngest age group. Because of this, therapeutic failure may cause consumers to either exceed the labeled dosage or repeat dosing before the recommended 3-hour interval. This was proposed to the Panel as a cause for overdosing. This new dosage schedule was proposed to prevent the problem of overdosing by initiating treatment with an adequate dosage and then repeating after 4 hours to maintain the desired effect.

The Panel further modified this proposal (Pediatric Schedule C) which is discussed more fully below. It should further be noted, that based upon a review of the use of aspirin in children, the Panel also considered the pediatric dosage schedules for acetaminophen, aspirin salts, and all other salicylates. While not included in the example for aspirin in Pediatric Schedule C, the Panel has included appropriate pediatric dosage recommendations for Category I ingredients, where applicable, in the appropriate sections of this document.

b. *Discussion.* The following dosage schedule based upon current recommendations given on many aspirin-containing products currently marketed for OTC use, was initially considered by the Panel:

Pediatric schedule A—representative current pediatric dosage schedule on marketed products for 81 mg (1.25 gr) aspirin tablets

Age (years)	Number tablets taken every 3 h (single dosage)	Total dosage (milligrams)
Under 3	(1)	
3	1	81
4 through 5	2	162
6 through 9	3	243
10 through 14	4	324

[1] As directed by physician

As was pointed out by one drug manufacturer, this dosage schedule was selected primarily on the basis of safety considerations to assure minimal potential for toxicity, particularly in the youngest group (Ref. 1).

In a survey of 2,241 pediatricians regarding the current pediatric dosage schedule on marketed products of as-

pirin tablets described in the above table, 2,202 (approximately 94 percent) stated that the labeled dosage is subtherapeutic (Ref. 1). Further, 72 percent believed that the labeled frequency of every 3 hours is too frequent a dosing interval. In addition, 78 percent of the physicians indicated that they usually use age as the basis for determining the appropriate aspirin dosage for their patients while 21 percent utilize body weight as the basis. In most cases, a dosage of 65 mg (1 gr) per year of age every 4 hours as needed was the preferred dosage schedule.

The medical literature lists many methods of calculating dosages based on either age, body weight or body surface area. Several clinical studies have been cited supporting the efficacy of aspirin dosage based on age (Ref. 1). Standard references such as *AMA Drug Evaluations* utilize the body weight of the child in a recommended schedule of 65 mg (1 gr)/kg of body weight daily, divided into four to six equal dosages (Ref. 3). In addition, body surface area has been used, for example 1.5 g/m² of body surface daily has been recommended. The official pediatric analgesic-antipyretic dosage in the *United States Pharmacopeia XIX* is 11 mg/kg of body weight (64 mg/kg/day) or 250 mg/m² of body surface, six times daily (1.5 gm/m²/day), to 16 mg/kg of body weight (64 mg/kg/day) or 375 mg/m² (1.5 mg/m²/day), of body surface, four times daily (Ref. 4). In this latter case, the official compendial regimen is based on patient parameters not likely to be understood by the consumer and in the Panel's view is inadequate for product labeling. However, as noted later, dosage by age is proportional to dosage regimens calculated by surface area up to age 12 years. Therefore, age can be used to indicate dosages based upon surface area calculations.

One drug manufacturer (Ref. 1) states: "based on available data, the best such basis for an effective therapeutic dosage for fever and pain in children appears to indicate 10 to 15 mg of aspirin per kg of body weight every 4 hours as required (not to exceed 5 doses per 24 hours) unless directed otherwise by a physician." This schedule has been reported as effective (Refs. 5 through 9) and is similar to that found in the dosage for body weight recommendation of the *United States Pharmacopeia XIX*.

The Panel considered the following pediatric dosage schedule proposed by industry:

Pediatric schedule B—drug industry proposal for pediatric dosages for 81 mg (1.25 gr) aspirin tablets

Age (years)	Number tablets taken every 4 h [1]	Total dosage (milligrams)
Under 2	[2]	
2 through 3	2	162
4 through 6	3	243
7 through 8	4	324
9 through 10	5	405
11 through 12	6	486
13 and older	8	648

[1] Not to exceed 5 dosages in 24 h except under the advice and supervision of a physician.
[2] As directed by physician.

The published results of two studies comparing the antipyretic effect of a single dosage of acetaminophen with the antipyretic effect of a single dosage of aspirin were also submitted to the Panel (Refs. 10 and 11). The comparison was made in children between the ages of 6 months and 72 months (6 years). For the same age groups, the acetaminophen dosages were approximately the same as the aspirin dosages. For example, the dosages for children 30 to 48 months of age in one study were 225 mg and 240 mg aspirin and acetaminophen, respectively (Ref. 10). In the second study, the dosage for children 30 to 42 months of age was 180 mg for both aspirin and acetaminophen (Ref. 11). These pediatric dosages are higher than the currently recommended dosages for this age group in the labeling of marketed aspirin-containing products.

The Panel also considered the dosage of salicylates for individuals 12 years and over as equivalent to adult dosages, a concept accepted by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products, as published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38419). This would conform to the dosage schedules for other therapeutic agents which are used in combination products with salicylates. The Panel concludes that because of the unusual pharmacologic characteristics of the salicylates, an adult dosage schedule would result in an unwarranted risk potential in children under 12 years of age. The data of Makela et al. (Ref. 12) clearly establish the potential for overdosing in children weighing more than 40 kg if inappropriate schedules, based upon children's weight, are used.

The Panel appreciates the desirability of standardizing the percent of the adult dosage required for different age ranges. Ideally, it would be advantageous to establish the pediatric dosage for a given age range as the same percent of the adult dosage as for drugs commonly used together. This is possible, however, only when these agents have similar changes in pharmacokinetic and dose-response characteristics as a function of increasing age. When two or more therapeutically active agents are used which do not have proportional changes in their dosage requirements for children in different age groups, fixed combinations may not be suitable for pediatric use. In some cases, the dosage of one or both agents may be different in the combination than when used alone. The dosage regimen would have to be adjusted relative to the agent of highest potential toxicity. The pediatric dosage of aspirin as a percent of the adult dosage regimen is listed below. The pharmacokinetic basis and clinical data supporting the recommended dosage regimen were discussed elsewhere in this document. (See part II, paragraph F.1. above—Statement on standard and nonstandard salicylate dosage schedules.)

As noted above, the Panel originally considered the currently used dosage regimen for marketed products (Pediatric Schedule A) but later considered industry's proposed regimen (Pediatric Schedule B) because the doses in the former are too low at lower ages. The latter schedule is based essentially upon the commonly used daily pediatric dosage of 65 mg/kg of body weight with a maximum of five dosages daily. It is commonly stated that this dosage is equivalent to a 1.5 g/m² daily dosage schedule based upon surface area. This is strictly true only at the ages (years) when the average surface area is 1.5 m². It is significant to note that after the age of 7 years, the weight increase is much greater than the increase in surface area. Therefore, after the age of 7 years, dosages based upon body weight will be greater than dosages based upon surface area.

The increasing deviation of body weight per age curve from the surface area per age curve may result in overdosing toxicity particularly in older children (body weight of 40 kg or more). This effect is clearly shown in the data of Makela et al. (Ref. 12) in which 100 mg/kg daily was administered every 8 hours. This dosage regimen generally resulted in plasma levels of 24 to 27 mg percent which is adequate for patients with rheumatoid arthritis but excessive for analgesic-antipyretic effects. Additionally, in 7 of the 19 subjects (37 percent), toxicity occurred which was associated with plasma levels of more than 35 mg percent (37.3 mg percent to 48.3 mg percent). In 50 percent of toxic cases, the patients were 11 years of age or older and weighed more than 40 kg. The 100 mg/kg schedule, therefore, is not suitable if it results in a schedule in which 3.0 g/m² daily is exceeded since every toxic case received dosages of more than 3.0 g/m² daily while those who were nontoxic received a dose of 2.4 g/m² daily.

This study illustrates several important points. First, body surface area is the most accurate predictor of dosage. There are two other reasons why the Panel believes that body surface area should be the standard means of calculating the salicylate dosage. The reason that the prediction of toxicity can be better done by dosing on the basis of surface area rather than body weight is clear from basic pharmacokinetic data.

Accumulation of drugs and toxicity occur when dosage input exceeds maximum output. Levy has shown that maximum output of salicyluric acid, the primary metabolite, is formed at a maximum rate (Vmax) which is proportional to body surface area (Ref. 13). Even though all subjects in the Makela study received usual rheumatoid arthritis dosage schedules of 100 mg/kg, salicylate levels were too high because the input calculated on a weight basis (D=100 mg/kg daily) was greater than 3.0 g/m² daily when calculated on the basis of surface area; greater than the maximum output of 3.0 g/m² daily found by Makela (Ref. 12) and also derived by the Panel from the data of Brewer (Ref. 14).

A second reason for calculating dosing regimens on the basis of surface area is that the body surface area is essentially (linearly) proportional to age for

children from ages 3 to 12 years. Body weight is a nonlinear function of age, however, in ages over 7 years. This explains the preference of the majority of clinicians for a dosing system based upon age.

Based on these pharmacokinetic considerations and clinical data, the Panel has revised the industry proposed schedule (Pediatric Schedule B) to conform with a daily dosage of 1.5 g/m² daily rather than 65 mg/kg daily. These two methods produce similar values at ages below 8 years and deviation between the Panel's recommended schedule (Pediatric Schedule C) and the industry proposal occur mainly at higher age levels where weight is not the best predictor of dosage.

The Panel concludes that the dosage should never exceed 2.5 g/m² daily (approximately 100 mg/m²/hour). Therefore the dose of 1.5 g/m² daily will provide effective plasma levels for analgesic and antipyretic effects and provide a safety margin in the event of an inadvertent 50 percent increase in dosage. This conversion of age to total dosage is approximated from ages 2 to under 12 years by the relationship:

mg/day=650 mg+(100 mg/year of age)

It is important to note that the use of the full maximum daily adult dosage at 12 or 13 years of age may exceed the critical dose rate toxicity level. The total daily dosage of salicylate divided by the usual body weight will be about 2.8 mg/kg/day which is equal to the lower level of the toxic level found by Makela (Ref. 12).

For children age 11 to 15 years, a 25 percent difference in dosage increase from 2.4 ± 0.2 g/m² daily dosage to 3.2 ± 0.5 g/m² daily will increase the plasma concentration from 25 to 29 mg/100 ml to 40 mg/100 ml. For children 4 to 7 years, a similar increase in dosage will result in a change of 20 to 25 mg/100 ml at the lower dosage to a plasma concentration of about 36 mg/100 ml.

The dosages established are based upon the 1.5 g/m² daily dosage for that age as described by Done (Ref. 15). Under the Panel's proposed schedule, the age minimum for OTC use is lowered to 2 years and the frequency of administration is increased by 1 hour to every 4 hours. The Panel concludes that this dosage schedule is more reasonable than that currently being used. The Panel further concludes that the regimen is safe and effective and is much clearer and more concise for the OTC drug consumer.

It should further be noted that, based upon a review of the use of aspirin in children, the Panel also considered and included a pediatric dosage schedule for acetaminophen. In addition, pediatric dosage schedules for other aspirin salts and all other salicylates were considered by the Panel. While not included in the example for aspirin and acetaminophen in Pediatric Schedule C which applies to all dosage forms, e.g., tablets, liquids, etc. for these ingredients, the Panel has included appropriate pediatric dosage recommendations for Category I ingredients, where applicable, in the appropriate sections of this document.

After consideration of the data and submitted comments, the Panel recommends the following pediatric dosage schedule for aspirin and acetaminophen:

Pediatric Schedule C—the Panel's proposed (new) pediatric single dosage schedule every 4 hours for 80 mg (1.23 gr) aspirin or acetaminophen

Age (years)	Pediatric (80 mg) dosage units [1]		Adult (325 mg) dosage unit [2]	
	Dosage units	Total dosage (mg)	Dosage units	Total dosage (mg)
Under 2	[3]	[3]	[3]	[3]
2 to under 4	2	160	½	162.5
4 to under 6	3	240	¾	243.8
6 to under 9	4	320	1	325.0
9 to under 11	5	400	1¼	406.3
11 to under 12	6	480	1½	487.5

[1] Not to exceed 5 single dosages in 24 h or to be used for more than 5 d except under the advice and supervision of a physician.
[2] Not to exceed 5 single dosages in 24 h or to be used for more than 5 d except under the advice and supervision of a physician.
[3] There is no recommended dosage except under the advice and supervision of a physician.

c. *Conclusion.* In view of these findings, the Panel concludes that it is appropriate to revise the currently marketed OTC pediatric dosage recommendations. In its evaluation, the Panel adopted the definition of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products, as published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38419): "Infant or baby (under 2 years), child (2 years to under 12 years), and adult (12 years and over)."

The Panel further concludes on the basis of the available data on the use of aspirin in children, that the duration of use for all OTC analgesic products should be limited to 5 days for children under 12 years of age rather than 10 days as recommended for adults. It is the opinion of the Panel that this restriction should also apply to acetaminophen to avoid confusion in the labeling of pediatric products. Therefore, labeling should contain the following warning: "Do not take this product for more than 5 days. If symptoms persist, or new ones occur, consult your physician". This recommendation is based upon reports from data available from poison control centers that there is a higher incidence of aspirin overdosage among children for periods longer than 5 days. This is also consistent with computer simulations, which demonstrate that while using the maximum daily recommended dosage, the plasma concentration could exceed 20 mg/100 ml among some smaller children of a particular age category following the recommended dosage schedule after 5 days.

The Panel concludes that the pediatric dosage unit of 80 mg (1.23 gr) of aspirin should be retained because there is long standing acceptance. One, two, or three pediatric units can easily be obtained by quartering or halving a standard 325 mg aspirin tablet, and surface area gain and age of children correlate closely over the first 12 years of life, permitting a regular increase in dosage according to age. While the Panel realizes that dosage by square meters of body surface alone would be more accurate, it believes that basing pediatric dosage recommendations on age will be more readily understood by the average consumer and acceptable since it correlates closely with dosages calculated on the basis of surface area.

d. *Recommendation.* The Panel recommends that the proposed (new) pediatric single dosage schedule described above (Pediatric Schedule C) be used in labeling of future marketed products. The Panel recognizes that, if their recommendation is implemented by the Food and Drug Administration, there will be of necessity an interim marketing period at which time both the old Pediatric Schedule A and new Pediatric Schedule C will be simultaneously available to the OTC drug consumer. The Panel recommends that the Food and Drug Administration establish an orderly process to reduce the likelihood of confusion in interpreting product labeling. Perhaps the improved labeling can be clearly identified as "new" or "revised" on the traditionally marketed products that consumers are accustomed to purchasing.

The Panel has examined the regulations of the Poison Prevention Packaging Act of 1970 as set forth in 16 CFR 1700.15(a), (b) and (c) of the regulations, that provide for poison prevention packaging standards for aspirin-containing products in a dosage form intended for oral administration. The standards for child-resistant safety closures required on the containers of these products are intended to protect children from intentional or accidental ingestion without hampering the adult-use effectiveness of the products. The Panel concurs with these standards and is of the opinion that the standards for child-resistant safety closures should apply to the containers in which acetaminophen oral products are packaged as well as to aspirin-containing products.

The Panel further recommends that the restrictions on the maximum number of tablets permitted in containers of aspirin products for child use should also apply to acetaminophen products formulated for use in children only. Therefore, acetaminophen products containing 80 mg (1.23 gr) tablets intended

for oral use in children should contain no more than 36 tablets to reduce the hazard of accidental poisoning, as set forth in 21 CFR 201.314(c)(2) for products containing 80 mg (1.23 gr) tablets of aspirin for pediatric use. The Panel recommends that the OTC packaging requirements for safety closures and the restriction on the maximum number of tablets in the containers of aspirin products for pediatric use should also apply to acetaminophen products for use in children.

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G. DRUG COMBINATION STANDARDS

1. *General comment.* The Panel has classified the active ingredients submitted for review into three pharmacological activities, i.e., analgesic, antipyretic and antirheumatic. For purposes of establishing standards for safe and effective OTC drug combination products, the Panel developed the policy not to include the antirheumatic pharmacologic activity in the standard. This policy is based upon the Panel's conclusion, described later in this document, that there are no acceptable Category I claims for OTC labeling as an antirheumatic. (See part V. paragraph B.1. below—Category I Labeling.)

Two major types of combination products were considered by the Panel. One group of products consists only of combinations of analgesic and/or antipyretic active ingredients reviewed for safety and effectiveness by this Panel. The other group of products consists of combinations of analgesic and/or antipyretic active ingredients combined with active ingredients having different pharmacologic activities, such as antihistamines or nasal decongestants. For this second group of combination products, the Panel only reviewed the rationale of combining nonanalgesic-nonantipyretic active ingredients with analgesic-antipyretic active ingredients. The nonanalgesic-nonantipyretic ingredients were deferred to other OTC Advisory Panels for a review of their safety and effectiveness. (See part I. paragraph C.3. above—Ingredients deferred to other OTC advisory review panels or other experts.)

The Panel is not opposed to the concept of combinations of active ingredients which have been shown to be individually safe and effective, provided that the specific combination has been shown to be at least as safe and effective as therapeutic doses of the individual active ingredients. For example, if two active ingredients A and B, with similar pharmacologic activity, are combined such that each is combined at one-half the usual therapeutic dose when used alone, the combination (AB) should be at least as safe and effective as the full therapeutic dose of either A or B when used alone.

It should be noted that for the drugs reviewed by this Panel three variations are possible. The variations would include combinations of analgesics, combinations of antipyretics or an analgesic-antipyretic combination. However, the Panel has found that the active ingredients submitted for review and classified as analgesics are also antipyretics. Therefore, even though three different variations are possible, in reality, the ingredients currently available all possess analgesic and antipyretic properties.

In the event that at a later date ingredients are identified as only having one of these pharmacologic activities, the Panel believes that the drug combination standard should provide for all possible safe and effective combinations of active ingredients and for all acceptable labeling. Therefore, the concept of combining analgesics, antipyretics or analgesic-antipyretics is acceptable.

The marketplace is filled with a variety of single ingredient analgesic-antipyretic products, and many of these ingredients are also present in combination products. The Panel has found that the concepts used to explain the reasons for marketing combination products have not yet been supported by adequate clinical data. The Panel concludes that combinations must be safe, effective and rational in order to be included in the proposed drug monograph.

A possible rationale for the use of analgesic-antipyretic combination products is that each ingredient's anticipated activity is additive or synergistic. The additive or synergistic effect could be due to the drugs acting by different mechanisms or perhaps exerting their effect at different locations within the body.

In reviewing combination ingredients in the market place, the Panel applied the OTC Drug Review regulation (21 CFR 330.10(a)(4)(iv)) which states:

> An OTC drug may combine two or more safe and effective ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel recognizes the regulation and believes that each active ingredient in a combination product must contribute to the claimed effects and that the combination provides rational concurrent therapy. It is the view of the Panel that it is irrational to use a combination product unless each of its active ingredients contributes to the effective treatment of at least one of the labeled symptoms for which the combination of ingredients is recommended. The specific combination should be at least as safe and effective as therapeutic doses of the individual active ingredients when used alone.

The Panel recognizes that safety and effectiveness studies are desirable, especially, when it becomes known or suspected that one of the drugs in the combination may influence the metabolism or the action of another drug. However, Category I ingredients, known to be individually safe and effective, may be combined as described below in Standard No. 4.

2. *Limitation of ingredients in combination products.* The Panel concludes that, in general, an OTC product with fewer ingredients provides safer use. Also, the interests of the consumer are best served by exposing the user of OTC drugs to the smallest number of ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness. The possibility of adverse reactions increases with the number of drugs ingested resulting in potential increased risk to the user without a concurrent increase in benefit. Therefore, with fewer ingredients there is a better chance of reduced risks due to toxic effects, undesirable additive or possibly synergistic effects, allergic and/or idiosyncratic reactions.

The Panel recommends that not more than two active analgesic-antipyretic ingredients from Category I be included in any combination without further study unless the addition of a third analgesic-antipyretic ingredient can be demonstrated to contribute to the effectiveness or safety of the combination. This does

not preclude the use of adjuvants or correctives which are discussed later in this document. (See part VI. below—Adjuvants and Corrective Agents.) The Panel bases this conclusion, not only on the fact that fewer ingredients generally provide safer use, but also on the fact that no combination was submitted to the Panel containing three Category I analgesic-antipyretic active ingredients. In addition, the Panel can find no data to support the combining of more than two analgesic-antipyretics in the same product. Therefore Category I combinations are limited to combinations of two analgesic-antipyretic ingredients. (See part II. paragraph G.4. below—Standards for Category I combination products.)

The Panel is aware of the inclusion of inactive ingredients (pharmaceutical necessities) in the preparations for use as preservatives, fillers, coatings, colorants, vehicles, aromatics, binders, sweeteners, flavoring agents, etc. Such inactive ingredients are acceptable for marketing purposes provided they are pharmacologically inert and do not adversely affect the bioavailability of the active ingredient(s). However, the Panel is of the opinion that such pharmaceutical necessities be studied by a separate body for the evaluation of their safety. Special attention needs to be given to the effects of these pharmaceutical necessities on children. The Panel considers it important that the advisability of including them in drug products be reviewed by an appropriate body. Since many of these inactive ingredients are used in the formulation of many drug products other than those reviewed by this Panel, it is not appropriate that they be dealt with specifically and solely in relation to analgesic, antipyretic and antirheumatic active ingredients, except as they might affect the actions of these active ingredients.

Nonanalgesic-nonantipyretic active ingredients may be included in products only if they are in safe and effective doses and either provide relief for symptoms designated by this or other panel(s) or beneficially influence the actions of the active ingredient(s).

In summary, marketed combination products should contain only those active and inactive ingredients that are rational for a safe and effective product as described above.

The Panel concurs with the following conclusions of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products, as published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38334), regarding the labeling of inactive ingredients:

> For various reasons, individuals may wish to avoid using certain inactive ingredients found in drug products. These reasons may be allergic reactions, idiosyncratic responses, fear of safety (whether valid or not), or personal dislike. It is impossible to make a free choice in this regard unless the full contents of drug products are listed on the label. Therefore, this Panel strongly recommends that the Food and Drug Administration require full ingredient labeling of inactive as well as active ingredients in descending order of quantities present in all drug products.

In support of this position the Panel notes that food products are already required to have such labeling, and since the purpose of a drug is to alleviate symptoms of disease, it would seem much more compelling to have this information on all drugs.

In line with the Panel's desire to expose the consumer to the smallest number of ingredients possible, the Panel has previously recommended that marketed products contain only those ingredients essential to the product.

3. *Labeling of active ingredients.* The Panel agrees that each claimed active ingredient in a combination product must make a contribution to the claimed effect(s).

Labeled indications should only be for the combinations of symptoms appropriate to the activity of the combined ingredients. The consumer should be adequately informed through the labeling of the therapeutic capabilities of the product by emphasizing the use of the product only when all such symptoms are present. Labeling should, therefore, fully reflect the activities of all active ingredients so that a consumer may select an appropriate product for relief of symptoms.

4. *Standards for Category I combination products.* a. Each active ingredient and its labeling in a combination product must be generally recognized as safe and effective (Category I).

b. One Category I analgesic-antipyretic active ingredient at the minimum effective dosage may be combined with one other Category I analgesic-antipyretic active ingredient at its minimum effective dosage. The Panel was unable to find data to support the use of more than two analgesic-antipyretic active ingredients in the same combination product.

c. One Category I analgesic-antipyretic active ingredient or a combination of two such ingredients as provided above in standard No. 4.b. may be combined with generally recognized as safe and effective antitussive active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

d. One Category I analgesic-antipyretic active ingredient or a combination of two such ingredients as provided above in standard No. 4.b. may be combined with generally recognized as safe and effective expectorant active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for expectorant action to help loosen phlegm (sputum) and bronchial secretions".

e. One Category I analgesic-antipyretic active ingredient or a combination of two such ingredients as provided above in standard No. 4.b. may be combined with generally recognized as safe and effective nasal decongestant active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for the temporary relief of nasal congestion due to the common cold (cold)".

f. One Category I analgesic-antipyretic active ingredient or a combination of two such ingredients as provided above in standard No. 4.b. may be combined with generally recognized as safe and effective antihistamine active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and to alleviate, decrease, or temporarily relieve running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

g. One Category I nonsalicylate analgesic-antipyretic active ingredient or a combination of two such nonsalicylate ingredients as provided above in standard No. 4.b. may be combined with antacid active ingredient(s) which meet the requirements of § 331.10 (21 CFR 331.10) of the OTC antacid monograph provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for acid indigestion".

h. Aspirin may be combined with antacid active ingredient(s) identified in § 331.11 (21 CFR 331.11) of the OTC antacid monograph such that the finished product contains at least 20 mEq of acid neutralizing capacity per 325 mg (5 gr) aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 (21 CFR 331.25) of the OTC antacid monograph and provided the product is identified as highly buffered aspirin for solution with labeling only as an analgesic and/or antipyretic.

The Panel is limiting labeled indications to "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever". In addition, the Panel has classified the following as Category III labeling which may be included in the principal display panel: (1) "Provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label".

(2) "Faster to the bloodstream than plain aspirin".

The Panel has discussed the above Category III labeling elsewhere in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

The Panel finds it irrational to provide claims for an antacid effect, e.g., "For the treatment of heartburn, sour stomach and acid indigestion", since aspirin may potentiate peptic ulcer, cause stomach distress or heartburn. Aspirin also

causes an increase in occult bleeding and in some individuals massive gastrointestinal bleeding. The adverse effects of aspirin on the gastrointestinal tract are discussed elsewhere in this document. (See part III. paragraph B.1.a.(2)(ii) below—Adverse effects on the gastrointestinal tract.)

i. Aspirin may be combined with antacid active ingredient(s) identified in § 331.11 of the OTC antacid monograph such that the finished product contains at least 1.9 mEq of acid neutralizing capacity per 325 mg (5 gr) aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of the OTC antacid monograph and provided the product is identified as buffered aspirin with labeling only as an analgesic and/or antipyretic: "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever".

In addition, the Panel classified the following as Category III labeling which may be included on the principal display panel:

(1) "Provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label".

(2) "Faster to the bloodstream than plain aspirin".

The Panel has discussed the above Category III labeling elsewhere in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

5. *Standards for Category II combination products.* a. Combination products containing a Category II analgesic-antipyretic or Category II labeling, except for the inclusion of caffeine used as an adjuvant, are classified as Category II. The classification and role of caffeine is discussed later in this document. (See part VI. paragraph B.3. below—Caffeine (citrated caffeine).)

b. Combination products containing Category I analgesic-antipyretic(s) combined with any active ingredient(s) not reviewed by this or other OTC advisory review panels or found to be either unsafe or irrational are classified as Category II.

c. Aspirin in combination with any generally recognized as safe and effective oral bronchodilator active ingredient is classified as Category II. Aspirin may cause a severe, and possibly fatal reaction in some asthmatics taking such a product. This adverse effect is discussed later in this document. (See part III. paragraph B.1.a.(2)(iii) below—Adverse effects on hypersensitive individuals.)

d. Combinations of analgesics with laxatives, or vitamins, are considered irrational since any conditions requiring such drugs should not be treated by fixed-ratio combination products. Conditions requiring treatment with such drugs should be treated with single ingredients. Vitamins combined with analgesic may encourage unnecessary prolonged use of analgesics and are therefore classified as Category II.

6. *Standards for Category III combination products.* a. Combination products containing a Category III analgesic-antipyretic active ingredient and no Category II analgesic-antipyretic active ingredient are classified as Category III.

b. Combination products containing any Category I analgesic-antipyretic active ingredient at less than the minimum effective dosage are classified as Category III.

c. Combination products containing more than two analgesic-antipyretic active ingredients are classified as Category III. (See Standard No. 4.b. above.)

d. Combination products containing one Category I analgesic-antipyretic active ingredient or a combination of two such ingredients as provided above in standard No. 4.b. combined with caffeine used as an adjuvant are classified as Category III.

The Panel concludes that there are insufficient data available to evaluate the adjuvant effect of caffeine. The Panel finds that there is little evidence to show that this ingredient contributes to analgesic, antipyretic and/or antirheumatic effects in the clinical situation. Additional studies are necessary as described below in this document. (See part VI. paragraph C.2. below–Combination products containing an analgesic, antipyretic and/or antirheumatic adjuvant.)

e. One Category I analgesic active ingredient or a combination of two such analgesic ingredients as provided above in standard No. 4.b. combined with a generally recognized as safe and effective nighttime sleep-aid active ingredient is classified as Category III provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for the relief of occasional sleeplessness". The Panel concurs with the recommendations of the Advisory Review Panel on OTC Sedative, Tranquilizer and Sleep-Aid Drug Products published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57315) that a suitable target population requiring both drugs concurrently should be defined. This Panel finds that an individual with e.g., headache and sleeplessness may be relieved of symptoms conveniently by such a combination product. However, it should be demonstrated that there is a well-defined target population requiring concurrent use of an analgesic and a nighttime sleep-aid. Otherwise, it is the Panel's opinion that it would be more desirable to alleviate the symptoms of pain which may in turn be the underlying factor causing the sleeplessness condition. The Panel concurs with the recommendation of the OTC Sedative, Tranquilizer and Sleep-Aid Panel that several studies using a factorial design should be completed to demonstrate that the combination is safe and effective for a significant proportion of the target population requiring relief from both symptoms of pain and sleeplessness.

f. One Category I analgesic-antipyretic active ingredient or a combination of two such ingredients as provided above in standard No. 4.b. combined with phenyltoloxamine (or methapyrilene fumarate, pheniramine maleate or pyrilamine maleate) used as an adjuvant is classified as Category III.

The Panel concludes that there are insufficient data available to evaluate the adjuvant effect. The Panel finds that there is inadequate data to show that these ingredients contribute to analgesic, antipyretic and/or antirheumatic effects in the clinical situation. Additional studies are necessary as described below in this document. (See part VI. paragraph B.4. below—Antihistamine-containing ingredients.)

7. *Standards for testing Category III combination products.* The Panel concludes that additional testing is required for Category III combination products.

Since aspirin serves as a standard for all drugs in this class, all combinations must demonstrate at least as much analgesia and/or antipyresis as 325 mg (5 gr) to 650 mg (10 gr) of aspirin in a single dose (2 dosage units) or in the recommended maximum dosage of 4,000 mg in 24 hours.

To establish Category I status for a Category III combination product requires a minimum of two studies by independent investigators which conform to the standards and guidelines included and discussed above for ingredients for which safety is unquestioned. (See part II. paragraph B.2. above—Safety and part II. paragraph G.4. above—Standards for Category I combination products.) If the ingredient is placed in Category III for reasons of safety, at least two, 3-month safety studies by independent investigators should be required. This requirement does not apply to antipyrine. (See part III., paragraph B.3.b.(5) below—Evaluation.)

Each study should include an appropriate number of subjects, a placebo, known drug controls, and should involve appropriate intervals of administration of the drug in question to controlled subject populations in whom side effects can be checked daily, and where applicable complete blood counts, urinalysis, and organ function tests are checked weekly or more often if necessary.

Clinical studies should be pertinent to each of the symptoms for which the combination is designed to give relief. The combination, a placebo, and each active ingredient alone should be subjected to well-controlled, suitably-blinded studies to determine both safety, e.g., adverse reactions or significant side effects, and effectiveness. In addition, where provided, objective methods should be employed as described elsewhere in this document. (See part III. paragraph B.3. below—Category III conditions for which the available data are insufficient to permit final classification at this time, and part IV. paragraph B.3. below—Category III conditions for which the available data are insufficient to permit final classifi-

cation at this time, and part V, paragraph B.3. below—Category III conditions for which the available data are insufficient to permit final classification at this time.)

H. DRUG INTERACTIONS WITH ANALGESIC, ANTIPYRETIC, AND ANTIRHEUMATIC AGENTS

Numerous reports have indicated possible harmful interactions between the salicylates and other drugs (Refs. 1 through 5). The Panel is concerned that the average individual using these agents, particularly aspirin, will consider the OTC drug innocuous and not realize the possibility of a drug interaction.

The Panel is aware that instances exist where individuals suffering from serious illness or other medical conditions are instructed by their physician to use OTC analgesics, antipyretics or antirheumatic drugs.

The Panel is also aware that many other individuals suffering from chronic illnesses will use OTC analgesics, antipyretics or antirheumatics on their own volition to alleviate pain, fever or inflammation. These individuals may not be aware of possible interactions between the salicylates, aspirin in particular, and prescription drugs.

Therefore, the Panel recommends that the labeling caution against the concurrent use of salicylates and some prescription drugs without consulting a physician. The Panel concludes that the warning on products containing salicylates should read *"Caution:* Do not take this product if you are presently taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout or arthritis except under the advice and supervision of a physician".

This salicylate drug interaction warning is based upon the concept that maintenance drugs prescribed for certain chronic illnesses or conditions may interact with salicylates, most often aspirin. A discussion of aspirin effects of concomitant use with other drugs or by persons with specific disease is discussed elsewhere in this document. (See part III, paragraph B.1.a.(2)(viii) below—Adverse effects of concomitant use with other drugs or by persons with certain disease states.)

The prescription drugs used in the treatment of these chronic illnesses and the drug interactions with salicylates which are hazards are as follows:

1. *Cardiovascular diseases.* Individuals with heart disease or other circulatory diseases who are currently taking anticoagulants, specifically of the coumarin type, will experience increased anticoagulation when large doses of salicylates, especially aspirin, are ingested. This phenomenon is due to depressed prothrombin formation in the liver and the displacement of the anticoagulant from secondary binding sites. These mechanisms may lead to severe hemorrhage unless the dosage of the anticoagulant is reduced or the individual ceases taking the OTC salicylate (Ref. 2).

2. *Diabetes.* Individuals taking oral antidiabetic drugs concurrently with salicylates may experience an additive hypoglycemic (low blood sugar) effect due to displacement of the antidiabetic drugs from protein binding sites. This can result in poor control of diabetes (Ref. 5).

3. *Gout.* Individuals with gout have high serum uric acid levels. Several drugs are prescribed for gout to decrease uric acid blood levels. These drugs include probenecid, the sulfinpyrazones, and allopurinol.

Probenecid and salicylates interfere with two kidney processes, i.e., secretion of uric acid by the distal tubule and reabsorption of uric acid by the proximal tubule of the kidney. The end result of taking both drugs at the same time depends on which process is predominant. At usual OTC doses, retention may be affected resulting in uric acid retention with a decrease in probenecid effects (Ref. 5).

In individuals receiving probenecid for gout therapy the effects of this drug are altered by salicylates because these agents when given with probenecid inhibit uric acid excretion by competing for active transport mechanisms in the proximal and distal tubules of the kidney.

Also, when analgesic doses of salicylates are taken concurrently with sulfinpyrazones the uricosuric effects are antagonized, and the effect of sulfinpyrazones is diminished (Ref. 5).

When phenylbutazone is taken with salicylates, uric acid retention results. This occurs because the phenylbutazone appears to compete successfully with uric acid and salicylate for excretion from the kidney. This combination of drugs produces mutual suppression of uricosuric action, thus negating any therapeutic benefit. Since both drugs are ulcerogenic, the possibility of gastrointestinal bleeding is increased (Refs. 1 and 5).

4. *Arthritis.* Certain individuals who suffer from arthritis have corticosteroids prescribed for them to relieve inflammation. Sometimes these individuals also take salicylates, especially aspirin, for the anti-inflammatory and analgesic effects. However, if corticosteroids and salicylates are taken together, the ulcer producing effect in the stomach is additive and thus increased danger of ulceration occurs. Also, corticosteroids may increase the excretion of salicylates and a withdrawal of the steroids while continuing salicylate medication may lead to signs of salicylate poisoning (Ref. 5).

Indomethacin is another drug prescribed as an anti-inflammatory agent for arthritis. Since both indomethacin and salicylates have an ulcer-producing effect on the mucous membrane of the stomach, their combined use may be especially dangerous (Refs. 1 and 5).

5. *Other drug interactions of varying significance.* Several other interactions between salicylates and prescription drugs occur, but due to the varying clinical significance, do not warrant inclusion of a warning on the labeling.

Methotrexate is a highly potent and very toxic drug which is prescribed for individuals with cancer or extensive psoriasis or psoriatic arthritis. Salicylates potentiate the therapeutic as well as the toxic effects of this drug (Ref. 5). The Panel is cognizant of the severity of this interaction. Yet, because of the toxicity of methotrexate physicians always carefully control the patient's use of all other medications, thereby negating the need for a warning.

Sulfonamides are antibacterials employed primarily in the treatment of urinary tract infections. Salicylates have been reported to increase serum sulfonamide levels by displacement from plasma protein binding sites (Ref. 5). Even though this interaction can potentially be serious, sulfonamides are usually used for treatment of acute infections not for chronic conditions and thereby do not merit inclusion in the warning.

Another interaction occurs between salicylates and drugs used to acidify the urine since acidic urine decreases the excretion rate of salicylates and thus increases their half-life (Refs. 4 and 5). Also, salicylism may result from a small increase in urine acidity when high doses of aspirin are used. Conversely, urine alkalinizers (Refs. 3 and 4) decrease activity of salicylates by increasing the excretion rate. While both of these instances demonstrate an interaction, the Panel does not consider them enough of a hazard to justify inclusion in the warning.

When salicylates are taken with ascorbic acid (vitamin C), the salicylates accumulate in the blood due to decreased salicylate excretion and ascorbic acid excretion rate is increased (Ref. 5). This interaction is probably not important since it is unlikely that the ascorbic acid-salicylate interaction will result in toxic salicylate levels in the blood.

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I. DEFINITIONS

The Panel has adopted and uses the following definitions throughout this document:

1. *Acetaminophen analgesic equivalence value.* The analgesic effectiveness for a product containing acetaminophen when compared to the standard acetaminophen 325 mg (5 gr) dosage unit.

2. *Acetaminophen (pediatric dosage unit).* A single dosage unit containing 80 mg (1.23 gr) acetaminophen for children under 12 years.

3. *Acetaminophen (standard dosage unit).* A single dosage unit containing 80 325 mg (5 gr) acetaminophen.

4. *Adjuvant.* An agent which, in the amount used, has no significant analgesic effect itself but contributes to the therapeutic effect of the active agent either directly or indirectly.

a. *Direct acting.* An adjuvant which enhances the pharmacologic response directly by synergistic or additive effects at the site of action.

b. *Indirect acting.* An adjuvant which does not have effects at the site of action, but indirectly increases the activity of the active agent(s) of the preparation by modifying the disposition (absorption, metabolism, excretion or distribution) of the active agent.

5. *Age (dosage) usage.* Infant or baby (under 2 years), child (2 years to under 12 years), and adult (12 years and over).

6. *Analgesic drug.* An agent useful to alleviate the symptoms of pain.

7. *Antacid.* An agent that reacts with acid, such as the hydrochloric acid in the stomach (gastric acid), to neutralize it (decrease its amount).

8. *Antipyretic drug.* An agent used to reduce fever.

9. *Antirheumatic drug.* An agent which reduces joint or muscle tenderness or swelling.

10. *Aspirin analgesic equivalence value.* The analgesic effectiveness for a product containing aspirin or aspirin salts, e.g., aluminum aspirin or calcium carbaspirin when compared to the standard aspirin 325 mg (5 gr) dosage unit.

11. *Aspirin (buffered).* A solid dosage form containing 325 mg (5 gr) aspirin with sufficient buffering capacity with antacid active ingredient(s) identified in § 331.11 of the OTC antacid monograph such that the finished product contains at least 1.9 mEq of acid neutralizing capacity per 325 mg of aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of the OTC antacid monograph and provided the product is identified as buffered aspirin with labeling only as an analgesic and/or antipyretic.

12. *Aspirin (highly buffered) for solution.* A solid dosage form to be dissolved in water prior to oral administration as a solution. The product shall contain 325 mg (5 gr) aspirin and sufficient buffering capacity with antacid active ingredient(s) identified in § 331.11 of the OTC antacid monograph such that the finished product contains at least 20 mEq of acid neutralizing capacity per 325 mg of aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of the OTC antacid monograph and provided the product is identified as highly buffered aspirin with labeling only as an analgesic and/or antipyretic.

13. *Aspirin (pediatric dosage unit).* A single dosage unit containing 80 mg (1.23 gr) aspirin for children under 12 years.

14. *Aspirin (standard dosage unit).* A single dosage unit containing 325 mg (5 gr) aspirin.

15. *Bioavailability.* The rate and extent of absorption as determined by the measurement of the blood levels of the parent drug and/or its active metabolites relative to a standard product. The standard product chosen must be one which has been demonstrated to be safe and effective.

16. *Corrective.* An agent in the drug delivery system intended to reduce some undesirable effect of the therapeutically active agent.

17. *Sodium salicylate analgesic equivalence value.* The analgesic effectiveness for a product containing sodium salicylate or other salicylates, e.g., choline salicylate, magnesium salicylate, or salsalate when compared to the standard sodium salicylate 325 mg dosage unit.

18. *Sodium salicylate (standard dosage unit).* A single dosage unit containing 325 mg sodium salicylate.

J. EFFECTS OF PRODUCT FORMULATIONS ON DRUG ABSORPTION AND PHARMACOLOGIC EFFECTIVENESS.

1. *General Comment.* Analgesic, antipyretic and antirheumatic drugs are the most frequently used of all OTC medications. Of these medications, aspirin is most commonly taken. These products may be purchased in a wide variety of dosage forms which may affect their absorption and ultimately their pharmacologic effectiveness. The Panel recognizes that these drugs are intensively promoted through labeling and advertising with a myriad of claims including "fast pain relief", "special pain relieving formula", "so strong and so gentle", "acts 5 times faster than aspirin", "reaches peak action 12 times faster than aspirin", "long-lasting pain reliever", "enhanced relief of pain", "night-time pain reliever", "faster to the bloodstream", etc. The claims are numerous and in the opinion of the Panel, many are confusing or misleading to the consumer. The Panel has discussed certain labeling claims classified as Category III elsewhere in this document. (See Part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

The Panel was charged to evaluate the safety and effectiveness of these OTC drugs and to review their labeling. It was necessary for this Panel to consider finished dosage forms because of their significant effect on the rate and extent of absorption and therefore potential effect on the therapeutic activity of the active ingredients. For example, buffered aspirin formulations must be considered because some buffered preparations may have significant effects on the rate of dissolution and subsequent absorption of aspirin (Ref. 1). The pharmaceutical characteristics of the finished dosage form are claimed to affect the performance of the active ingredients. By definition, therefore, these agents might be considered as indirect acting adjuvant agents as discussed elsewhere in this document. (See part VI. below—Adjuvants and Corrective Agents.)

For many years drug manufacturers were primarily concerned with the appearance of their product for consumer acceptability. Later, product stability became increasingly important. In the past decade it has become evident that the materials and methods used in the finished dosage forms (tablets, capsules, etc.) can greatly affect the onset, duration and intensity of the pharmacologic effects of some drugs. The relationships between dosage formulations and the effect of changes in the rate and extent of absorption and resultant plasma concentrations are the basis of the new area of study termed biopharmaceutics. Bioequivalence is a closely related term which is used to describe the situation when the rate and extent to which the active ingredient is absorbed into the bloodstream from the finished dosage form being tested relative to some standard product which has been shown to be clinically effective. It is assumed that the test drug is available to the site(s) of the drug's action to the same extent as the standard drug product when the plasma concentration time curves are identical with respect to the same active substances. It is important to note that the use of bioequivalence as established by essentially identical plasma concentration time curves is valid only when two different drug delivery systems deliver only the same active principle(s) to the general bloodstream. Furthermore, unless additional correlations between biological response and plasma levels have been established, it is not possible to use differences in the plasma time curves of the active substances to infer that differences in biological response will necessarily occur. For example, one could compare the blood levels of aspirin and the active metabolite salicylic acid obtained from a capsule formulation which used a calcium salt of aspirin and a standard aspirin tablet previously shown to produce clinical effects. If the blood level time curves were superimposable, it would be reasonable, based on all known studies, to assume that the formulations would have equal onset, duration and intensity of pharmacological effects. However, if one product were substantially more rapidly absorbed than the other, one cannot conclude that there is necessarily a corresponding difference in onset of effect. The mathematical relationship between changes in blood levels and corresponding changes in onset, or intensity of analgesia response is not presently known for aspirin.

The Panel finds that there are several processes and factors that govern the ultimate effectiveness of an active ingredient from the time of its administration until its pharmacologic effects, e.g., relief of minor aches and pains, become evident. These factors include the disintegration or breakup of the dosage form (solids) into granules or aggregates in the aqueous fluid, of the stomach or intestine. Another critical factor is the rate and extent of dissolution which involves the further transfer of drug in the fine solid particles into a dispersion of molecules or ions in an aqueous solution. The disintegration and dissolution

of the dosage form are actually two different processes. Until recently, however, rapid disintegration was thought to be the most critical factor involved with rapid availability of the drug for absorption into the circulation. Official standards only required disintegration data from most tablets.

It is now understood that it is the dissolution rate of the drug that most often determines the overall rate of absorption into the systemic circulation, and consequently its distribution to the desired site of action and its pharmacologic effect at that site.

As will be described later in this discussion, various studies have clearly demonstrated that each finished dosage form, e.g., tablet, solution, etc., directly affects the dissolution rate and consequently the bioavailability of the active ingredient. There are also data that demonstrate differences even in the dissolution rates for the same dosage form, for example, between two unbuffered aspirin tablets, or between an unbuffered and buffered aspirin tablet.

Whereas the Panel can find correlations between changes in product formulations and the drug levels achieved in the blood, the relationship of these blood levels to the degree and onset of pharmacologic effect is not yet understood (Ref. 2). It is obvious that a given level of drug in the blood is required to produce analgesia. However, for most OTC analgesics, because of the insensitivity of the current methodology, the possible increase in analgesia cannot be quantitated.

2. *Marketed product formulations.* The active ingredients in OTC drug products are available in the marketplace in several finished dosage forms (formulations), e.g., tablets, capsules, solutions, suppositories, etc. As part of its evaluation of the safety and effectiveness of OTC internal analgesic, antipyretic and antirheumatic active ingredients, the Panel reviewed submissions for drug products manufactured in 14 different dosage forms. The Panel finds that an assessment of the safety and effectiveness of each active ingredient must take into consideration the influence of product formulation on the absorption and pharmacologic effectiveness of the active ingredient. Differences in formulation such as the difference between a tablet and a solution can affect the absorption characteristics of a drug product and consequently its therapeutic performance. However, the Panel emphasizes that despite any apparent correlation between formulation and bioavailability, there is no evidence that blood drug levels (a measure of bioavailability) correlate directly with pharmacologic effectiveness.

The submissions to the Panel for 14 different dosage forms (formulations) of OTC internal analgesics, antipyretic and antirheumatic active ingredients are listed in the following chart:

DOSAGE FORMS IN SUBMISSIONS OF MARKETED DRUG PRODUCTS

	Number of product submissions
Solid dosage forms:	
Tablets:	
Unbuffered	62
Buffered	13
Chewable	3
Enteric-coated	1
Timed-release	3
Capsules	1
Powders	4
Gums	1
Liquid dosage forms:	
Drops	4
Elixirs	7
Highly buffered (effervescent) aspirin for solution	2
Suspensions	3
Syrups	3
Suppository dosage forms:	
Suppository	1

a. *Solid dosage forms.* It is evident from the above chart that the greatest number of OTC internal analgesic, antipyretic and antirheumatic drug products are marketed in a solid dosage form. Of these, the tablet in several variations, i.e., unbuffered, buffered, enteric-coated, timed-release and chewable, is the most predominant solid dosage form used to market these products. Even though all of these formulations are in tablet form, formulation variations between them can affect the bioavailability, i.e., bioavailability as manifested in blood levels of the active ingredient(s) contained in them. The Panel, recognizing the variety of claims made for these different formulations, has attempted to evaluate the safety and effectiveness of active ingredients. Some evidence relating to possible differences between dosage forms was developed by the drug manufacturers to meet other needs of the consumer, such as decreasing the incidence or severity of a drug's side effects, e.g., the buffering of aspirin to modify its irritating effects on the lining of the stomach, or to provide dosage forms that can be more conveniently taken, e.g., timed-release forms, etc. The Panel has considered the advantages and disadvantages of these formulations which are briefly described below.

Unbuffered (plain) aspirin tablets are the most common dosage form available in the marketplace. One might assume that all the products containing unbuffered aspirin are comparable with respect to their bioavailability, i.e., the amount of aspirin absorbed into the blood in a given time. This unfortunately has not been demonstrated to be the case in those studies in which the dissolution rates of commercial unbuffered aspirin products have been compared, as discussed below. The rate of bioavailability of most of the analgesics, such as aspirin, is related to its dissolution rate.

Several studies have shown that all aspirin products do not have the same ability to be absorbed and therefore to produce comparable blood levels in a specified time. The Panel concludes that significant variation in dissolution rate and absorption rate between aspirin products demonstrates the need for a standard dissolution test which can be used to detect preparations which will be so slowly absorbed as to potentially increase local adverse effects on the gastric mucosa or decrease therapeutic effects due to decreased bioavailability. The Panel has proposed a standard tablet dissolution test elsewhere in this document. (See part VI. paragraph C.1.b. below—Aspirin (plain and buffered) tablet dissolution testing procedure.)

The other major tablet solid dosage form is buffered aspirin products. Buffering agents have been used for aspirin tablets to increase the dissolution rate in an attempt to hasten the onset of activity and reduce gastric irritation. The testing of buffered aspirin is discused later in this document. (See part VI. paragraph C.1.a below—Buffered aspirin acid neutralizing testing procedure.) The labeling of buffered aspirin is also discussed later in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

Two forms of buffered aspirin are commonly used which the Panel has distinguished as "buffered" and "highly buffered for solution".

The Panel has defined a buffered aspirin product as a solid dosage form containing 325 mg (5 gr) aspirin and sufficient buffering capacity with antacid active ingredient(s) identified in the OTC antacid monograph (21 CFR 331.31) such that the total acid neutralizing capacity of each minimum labeled dosage unit contains at least 1.9 mEq of acid neutralizing capacity following the testing procedures discussed later in this document. (See part VI. paragraph C.1.a. below—Buffered aspirin acid neutralizing testing procedure.)

The quantity of alkaline buffers is sufficient to increase the dissolution rate of the product without necessarily increasing the pH of the gastric fluid. The principal reason for increasing the dissolution rate of aspirin is to facilitate its removal from the stomach as rapidly as possible to reduce the irritating effects of the drug on the gastric mucosa.

Buffered aspirin preparations are claimed to reduce the possibility of gastric distress due to the aspirin. Even though the amount of buffer is not sufficient to markedly affect the pH of gastric fluids, the buffering agent will increase the pH immediately around the dissolving particles, resulting in more rapid dissolution and removal from the stomach and hence decrease the likelihood of local gastic irritation.

The Panel concurs with the general consensus of a large number of studies which demonstrate that buffered aspirin is more rapidly absorbed from the gastrointestinal tract. The evidence also

seems to indicate that some individuals in the small subset of persons who regularly experience subjective symptoms of gastric distress may experience less gastric intolerance with some buffered aspirin compared to unbuffered (plain) aspirin. Suitable Category III labeling claims are discussed elsewhere in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

The dissolution is usually the rate limiting process for gastrointestinal absorption of salicylates given in solid form. The greater dissolution rate of aspirin in the presence of buffers is reported to be one of the factors responsible for the more rapid absorption of buffered aspirin (Ref. 3).

The Panel has defined a highly buffered aspirin for solution product as a solid dosage form which must be dissolved in water prior to oral administration as a solution. The product shall contain 325 mg (5 gr) aspirin and sufficient buffering capacity with antacid active ingredient(s) identified in the OTC antacid monograph (21 CFR 331.11) such that the total acid neutralizing capacity of each minimum labeled dosage unit contains at least 20 mEq of acid neutralizing capacity by the testing procedures described later in this document. (See part VI. paragraph C.1.a. below—Buffered aspirin acid neutralizing testing procedure.)

The quantity of alkaline buffers in these highly buffered preparations is greater than that in buffered tablet preparations. In this case, the pH of the gastric fluid is increased. Some highly buffered aspirins have been shown to significantly decrease gastric occult bleeding that results from direct effects of aspirin on the gastric mucosa and are discussed later in this document. (See part III. paragraph B.1.a.(2) below—Safety.) The Panel finds that this is a desirable method of taking aspirin because of the rapid absorption. As with buffered aspirin, it may also be the case that some individuals in the small subset of persons who regularly experience subjective symptoms of gastric distress, may experience less gastric intolerance with some highly buffered aspirin for solution products compared to unbuffered (plain) aspirin. However, the Panel has also concluded that this or any other dosage form does not necessarily reduce the potential for massive gastrointestinal hemorrhage. Suitable Category III labeling claims are discussed elsewhere in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

Although numerous buffering agents are available for tablet formulations, few studies have been done to compare the effects of different buffering agents on the dissolution rate of aspirin from solid dosage forms. In one study (Ref. 4) the investigators found a definite difference in the rate of dissolution of aspirin from tablets depending on the agent used to buffer the aspirin. Eleven different buffering agents were studied. The time required for 50 percent of a given aspirin sample tablet to dissolve ranged from 1 to 20 minutes depending on the buffering agent used. In general, it was determined that carbon dioxide producing buffering agents (sodium bicarbonate, magnesium carbonate and calcium carbonate) gave more rapid dissolution than the readily water-soluble buffering agents (sodium ascorbate and sodium citrate), and both of these classes of buffering agents gave much faster dissolution than water-insoluble buffering agents such as aluminum compounds and magnesium compounds other than magnesium carbonate.

From the available data, the Panel finds that simply adding buffering agents to aspirin does not guarantee an increased dissolution rate over unbuffered aspirin. Important factors appear to be the type of buffering agent used and other undefined factors, e.g., tablet compression during manufacturing, etc. This may be an explanation for the discrepancy between studies comparing unbuffered aspirin with buffered aspirin. The buffering agent used with the aspirin may to some extent determine the outcome of the study. For this reason, actual testing of the dissolution rate of buffered aspirin products is necessary to determine if the buffering agent actually does affect the dissolution rate of the aspirin products and to what extent.

Also, the Panel notes that an adequately buffered aspirin product may not have an advantage over a well-formulated unbuffered product. In some studies, unbuffered aspirin performs as well as buffered aspirin products.

The totality of formulation variables of unbuffered and buffered aspirin products therefore plays a very important role in determining their dissolution times. Levy has compared the dissolution of commercial unbuffered aspirin products with the dissolution of an aspirin product buffered with aluminum glycinate and magnesium carbonate (Ref. 5). In this study, three unbuffered products were tested. He found that 68 percent of the 300 mg buffered aspirin tablet dissolved in 10 minutes, whereas the amounts of the three 300 mg unbuffered aspirin tablets that dissolved in 10 minutes were lower and varied among the three products. The three values were 42, 52 and 55 percent. There was a 13 percent difference between the fastest dissolving unbuffered product and the buffered product, the same difference as between the fastest and slowest dissolving unbuffered products. He concluded that the variation in dissolution times among the unbuffered products could be due to differences in the formulation between the three products. It is evident that the variation in dissolution rates among unbuffered aspirin products can be as great as the difference between unbuffered and buffered aspirin products. It is interesting to note that in this study another unbuffered salt of aspirin, namely calcium acetylsalicylate, had a dissolution rate of 81 percent in 10 minutes, which was greater than the dissolution rate of the buffered aspirin product.

In another study, Levy and Hayes compared six commercial unbuffered aspirin products with an aspirin product buffered with aluminum glycinate and magnesium carbamide (Ref. 6). The dissolution half-times (the time required for half (150 mg) of a 300 mg tablet to go into solution) were determined. The dissolution half-time of the buffered aspirin product was less than 5 minutes as compared to dissolution half-times of the six unbuffered aspirin products, which were all greater and ranged from 8½ to 13¾ minutes. In determining the dissolution rate, samples were not measured at less than 5 minutes so that an accurate measure of the dissolution half-time of the buffered aspirin was not ascertained. A product consisting of a calcium acetylsalicylate carbamide complex was also tested in this study and its dissolution half-time, like that of the buffered aspirin, was less than 5 minutes. Actually this product dissolved somewhat faster than the buffered aspirin. Whereas 68 to 72 percent of the buffered aspirin dissolved in 10 minutes, 81 percent of the calcium acetylsalicylate carbamide complex dissolved in that time. This study showed again that marketed unbuffered aspirin products have a wide range of dissolution rates. The six products showed dissolution half-times of 8½, 8¾, 10¾, 11, 11¾ and 13¾ minutes. There was approximately a 62 percent difference between the fastest and the slowest values.

It is apparent that different nationally distributed brands of unbuffered aspirin exhibit significant differences in dissolution rate. These product-to-product differences probably account for some of the conflicting clinical reports concerning the relative advantages of unbuffered and buffered tablets. Some investigators have reported that the buffered form is more rapidly absorbed and causes less gastric irritation than the unbuffered drug. Other workers could find no difference between unbuffered aspirin and buffered aspirin. It is now clear that because of the differences in dissolution rates of different brands of both unbuffered and buffered aspirin products, different results would be expected depending on the products compared. Since the dissolution rates of buffered products might vary because of the type of buffering agent used and the dissolution rates of unbuffered aspirin products might vary because of formulation differences, the Panel concludes that unbuffered (plain) aspirin products should be tested for dissolution rate as well as buffered aspirin products. The Panel has proposed suitable testing procedures elsewhere in this document. (See part VI. paragraph C.1. below—Aspirin standard testing procedures.)

Chewable tablets offer a convenient method of administering the drug to individuals who have difficulty in swallowing whole tablets. This dosage form is especially popular for use in children. There are many marketed children's chewable aspirin tablets, which are usually flavored, containing 80 mg (1.23 gr) of aspirin per dosage unit. These

tablets may be chewed, crushed on a spoon, dissolved on the tongue or even swallowed as a conventional tablet. The Panel finds these chewable, flavored tablets acceptable and recommends that all such tablets containing salicylates for children under 12 years be labeled, "Drink water with each dose". In addition, as noted elsewhere in this document, because aspirin can increase bleeding, the Panel recommends that chewable aspirin-containing tablets be labeled with the warning, "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician". (See part III, paragraph B.1.a.(2)(ii)(*b*)(*1*) below—Mucosal erosion of the mouth.)

The Panel is aware that in the case of aspirin most of these products are packaged with safety caps to prevent accidental opening by small children. However, regardless of the method of packaging, the Panel recommends that the container be labeled with the warning, "Keep this product and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately".

Enteric-coated tablets were developed in an attempt to eliminate the local irritation in the stomach caused by some analgesics. Accordingly such tablets were designed to dissolve in the small intestine rather than in the acid gastric fluids. Therefore, when taking an enteric-coated tablet, the individual must take into consideration the delayed action to be anticipated in the initial use of this dosage form. The use of these preparations for the treatment of acute symptoms such as the occasional headache, is not as desirable as a plain (uncoated) analgesic tablet which is expected to give relief in a shorter period of time. However, for the treatment of chronic conditions such as arthritis, these products may be more useful once an adequate blood level is established and maintained.

In a study of single doses of aspirin or sodium salicylate, uncoated tablets and two different enteric-coated preparations of the two drugs were compared (Ref. 7). The results of the study showed that enteric-coated aspirin delayed absorption and adequate salicylate serum levels were usually not evident for 6 hours or more. The absorption of uncoated aspirin was more rapid and salicylate serum levels appeared within 1 hour and were maintained for the next 3 hours. The absorption characteristics of enteric-coated sodium salicylate resembled uncoated aspirin but was delayed by about 4 hours.

Studies have shown that some enteric-coated formulations pass through the entire intestinal tract without dissolving or have erratic dissolution rates resulting in unpredictable blood levels (unpredictable absorption rates) and consequently unreliable therapeutic effectiveness (Ref. 2). Other studies with enteric-coated aspirin tablets of different formulations have shown effective blood salicylate levels (Ref. 8).

It has been found that a significant proportion of commercially available enteric-coated tablets are either not resistant to gastric fluid or not fully absorbed after reaching the small intestine (Ref. 9). Part of the problem may be due to the tendency of some types of coated tablets to undergo changes on aging which can markedly alter their release characteristics (Ref. 10). In addition, the absorption of aspirin from physiologically available enteric-coated tablets is highly variable depending upon individual factors such as gastric emptying time.

The Panel has therefore classified enteric-coated tablets as Category III until adequate testing can demonstrate the bioavailability (blood levels).

Timed-release dosage forms encompass the principle of a controlled release of drugs from oral dosage units. They provide the advantages of increasing the intervals between dosing and at the same time increasing the duration of action. However, effective preparations of timed-release drugs have been difficult to achieve in the past, because of technical problems associated with their manufacture. Theoretically, timed-release products are formulated so as to dissolve in gastrointestinal fluids in a controlled manner so that the total dose will be absorbed in increments over a longer period of time, e.g., over 3 to 6 hours rather than 1 hour, and the duration of drug action will be extended over a longer period, e.g., 8 to 12 hours rather than 3 to 6 hours.

These formulations usually contain more than one single dosage of the drug intended to be released in a continuous and controlled manner so that the duration of the claimed effect is increased. However, it can be debated whether a 1,300 mg aspirin sustained-release tablet is as effective as two 650 mg doses of aspirin given 4 hours apart (Ref. 2).

Sevelius and Colmore (Ref. 11) showed in a clinical study that a sustained-release aspirin preparation had analgesic properties comparable to unbuffered aspirin and buffered aspirin, but was not superior to these forms of aspirin with respect to the duration of analgesic effect in postpartum patients. Stubbe et al. (Ref. 12) suggest that a cellulose acetate phthalate coating on tablets slows salicylate release and increases the duration of action. There was little gastrointestinal blood loss with this coating and the salicylate blood levels were higher the following morning than with uncoated aspirin.

Several timed-release aspirin preparations are currently marketed. The labeling on these products suggests that they provide long lasting relief, are useful at bedtime for relief of pain during the night, etc. The Panel has classified these timed-release products with such labeling in Category III until it is demonstrated that blood levels (rate and extent of absorption) or pharmacologic effectiveness are comparable to, and the incidence of side effects are not greater than, those seen with preparations given in conventional dosage.

Micronized aspirin refers to aspirin formulated in smaller than the usual size of particles. Such forms are as safe and effective as ordinary aspirin but if special claims relate to such characteristics as rapidity of onset or higher blood levels they are classified as Category III since no convincing data are available that micronizing confers any favorable properties to aspirin beyond those found with regular aspirin.

Capsules are solid dosage forms in which the active ingredient(s) is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. Its principal advantage in OTC products is that some individuals find it easier to swallow capsules than tablets. Otherwise, considerations of absorption and pharmacologic effectiveness are similar to those for tablets.

Powders are a dosage form which are not as commonly used. They are rapidly absorbed however, often reaching peak blood levels more rapidly than the tablet dosage form. The rapid absorption from finely divided powders is directly related to the large surface area of these products. Powders have the advantage of ease of administration to young children who cannot swallow capsules or tablets. They may present problems if the dosage unit is not individually packaged. The chief disadvantage for bulk products is in measuring an accurate dose of a powder. Consequently, the use of bulk powders as a dosage form should be discouraged unless there is assurance that an adequate measuring device is attached and likely to be used routinely. The Panel recommends that powders containing salicylates be mixed with a full glass of water and stirred prior to use.

Historically, aspirin has been used as a gargle for the treatment of minor sore throat pain. Chewing gum formulations containing aspirin in a gum base were developed to provide for greater retention and absorption of the drug and to produce a topical, local effect on the surrounding tissues. These formulations may also make the medication more pleasant to take. Chewing gums with aspirin are primarily used and labeled for "relief of minor sore throat pain". However, other traditional labeling is also included such as "for headache, muscular aches and pain". The latter claims can only be attributed to the absorption of the drug into the systemic circulation.

The Panel concludes that aspirin or any analgesic in a gum base, with the specific claims for the relief of sore throat, has not been adequately tested for effectiveness. This use of aspirin may not be desirable or safe particularly if the tissue is highly inflamed or abraded because aspirin is irritating to the mucosal tissue as discussed above. The Panel recommends that claims of aspirin-containing gum for the relief of sore throat or the use of aspirin as a gargle for a local effect properly belongs in a review of ingredients claimed for treatment of sore throat in general and should therefore be deferred to the Advisory Review Panel on OTC oral cavity drug products for evaluation.

The Panel finds marketing of an OTC analgesic, in a chewing gum formulation acceptable if the product contains the dosage and Category I labeling claims recommended by the Panel. (See part III. paragraph B.1. below—Category I Labeling.) However, such product formulations containing aspirin should include the warning, "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician". As with chewable tablets discussed above, oral mucosal damage may occur from the use of chewing gum aspirin products and the effect of aspirin on blood clotting may be a factor in such situations.

b. *Liquid dosage forms.* Although liquid dosage forms are used for OTC internal analgesic, antipyretic and antirheumatic drug products, they are not as commonly available as the solid dosage forms. For chemical reasons, aspirin is not readily available in liquid form. It is reasonably stable in dry air, but in the presence of moisture is slowly hydrolyzed to acetic acid and salicylic acid. Currently only acetaminophen, choline salicylate and salicylamide are available in liquid preparations. Theoretically, liquid dosage forms, i.e., drops, elixirs, suspensions and syrups, should have one chief advantage over solid dosage forms in that they are more rapidly absorbed and consequently should have a more rapid onset of action. However, unless a significant difference in the onset of clinical analgesia can be shown, this theoretical speculation is moot.

These preparations, which are usually flavored for consumer acceptability, are promoted for use as drops for children to relieve the pain and discomfort of teething, tonsillectomy, etc. Drops may be administered orally directly from a calibrated dropper or mixed with food or liquid prior to use. The elderly and individuals who have difficulty swallowing solid dosage forms may find the liquid dosage forms easier to take.

As pointed out above, with more rapid absorption of liquid dosage forms, one would expect peak blood levels and therapeutic effectiveness to be attained sooner than with solid dosage forms. No significant advantage in this respect, however, has been demonstrated.

c. *Rectal suppository dosage forms.* Practical reasons underlie the necessity for the use of the suppository dosage form. Its use is indicated, for example, in individuals who are vomiting, are unconscious, are suffering from extreme gastric irritation, or are otherwise debilitated and not able to take an oral dosage form. In such individuals, rectal administration may be practical. Suppositories are dosage forms that melt and undergo dissolution, after rectal insertion, releasing the active ingredient(s) which are then absorbed and produce their pharmacologic effect. There are limiting factors which can influence each step of melting, dissolution, or absorption. The composition of the suppository base can be a very important limiting factor. If it fails to melt at body temperature or melts too slowly, the individual may pass the intact suppository without receiving any pharmacologic effect. On the other hand, if the base melts too rapidly and the active ingredient(s) is very irritating to mucous membranes, adverse effects may result (Ref. 13). This is a problem, especially for drugs such as aspirin which may cause local irritation.

Variability in the melting time of suppository bases may result in variations in the blood levels of the active ingredient (bioavailability) so that the pharmacologic and therapeutic effectiveness of the drug is not achieved. An example of variations in the bioavailability of suppositories is demonstrated in a study in which the salicylate absorption from five brands of commercially available aspirin rectal suppositories was studied in four adult male subjects (Ref. 13). All subjects received each of the five brands at intervals of at least 1 week. The urinary excretion rates of total salicylate served as an index of the extent of absorption from the five brands of suppositories. The rate of absorption from the suppositories was slow compared to absorption of the drug given orally in tablet form. Within a 2-hour retention period, only about 40 percent of the dose was absorbed from one of the five brands, and an average of only about 20 percent of the dose was available from the other four brands. It was found that longer retention times tended to diminish the differences in absorption between brands. Only after a 10-hour retention period was absorption of the drug nearly complete in most cases. Generally, the slow absorption from the suppositories, and the inability to control the retention time due to defecation needs, make the use of suppositories a questionable dosage form for aspirin or salicylate therapy.

Because suppositories may have different melting or dissolution rates and therefore provide unpredictable bioavailability of the drug contained in them, the blood levels achieved may be too low to be therapeutically effective or very high and produce toxic effects. Therefore, the Panel has classified suppositories in Category III. The Panel recommends that suppository formulations demonstrate blood levels (rate and extent of absorption) or pharmacologic effectiveness comparable to and the incidence of side effects (including irritation) not greater than, those seen with preparations given in conventional dosage. Furthermore, suppositories can produce irritation to the rectal mucosal cells. The extent of the irritation depends on the active ingredient and the chemical composition of the base. For these reasons, each suppository formulation must be subjected to study in human subjects. (See part III. paragraph B.1.a(2)(ii)(*b*)(2) below—Rectal irritation.)

3. *Factors affecting drug absorption.* A decrease in the rate and extent of gastrointestinal absorption (bioavailability) of a drug may produce a decreased pharmacologic effect of the drug. Not only can the formulation influence drug absorption but physiological variables of gastrointestinal function can profoundly determine the bioavailability of the drug. Factors affecting gastrointestinal function such as gastric emptying, intestinal transit time, and intestinal and hepatic metabolism may greatly affect the availability of the drug for absorption into the systemic circulation. Poorly absorbed drugs have a longer residence time in the gastroinstestinal tract. In some cases this may lead to adverse local effects on the gastrointestinal mucosa.

The blood levels of a drug depend on the rate and amount of drug absorbed. Blood levels will rise and fall in proportion to the dose of the drug available and be subject to the vicissitudes of formulation and to physiological variables such as gastrointestinal function. For example, if only one-half the drug is absorbed, the effect is equivalent to lowering the dose. If absorption is sufficiently slow, minimum pharmacologic effectiveness may never be attained. On the other hand, if the rate of absorption is too rapid, toxic levels can be achieved. This assumes that there is a direct correlation between blood levels and the pharmacologic effect of a drug. In the case of analgesic agents, the relationship between blood levels and pharmacologic effectiveness has not been well established. A comparison of blood levels may offer a basis of comparison between different formulations of the same agent but are at present almost meaningless in comparing chemically different classes of analgesic agents.

4. *Determination of pharmacologic effectiveness. Evaluation of pharmacologic groups.* a. *Analgesic effectiveness.* The most important measurement in evaluating the effectiveness of an OTC analgesic is its ability to relieve minor aches and pains, and headache in a suitable target population. However, pain, which is discussed later in this document, is a subjective symptom and presently our knowledge is limited as to its etiology and as to the detection of its presence, absence, or modification. (See part II. paragraph A.1. above—Pain.) The study of analgesics, or analgesiometry, must be based primarily on observations in man. The medical literature stresses the need for laboratory animal procedures, as yet not fully reliable, which will yield results that can be correlated with those in man. Hence, the Panel finds that the literature on analgesics is conflicting as to the effectiveness of specific drugs because of the subjective, imprecise methods of testing and the difference of opinion regarding suitable methods of testing.

The Panel notes that the most successful efforts to quantitate pain in the clinical situation have been those that have accepted the patient's own reports as appropriate indices of the pain experience and of relief resulting from analgesic administration. The Panel's recommendations pertaining to the evaluation of the effectiveness of a claimed OTC analgesic drug is discussed later in this document. (See part III. paragraph C. below—Data Required for Evaluation.)

b. *Antipyretic effectiveness.* The obvious measurement in evaluating the effectiveness of an OTC antipyretic is its ability to reduce fever. This is a clinical sign that can readily be determined by objective measurement. The Panel has recommended that clinical studies be conducted in several populations of patients, such as, patients with fever secondary to cancer and associated infections, and fever in children and adults with acute infectious diseases. The Panel's recommendations pertaining to evaluation of the effectiveness of a claimed OTC antipyretic drug is discussed later in this document. (See part IV. paragraph C. below—Data Required for Evaluation.)

c. *Antirheumatic effectiveness.* The critical measurements in evaluating the effectiveness of an OTC antirheumatic agent is its ability to restore joint function and prevent progression of the disease. These drugs reduce joint or muscle tenderness or swelling. Rheumatoid arthritis is still not curable and therefore treatment must include the use of anti-inflammatory agents. One problem in assessing a claimed antirheumatic drug is the fact that the disease itself may change spontaneously. Adequate study design is critical in the assessment of antirheumatic effectiveness.

Aspirin is one of the most commonly prescribed drugs for the treatment of rheumatic diseases and is used not only as an analgesic but as an anti-inflammatory agent. To achieve the desired effect, large doses administered over a prolonged period of time are usually necessary. The Panel's recommendations pertaining to the evaluation of the effectiveness of a claimed OTC antirheumatic drug are discussed later in this document. (See part V. paragraph C. below—Data Required for Evaluation.)

d. *Drug blood level determinations.* Many of the studies the Panel has reviewed either in the literature or in data submissions to the Panel, have utilized drug blood levels as a measure of analgesic effectiveness. Aspirin is commonly used as a standard analgesic drug for comparison with other drugs in which assays of blood salicylate levels are made rather than direct measurements of the analgesic effectiveness of these agents. The Panel has evaluated this technique and concludes that there is inadequate evidence that the amount of drug in the blood correlates directly with clinical analgesia. The Panel emphasizes that this is not to say that a relationship between blood levels and clinical response does not exist, but rather, that the relationship is complex and not presently understood. However, the Panel does recognize that an important value of drug blood level comparisons is that they do give an indication of comparative dissolution rates. If an analgesic product produces a blood level higher than another product within a given period of time, e.g., 10 to 20 minutes after administration, the higher absorption rate of the product might be attributed to a faster dissolution rate. The Panel concludes that there should be no reference to blood levels in the labeling which implies a corresponding clinical effect without substantiation of a correlation between blood level and clinical analgesia.

e. *Onset, duration and intensity of pharmacologic effects.* The Panel recognizes that drug labeling related to the onset, intensity and duration of pharmacologic effects can influence the consumer's selection of a product but can find no convincing evidence to support labeling claims which suggest a faster onset of effectiveness, e.g., "fast pain relief". Other than possibly for timed-release preparations no evidence was found to support claims such as "nighttime pain reliever". There is also no direct evidence available to the Panel which suggests a greater intensity of analgesia for comparable products with claims such as "enhanced relief of pain".

In the discussion above, the importance of product formulation on drug absorption has been stressed. The dissolution rate of the drug determines the rate of absorption. As mentioned earlier, studies have demonstrated that the addition of small amounts of some buffering agents to aspirin enhances the rate of absorption of the drug, thus causing less gastric irritation. Consequently, some buffered aspirins are somewhat more rapidly absorbed from the gastrointestinal tract than unbuffered aspirin and might also be expected to show earlier higher salicylate blood levels. On the other hand, there are buffered aspirin preparations that are not absorbed any faster than unbuffered aspirin products, as noted above. However, the Panel is unaware of any data that demonstrate that buffered aspirin provides a more rapid onset, a greater peak intensity or a more prolonged duration of analgesic effectiveness than unbuffered aspirin.

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K. ABSORPTION, DISTRIBUTION, BIOTRANSFORMATION (METABOLISM) AND EXCRETION OF ASPIRIN AND SALICYLATES IN MAN

1. *Absorption.* Aspirin and salicylate absorption occur by passive diffusion primarily of the nondissociated lipid-soluble molecules (salicylic acid and acetylsalicylic acid) across gastrointestinal membranes and is influenced by gastric pH. If the pH is increased, salicylate is more ionized and this tends to decrease rate of absorption; however, a rise in pH also increases solubility of salicylate, which has the opposite effect on absorption. Actually, there is little meaningful difference between the rates of absorption of sodium salicylate, aspirin and the numerous buffered preparations of salicylates. For example, in man, the absorption half-time for unbuffered aspirin is about 30 minutes, for buffered aspirin about 20 minutes, and for an aspirin solution only slightly less. The presence of food delays absorption of salicylates. Orally ingested salicylates are absorbed rapidly, partly from the stomach but mostly from the upper small intestine. Appreciable plasam concentrations are found in less than 30 minutes; after a single dose, a peak value is reached in about 2 hours and then gradually declines. Rate of absorption is determined by many factors, particularly the disintegration and dissolution rates if tablets are given, the pH at the mucosal surfaces, and gastric emptying time.

2. *Biotransformation.* Aspirin, which is absorbed as such, is first rapidly hydrolyzed to salicylic acid by esterases present in the gastrointestinal tract, red blood cells, and serum, but primarily in the liver. This is a rapid reaction which has a half-life of 15 to 20 minutes (Refs. 1 and 2). As a result of this rapid hydrolysis, plasma concentration of aspirin is low (less than 20 micrograms/ml) at the usual therapeutic doses (Ref. 2). Salicylic acid, then undergoes biotransformation which occurs in many tissues but particularly in the liver by the enzymes

from the microsomal drug metabolizing system.

The three chief metabolic products are salicyluric acid (the glycine conjugate), the ether or phenolic glucuronide, and the ester or acylglucuronide. In addition, a small fraction is oxidized to gentisic acid (2,5-dihydroxybenzoic acid) and to 2,3-dihydroxybenzoic and 2,3,5-trihydroxybenzoic acids. These metabolites are found in the urine; the conjugates and gentisic acid have also been identified in plasma, liver, and some other tissues. The concentration of the metabolites in plasma is generally only about 1 percent of the total plasma salicylate.

The biotransformation routes of aspirin in man have been reviewed by Levy and Leonards (Ref. 3). Aspirin is hydrolyzed rapidly in the body to salicylic acid which is conjugated in part with glycine to form salicyluric acid and with glucuronic acid to form acyl and phenolic glucuronides. A small fraction of salicylic acid is further hydroxylated to gentisic acid. There may be several other minor metabolites. Free salicylic acid and its metabolites are eliminated from the body by renal excretion.

The conjugates (salicyluric acid, phenolic and ester glucuronide) and the other minor metabolites are excreted almost exclusively in the urine (Refs. 1 and 2). Levine (Ref. 1) in her short review of salicylate metabolism states:

> All the processes of biotransformation and excretion are first order with the exception of the conjugation of salicylic acid with glycine to form salicyluric acid and with glucuronic acid to form the ether glucuronide * * * Salicyluric acid formation has been found to change from first-order to near zero-order kinetics when the amount of salicylic acid in the body exceeds the quantity derived from the biotransformation of about 1 g of aspirin; the glucuronide conjugating system is saturated at somewhat higher levels of salicylic acid. When conventional dosage forms are administered and the aspirin is absorbed normally, it would take only two tablets to reach the level at which salicyluric acid formation ceases to be a first-order phenomenon.
>
> When the salicylic acid derived from aspirin in the body is below saturation levels, the overall rate of elimination of salicylate follows first-order kinetics because all the elimination processes are first order, for the elimination of the 0.25 mg [sic] dose of aspirin. The half-time of elimination under first-order conditions is about 3.1 hours. At these low doses the major process responsible for salicylate elimination is its conjugation with glycine, since the first-order rate of salicyluric acid formation is much faster than the rates of the glucuronide syntheses. When doses of aspirin of 1 g or more are administered, the glycine conjugation reaction becomes practically zero order and the glucuronide conjugation with the phenolic group of salicylate also approaches the limit of its capacity. As a consequence, the overall rate of elimination of the salicylate derived from large doses of aspirin displays complex kinetics, indicative of a mixture of apparent zero-order and first-order processes * * * The curves for the 1.0 and 1.5 g doses of aspirin do not become linear until the salicylic acid remaining in the body drops to the quantity equivalent to about 300 mg of aspirin. This indicates a lack of conformity with first-order kinetics. Below 300 mg the curves for all three doses are linear and first order. Moreover, the time required to eliminate 50 percent of the salicylate in the body lengthens as the dose of aspirin increases, because less of the more rapidly formed salicyluric acid is contributing to the overall elimination process.

This was reported originally by Levy (Ref. 4) who in 1965 reported:

> Salicylate elimination kinetics was studied over a dose range of from 0.25 to 2.0 gm. of aspirin. It was found that when the amount of salicylate in the body of normal adult test subjects exceeded approximately 360 mg. aspirin equivalent, conjugation of salicylic acid with glycine reached a maximum rate and thus proceeded by zero-order kinetics. The overall elimination of salicylate was found to proceed by first-order kinetics at very small doses and by parallel zero and first-order processes at higher doses. A kinetic model was developed, and values for appropriate rate constants were determined which make it possible to reconcile apparent half-lives for salicylate elimination ranging from about 3 hr. to over 20 hr. which have been reported in the literature. The pharmacokinetics of salicylate elimination were found to be unusual both qualitatively and quantitatively, and the results of the present study have potentially important therapeutic, toxicologic, and pharmacogenetic implications.

The half-life of salicylate in doses between 300 and 650 mg has been reported to be between 3.1 to 3.2 hours (Ref. 1). However, if the dose is increased to 1 g the half-life is increased to 5 hours (Refs. 4 and 5). If the dose is increased to 2 g the half-life is increased to about 9 hours (Ref. 4). Not only is the half-life markedly increased, but the urinary excretion also decreases as the dose is increased from 0.32 g to 0.97 g (Refs. 4 and 6).

If the urinary excretion is decreased, more salicylate will be retained in the body with a great toxic potential since it probably will occupy most of the available albumin binding sites and displace other drugs or endogenous products, e.g., bilirubin.

The percent of the dose recovered in 7.5 hours of urine collection is 71.5 percent after a 0.32 g dose, 55 percent after a 0.64 g dose and 52.1 percent after a 0.97 g dose (Ref. 6). The subject becomes more complicated if one considers the great variability of salicylate metabolism and elimination when large doses (1 g) of aspirin are given. Levy and Hollister (Ref. 5) found an appreciable variation between normal, healthy volunteers. They commented:

> The marked intersubject variation of salicylate-elimination rate is very significant. Expressed in terms of biological half-life ($t_{\frac{1}{2}}$) the time necessary to reduce body drug content by 50%, values ranged from 2.55 to 8.5 hours. It is likely the studies of a larger number of subjects would reveal even greater differences in salicylate elimination rates. The possible implications of these differences between subjects can be illustrated by considering the amount of salicylate in the body immediately after administration of one loading dose (D*) and as few as three maintenance doses (D). Based on the average salicylate half-life found in the group (5.0 hours), one may administer a loading dose (D*) followed by maintenance doses of half that size (D=0.5D*) given at five-hour intervals. Assuming that the drug is administered in rapidly absorbed form, the body salicylate content in a subject who eliminates the drug at the observed average rate (elimination-rate constant 0.138 $hr.^{-1}$) is about D* shortly after administration of the third maintenance dose. In other words, the body drug content is maintained at its initial (and desired) level. On the other hand, the same dosage schedule, if used for the most rapid salicylate eliminator in the group studied, would yield a body salicylate content of only about 0.67D*. Given to a subject who eliminates salicylate at the lowest rate found in this study, the average dosage regimen described above would result in a body salicylate content of about 1.4D* (40% greater than the loading dose) after the third maintenance dose.
>
> These examples illustrate the need to adjust salicylate dosage regimens individually on the basis of a subject's predetermined elimination rate if the incidence of therapeutic failure (due to subtherapeutic drug levels) or toxic effects (due to drug accumulation) is to be minimized.

The authors (Ref. 5) also recommended adjusting individual dosage intervals as follows: "The appearance of side-effects (such as tinnitus), indicative of overdosage due to drug accumulation, may call for a change in dosing intervals rather than in amount of drug per dose, if therapeutically adequate drug concentrations are to be maintained at all times."

Individual differences in apparent half-life probably reflect differences in salicyluric acid formation capacity (glycine conjugation) and is probably genetically determined. Levy has pointed out (Ref. 4) that: "Any search for genetic differences in salicylate elimination by salicyluric acid formation must be directed not only toward the determination of individual first-order rate constants for this process (which requires that the administered doses be small), but must also include the determination of individual maximum salicylurate formation rate capacities. Either one or the other (or both) could show genetically determined differences, if existent." He has also expressed concern (Ref. 4) about how little is known concerning the formation of salicyluric acid in children (as a function of age) and in arthritics and other individuals taking large doses of salicylates. Levy et al. (Ref. 7) have studied the kinetics of salicyluric acid formation in man and have confirmed that this is the limiting step for the excretion of salicylate in urine.

There is no information available in the literature to suggest that salicylates induce their own metabolism, hence more caution is necessary when large, frequent doses are used. Some data are available from a study in dogs (Ref. 8) which showed no change in the kinetics of salicylate elimination after repeated dosing. However, it is not known how validly this data can be extrapolated to man.

3. *Plasma concentration and distribution.* This subject has been reviewed by Davidson and Mandel (Ref. 9) as follows:

PLASMA CONCENTRATION AND DISTRIBUTION

After a single oral dose of 0.6 Gm of aspirin in normal men, the average peak salicylate level in the plasma is approximately 4 mg/100 ml and is reached in 100 to 120 min. After ingestion by a fasting human subject, the drug may reach its peak plasma level in 40 min; after a heavy meal, however, it may take 3 hr. In the treatment of rheumatic fever, the desired plasma level is in the range of 30 mg/100 ml, which requires doses of 2 Gm several times daily. Sustained-action tablets are also available, which may plateau over many hours and require less frequent dosage. As noted under excretion, however, after larger doses salicylates tend to be excreted less rapidly, thereby reducing the need for sustained tablets.

A large part of the salicylate in the blood is bound to plasma proteins. Of this fraction, at least 85 percent is bound to albumin, with the remainder adhering to alpha and beta globulins. The percentage which is protein-bound ranges from 85 percent at 20 mg/100 ml salicylates to 50 percent at 50 mg/100 ml. Binding involves primarily the free carboxyl group, but the phenolic group markedly enhances the attraction for proteins. Aspirin itself, however, undergoes little or no binding. Binding may be strikingly altered in disease states. Although the albumin present still binds to the same degree per molecule, the total albumin concentration may be markedly lowered, thus reducing binding by as much as 50 percent.

The salicylate concentration is usually greater in the serum than in whole blood. It appears that the red cell membrane is readily permeable to salicylate and that the drug is not bound by the proteins of the erythrocytes.

The exact significance of blood levels of salicylate is still unclear. In dogs salicylate levels after oral administration can actually still be increasing after the analgesic response to bradykinin has worn off. It seems obvious that assays at the site of action are more meaningful than in blood but are more difficult to obtain. In a few cases salicylate concentrations in joint fluids have been measured. Although unbound concentrations in plasma and synovial fluid are essentially equal, the total concentration in joint fluid is only one-half of the peak plasma concentration, since joint fluid contains less protein and therefore less protein-bound drug. However, the synovial fluid drug concentrations remain higher for considerably longer periods.

The salicylates are distributed through a volume of body water much greater than that of the extracellular fluid. Studies on rats showed that the concentrations in the liver, kidney, and lung were similar to those in the serum. When the salicylate concentration is calculated on the basis of water content, the liver contains about two-thirds as much as the serum, and muscle approximately one-fifth as much.

Passage across the blood-brain barrier is relatively incomplete. After the administration of either aspirin or salicylate, salicylate is found in brain water in rats and reaches a maximum of about 10 percent of the plasma concentration. In four mammalian species, including the monkey, no free aspirin was found in the brain. It is apparently completely hydrolyzed to salicylate in the blood or brain, or else it does not penetrate the brain. Salicylates show some selective concentration effects in certain portions of the brain. At first, the more vascular gray matter takes up the drug more rapidly, but at equilibrium, these differences have disappeared. It has been shown with other analgesic agents such as morphine, that the uptake is related to the vascularity of tissue. In contrast, the pituitary gland of several mammalian species contains a twofold or threefold excess concentration compared to the other portions of the central nervous system. Goldberg has reported the effects of alterations in carbon dioxide tension on the penetration of salicylate into brain. Hypercapnia (with plasma pH 6.81) may produce a twofold to threefold increase in brain penetration of drug whereas hypocapnia (with plasma pH 7.86) produces a 30 percent decrease. These observations may be of importance in salicylate toxicity.

It is of interest that insulin markedly increases analgesic action of salicylates and raises its concentration in brain and other tissues, both in normal and alloxan diabetic animals.

Apparently salicylates cross the placental barrier readily. When pregnant rabbits are given large doses of sodium salicylate, the concentration of salicylate in the fetal serum is approximately two-thirds that in the maternal serum. Salicylates have also been found in milk.

As far as traversing the placental barrier, Woodbury (Ref. 2) states this fact more emphatically: "The drug readily crosses the placental barrier." Woodbury also mentions in reference to distribution that:

The volumes of distribution of aspirin and sodium salicylate in normal subjects average about 150 ml/kg of body weight, a value equivalent to that of the extracellular space; since salicylate is present within cells in various tissues, this suggests a markedly uneven distribution of salicylate in the body. The concentration of salicylate in intracellular fluid is lower than in plasma, in part because of the lower pH of the former. The movement of salicylate across some cell membranes is pH dependent and appears also to be insulin dependent. Salicylate does not accumulate in pathological fluids, such as joint effusions in acute rheumatic fever; hence, a selective distribution is not the basis for its therapeutic effects.

Furthermore, Woodbury adds that "only traces (of aspirin) are present in sweat, bile and feces."

4. *Excretion.* It has already been mentioned how salicylates are excreted in the urine (vide supra) (Ref. 2):

Practically all of a given dose can be recovered in the urine as free, unaltered salicylate and as the metabolites described above, the nature and the relative amounts of which vary in health and disease with the dosage and with the pH of the urine. Studies in man indicate that salicylate is excreted in the urine as free salicylic acid (10%), salicyluric acid (75%), salicylic phenolic (10%) and acyl (5%) glucuronides, and gentisic acid (less than 1%).

Urinary pH plays an important role in excretion. As stated by Woodbury (Ref. 2):

Changes in urinary pH in the acid range have negligible effects on salicylate clearance; however, the mean clearance is about four times as great at pH 8.0 as at pH 6.0. The clearance is well above the glomerular filtration rate at pH 8.0 but considerably below it when the urine is acidic. This is due to the fact that salicylate and salicylurate are highly ionized at pH 8.0 and little diffuses back from the renal tubular lumen. At a urinary pH 6.0 large amounts of salicylate and salicylurate are nonionized and readily back-diffuse. High rates of urine flow decrease tubular back diffusion, whereas the opposite is true in oliguria. The conjugates of salicylic acid with glycine and glucuronic acid are water-soluble organic acids that do not readily back-diffuse across the renal tubular cells. Their excretion, therefore, is both by glomerular filtration and proximal tubular secretion and is not pH dependent.

Furthermore, conditions that decrease the glomerular filtration rate or reduce the secretory Tm (transport maximum) of the proximal renal tubules, such as renal disease or the presence of inhibitors (such as probenecid) will decrease excretion and consequently increase plasma concentration which could be dangerous if the concentration in plasma approaches toxic levels.

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L. ABSORPTION, DISTRIBUTION, BIOTRANSFORMATION (METABOLISM) AND EXCRETION OF ACETAMINOPHEN

Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract (Ref. 1). It has been suggested that some dietary components could alter the absorption of acetaminophen administered orally. In particular, high carbohydrate test meals have been found to retard acetaminophen absorption (Ref. 2). Acetaminophen absorption has also been found to be inhibited by activated charcoal (Ref. 3). The authors found that 10 g activated charcoal administered immediately after the oral administration of 1 g acetaminophen reduced absorption by 69 to 77 percent in 2 subjects (Ref. 3).

Peak plasma concentrations after the administration of acetaminophen have been reported to occur in 30 to 60 minutes (Ref. 1). In an unpublished study, it was found that peak plasma levels after acetaminophen administration were reached between 40 and 67 minutes.

using different pharmaceutical forms of acetaminophen (Ref. 4).

The plasma half-life has been reported to be from 1 to 3 hours (Ref. 1). In an unpublished study (Ref. 5), the mean plasma half-life using several pharmaceutical forms was 148±43 minutes.

Acetaminophen is relatively uniformly distributed throughout most body fluids (Ref. 1). Binding of the drug to plasma proteins is variable and depends on the dose. During acute intoxication, as much as 20 to 50 percent may be bound to plasma proteins (Ref. 1). Dearden and Tomlison (Ref. 6) studied the protein binding affinities of some p-substituted acetanilid derivatives including acetaminophen and found that at therapeutic doses the association constant was low, which would permit high free drug concentration in blood and plasma for a relatively long period of time.

Acetaminophen is conjugated in the liver to form glucuronide and sulfate conjugates. Cummings et al. (Ref. 7) showed that acetaminophen is eliminated mainly by these two pathways. By chromatography and infrared spectrophotometry they characterized the sulfate and glucuronide of acetaminophen. They found that 26 percent of acetaminophen administered was excreted as the sulfate and 49 percent as the glucuronide.

It seems that the formation of acetaminophen sulfate in man may be capacity-limited in the 1 to 2 g dose range (Ref. 8). This has been shown by Levy and Yamada by the fact that acetaminophen sulfate excretion reaches a plateau following the administration of 2 g acetaminophen. Acetaminophen is also conjugated to a lesser degree with cysteine and the corresponding mercapturate.

The metabolites of acetaminophen have been separated and determined quantitatively in urine by gel filtration using Sephadex G 10 (Ref. 9). These authors also found the most important metabolites to be the glucuronide and sulfate. Other metabolites found were S-(1 - acetamino - 4 - hydroxy phenyl) - cysteine and 1 - acetamino - 4 - hydroxy phenyl mercapturic acid. Using this technique minor quantities of free acetaminophen were also found in the urine. Using this technique the total recovery was 95 to 100 percent and the administered dose was accounted for as follows:

30.5 to 58.5 percent as glucuronide.
17.5 to 33.9 percent as sulfate.
4.5 to 6.1 percent as mercapturate.
0.4 to 5.9 percent as cysteine conjugate.
3.5 to 4.5 percent as free acetaminophen (Ref. 9).

It has been suggested that the hydroxylated metabolites are responsible for methemeglobin formation and hepatotoxicity (Ref. 1). The administration of acetaminophen to patients with impaired renal function results in increased accumulation of acetaminophen conjugates in the plasma because of poor excretory capacity but only in minor changes in the plasma concentrations of free acetaminophen (Ref. 1).

The metabolism of acetaminophen has been shown to be markedly changed by the concurrent administration of salicylamide (Ref. 8). The authors found evidence of competitive inhibition by salicylamide in the formation of acetaminophen glucuronide and sulfate. This effect was counteracted or prevented by the administration of L-cysteine (a source of sulfate). This interaction may have therapeutic and/or toxicological implications since the inclusion of salicylamide in an analgesic mixture will inhibit the two major processes for the elimination of acetaminophen. This interaction with salicylamide becomes more important if one considers the capacity-limited formation of sulfate described above (Ref. 8). On the other hand, concurrent administration of salicylic acid has been found not to exert any significant effect on the formation of acetaminophen glucuronides or sulfate or in the half-life of acetaminophen (Ref. 10).

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The Panel considered all pertinent data and information in arriving at its conclusions and recommendations. The Panel was charged with the review of OTC internal analgesic, antipyretic, and antirheumatic drug products. After carefully reviewing all of the available data, the Panel has classified the data into analgesic, antipyretic and antirheumatic agents. (See part II, paragraph I. above—Definitions.)

III. Analgesic Agents

A. General Discussion

The Panel has defined OTC analgesic drugs as agents useful to relieve occasional minor aches, pains and headache. These agents are intended for the relief of the type of pain that is self-limited and requires no special treatment or prior diagnosis by a physician. Such analgesic agents are commonly referred to as the mild analgesics in contradistinction to the strong analgesics such as the potent narcotic or morphine-like analgesics. The mild analgesics can be chemically divided into two main subgroups: Those agents chemically related to the strong analgesics, e.g., codeine, ethoheptazines, and propoxyphene; and those analgesics like aspirin, with antipyretic and anti-inflammatory or antirheumatic activity, e.g., salicylates, salicylamide, aniline derivatives, phenylpyrazoles, etc. It is the latter group of mild analgesics that have generally been associated with OTC use.

The mild analgesics which are acceptable for OTC use include the salicylates, e.g., aspirin and the nonsalicylates, e.g., acetaminophen. All of these agents are administered orally and in special cases rectally. Since these agents are not as potent as the strong analgesics the milder agents are most effective for relief of mild to moderate pain. Mild analgesics probably achieve their effect through several mechanisms. The salicylates which are the most commonly used OTC analgesic agents are believed to alleviate pain by both a peripheral and a central nervous system (CNS) effect. Direct effects of salicylates on the CNS have been described and suggest a hypothalamic site for the analgesic as well as the antipyretic effects. This is supported by the fact that analgesic doses do not cause mental disturbances, hypnosis, or change in modalities of sensation other than pain. Both the peripheral and CNS factors contribute significantly to the pain relief afforded by this class of drugs.

The types of pain amenable to relief by OTC analgesics are generally those of relatively low intensity, particularly headache, myalgia, arthralgia and other pains arising from integumental structures. The salicylates have lower maximal effects than do the narcotic analgesics and hence are used only for pain of mild to moderate intensity. The salicylates are more widely used for pain relief than any other class of drugs.

Although OTC analgesics may effectively ameliorate the pain due to various physical conditions, disease entities, or specific physical sites, the listing of a multitude of conditions and sites in order to be factual and all inclusive would not only result in a lengthy list that would tend to be confusing but could also mislead the consumer by the implied assumption that the product treats the physical condition and/or disease rather than just temporarily relieves the pain associated with the physical condition and/or disease. For this reason, the Panel has recommended that OTC analgesics be simply indicated "For the temporary relief of occasional minor aches, pains and headache".

The Panel concludes that no OTC analgesic product should be taken by adults for more than 10 days or by children for more than 5 days except under

the advice and supervision of a physician. If the consumer feels the need to continue self-medication beyond 10 days, it may be indicative of an underlying serious condition requiring medical supervision. Self-medication without consulting a physician may in some conditions cause irreparable damage. It is the Panel's opinion that if symptoms require the use of an OTC analgesic for more than 10 days, the individual is sufficiently ill to require consulting a physician. The 10 day limit is based on historical precedent and past marketing experience. The Panel has concluded elsewhere in this document that the duration of use of all analgesics should be limited to 5 days for children under 12 years of age (See part II. paragraph F.3. above—Statement on children's dosage.) Therefore, the Panel recommends that all OTC analgesics contain the warning for adults, "Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician", and for children under 12 years of age, "Do not take this product for more than 5 days. If symptoms persist, or new ones occur, consult your physician".

B. CATEGORIZATION OF DATA

1. *Category I conditions under which analgesic agents are generally recognized as safe and effective and are not misbranded.*

CATEGORY I—ACTIVE INGREDIENTS

The Panel has classified the following analgesic active ingredients as generally recognized as safe and effective and not misbranded:

Aspirin	Magnesium salicylate
Acetaminophen	
Calcium carbaspirin	Sodium salicylate
Choline salicylate	

a. *Aspirin.* The Panel concludes that aspirin is a safe and effective OTC analgesic when taken in the recommended dosage of 325 to 650 mg every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* Aspirin is by far the most widely used OTC ingredient in the U.S. In fact, almost 19 billion dosage units are sold annually. During the 75 years that have elapsed since aspirin was introduced to the U.S. market, and because of its immense popularity in this country, it has been extensively discussed in the medical and scientific literature.

Aspirin is useful in mild to moderate pain not only when the pain is localized but also when it is widespread. Studies on cancer pain suggest that aspirin may also relieve mild to moderate pain of visceral origin.

Thousands of articles have been written on aspirin since the first pharmacological data were reported in the literature by Dreser in 1899 (Ref. 1). Virtually all of the experiments discussed in the articles showed aspirin to be superior to placebo in "mild" to "moderate" pain. Kantor states that "modern clinical pharmacologic testing has established that aspirin is an effective analgesic in a variety of pain states" (Ref. 2). Beaver, in an extensive discussion of mild analgesics in 1965, summarized the findings of over 40 controlled human analgesic studies which demonstrated the superiority of aspirin to placebo (Ref. 3).

The Panel has included the following table which summarizes the studies reported by Beaver (Ref. 3):

Controlled human studies demonstrating the superiority of aspirin to placebo prior to 1965

Investigator(s)	Type of patient, etiology of pain, or both	Aspirin dose (milligram)
Beecher et al.	Postoperative	600.
Boyle et al.	Mixed chronic	650.
Brennan	Postoperative dental, outpatients	650.
Bruni and Holt	Postpartum	650.
Carlsson and Magnusson	Headache, outpatients	1,000.
Cass and Frederik	Mixed chronic	300 to 650.
Cass et al.	Mixed chronic	325 to 600.
Currier and Westerberg	Headache, outpatients	650.
DeKornfeld and Lasagna	Postpartum	600.
DeKornfeld et al.	do	650.
Feinberg et al.	Mixed musculoskeletal, outpatients	325 or 650.
Forrest	Mixed acute and chronic	300 and 900.
Frey	Headache, inpatients and outpatients	650.
Houde et al.	Cancer	600.
Houde & Wallenstein	do	400, 600 and 900.
Kantor et al.	Postoperative and fracture	600.
Do.	Postpartum	600 and 1,200.
Lasagna et al.	do	600 (?).
Magee & DeJong	Headache, outpatients	600 and 1,200.
Marrs et al.	Mixed chronic and acute	325.
Murray	Headache outpatients	162, 325 and 650.
Orkin et al.	Postpartum	600.
Settel	Mixed chronic	650.
Sevelius & Colmore	Postpartum	325 (?).
Sunshine et al.	Mixed acute	650.
Uhland	Postpartum and mixed	625 or 650.
Valentine & Martin	Postoperative	325.
Zelvelder	Mixed chronic and acute	500.

Beaver also noted that because of the consistency of aspirin's analgesic activity in well-controlled analgesic studies, most researchers often included it as a standard in their experiments. For example, Lasagna (1962), in a series of 23 separate consecutive studies conducted on patients with postpartum pain (after childbirth) found in 22 of these studies that the analgesic response to 600 mg of aspirin was superior to that of placebo (Ref. 4). Similarily, Houde demonstrated a significant superiority of aspirin over placebo in 9 of 10 studies in patients with cancer (Ref. 5).

The Panel has included the following table which summarizes some other more recent studies which also demonstrate the superiority of aspirin to placebo.

Controlled human studies demonstrating the superiority of aspirin to placebo since 1965

Investigator(s)	Type of patient, etiology of pain, or both	Aspirin dose (milligram)
Bloomfield, et al. (reference 6)	Episiotomy	600.
Bloomfield and Hurwitz (reference 7)	Tourniquet and episiotomy	1,200.
Bloomfield et al. (reference 8)	Episiotomy	900.
Calimlim et al. (reference 9)	Postoperative	650.
Cooper and Beaver (reference 10)	Oral surgery	650.
Hill and Turner (references 11 and 12)	Postoperative	600.
Lamphier et al. (reference 13)	Postoperative	325.
Moertel et al. (reference 14)	Pancreatic cancer pain	650.
Moertel et al. (reference 15)	Various, mild to moderate	650.
Moertel et al. (reference 16)	Cancer	650.
Murray (reference 17)	Headache	648.
Parkhouse et al. (reference 18)	Postoperative	300 to 1,200.
Parkhouse et al. (reference 19)	Postoperative	600.
Stenport (reference 20)	Orthopedic, postoperative	600.

In 1967, Murray compared placebo, 648 mg aspirin, 325 mg acetaminophen plus 325 mg salicylamide, and 487 mg acetaminophen plus 487 mg salicylamide in medical and pharmacy students with pain due to headaches (Ref. 17). He found that aspirin produced relief in 78 percent of the cases, placebo in 46 percent and the acetaminophen-salicylamide mixtures in 69 percent and 76 percent, respectively. All medications were found to be statistically superior to placebo but no significant differences were found among the drugs tested. The importance of this study is that the pain evaluated was that from common headache, the most frequent reason for aspirin ingestion.

The blood level below which aspirin is ineffective as an analgesic has not been adequately demonstrated because analgesia has not been shown to correlate directly with levels of salicylates in the blood. However, Beaver noted that the use of graded doses can illustrate the threshold phenomenon (Ref. 3).

In another study by Murray, a group of medical and pharmacy students used graded doses of aspirin to treat headache (Ref. 21). He showed that 163 mg

and 325 mg doses of aspirin did not statistically differ from placebo response. Results were significant, however, in those using 650 mg of aspirin. An intermediate dose of about 500 mg was not used in this study. It would appear that a minimum dose of between 325 and 650 mg is necessary for significant headache analgesia; but additional studies are necessary to confirm this.

In addition, once some measurable level of analgesia is achieved, its duration and intensity also do not necessarily correlate with salicylate levels in the blood (Ref. 3).

However, with regard to intensity of analgesia, Murray demonstrated an increase in analgesia when the dose of aspirin was increased from 325 mg to 650 mg (Ref. 21). A study by the Veterans' Administration Cooperative Analgesic Study Group also showed a difference in analgesic effect between 300 and 900 mg aspirin in patients with postoperative pain (Ref. 22). In this study even the low dose of 300 mg was significantly better than the placebo.

In another study, Modell and Houde showed a dose related increase in pain relief when 400 mg, 600 mg and 900 mg aspirin were administered to patients with cancer (Ref. 23).

Kantor found that within a population of postpartum patients there were two response groups. The patients whose main complaint was pain following episiotomy (a surgical incision made to aid removal of the infant from the vagina) were able to discriminate between 300 mg and 600 mg doses of aspirin while those patients whose main complaint was uterine cramp pain could not (Ref. 2).

Bloomfield et al., in a double-blind study performed in 1967, were unable to show a significant difference between the analgesic effects of 300 mg and 600 mg doses of aspirin. However, both levels of aspirin were significantly more effective than placebo (Ref. 6). Later in 1970, Bloomfield et al. confirmed Kantor's results regarding the differing levels of effectiveness of aspirin in relieving the pain of episiotomy (Ref. 7).

Hill and Turner (1969) approached the analgesic evaluation problem from a different point of view. In a double-blind study, aspirin was compared to the narcotic analgesic meperidine in patients with post-operative pain ranging from "mild" to "severe." They concluded that aspirin was preferred at the milder levels of pain while meperidine was preferable at the severe pain levels (Ref. 11). However, these same researchers in another double-blind study in patients with pain following gynecological surgery could not differentiate meperidine, aspirin and placebo "in the patient population as a whole" but could distinguish them when patients were classified as to the initial severity of their pain (Ref. 12). This latter study could have been insensitive if the pain intensity had not been considered and illustrates one of the inherent difficulties in analgesiometry.

Moertel et al. (1971) have evaluated the analgesic effect of 650 mg aspirin as compared with 60 mg codeine sulfate in patients with pain due to unresectable carcinoma (cancer) and found that pain relief with aspirin exceeded that of codeine (Ref. 14).

Moertel et el. (1972) compared 650 mg aspirin to 250 mg mefenamic acid, 50 mg pentazocine, 650 mg acetaminophen, 650 mg phenacetin, 65 mg codeine, 65 mg propoxyphene, 25 mg promazine, 75 mg ethoheptazine, and placebo all given orally to patients with pain due to unresectable cancer (Ref. 16). They concluded that aspirin was "superior to all agents tested."

Recently, Moertel et al. (1974) studied aspirin as a single ingredient and in combination. Aspirin 650 mg again proved significantly better than placebo. Neither 32 mg pentobarbital nor 65 mg caffeine appeared to increase efficacy in patients with cancer. However, adding 65 mg codeine, 25 mg pentazocine, or 9 mg oxycodone did significantly increase pain relief (Ref. 15).

While the effectiveness of aspirin is undisputed, there are limitations to its use which must be kept in mind. There are wide individual variations in response to all analgesics, and while aspirin is generally effective in relief of mild to moderate pain, it is only of limited value in relief of severe pain.

The Panel recognizes that pain is only a symptom of an underlying pathologic state and if it is severe or persists, medical attention should be sought. Thus, it finds the following warning necessary, "Do nor take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician".

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(2) *Safety.* As noted earlier in this document, aspirin is the most widely used single drug in the United States. The Panel believes that in light of this extensive use and long marketing history and the relatively low incidence of serious toxic effects associated with short term use of presently recommended doses, the safety of aspirin has been well-established for the majority of the population and the risk benefit ratio is low. However, the Panel wishes to make clear that this does not mean that aspirin has no adverse effects. In fact, the Panel has identified eight areas of concern where aspirin may have some potential for adverse effects including effects on organ systems, i.e., gastrointestinal tract, central nervous system, kidney, liver and the blood; specialized effects on hypersensitive individuals, persons with certain disease states or during pregnancy; or when used concomitantly with other drugs. The Panel believes that subsets of the population at risk can be identified so that adequate

labeling can be established to provide for safe OTC use of the drug. The safety of aspirin is discussed below. The Panel has reviewed the metabolism of aspirin elsewhere in this document. (See part II, paragraph K. above—Absorption, Distribution, Biotransformation (Metabolism) and Excretion of Aspirin and Salicylates in Man.)

Because of the extensive use and research on this drug, the Panel has been able to identify many of the safety considerations and has summarized them in the following table:

SUMMARY OF SAFETY CONSIDERATIONS WITH USE OF ASPIRIN

ADVERSE EFFECTS ON THE BLOOD

Aspirin interferes with blood clotting. Persons with a history of blood coagulation defects, or receiving anticoagulant drugs or with severe anemia should avoid the drug.

ADVERSE EFFECTS ON THE GASTROINTESTINAL TRACT

The drug may potentiate peptic ulcer, cause stomach distress or heartburn. Aspirin causes an increase in occult bleeding and in some persons massive gastrointestinal bleeding.

ADVERSE EFFECTS ON HYPERSENSITIVE INDIVIDUALS

Aspirin produces allergic and anaphylactic reactions in hypersensitive individuals, especially certain types of asthmatics, ranging from rash, hives and swelling to asthmatic attacks which may be life-threatening.

ADVERSE EFFECTS DURING PREGNANCY

Aspirin interferes with maternal and infant blood clotting and lengthens the duration of pregnancy and parturition time. Aspirin produces teratogenic effects in animals and increases the incidence of stillbirths and neonatal deaths in humans.

ADVERSE EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Aspirin when taken in overdose produces stimulation (often manifested as tinnitus) followed by depression of the central nervous system.

ADVERSE EFFECTS ON THE KIDNEY

Aspirin may rarely cause an increase of existing severe kidney disease.

ADVERSE EFFECTS ON THE LIVER

High doses may produce a reversible hepatic dysfunction.

ADVERSE EFFECTS OF CONCOMITANT USE WITH OTHER DRUGS OR BY PERSONS WITH CERTAIN DISEASE STATES

Aspirin interferes with some anticoagulant and antidiabetic drugs, some drugs used for the treatment of gout and may have an additive ulcer-producing effect with some drugs used in arthritis.

ADVERSE EFFECTS RESULTING IN IRON DEFICIENT ANEMIA

Aspirin used chronically may cause a persistent iron deficient anemia.

(i) *Adverse effects on the blood.* In addition to the well-known association between aspirin ingestion and gastrointestinal bleeding discussed below, aspirin and salicylic acid have been implicated but not always proven as factors in bleeding from the skin, throat (posttonsilectomy), nose, rectum, vagina, postsurgical wounds and dental extraction sites (Refs. 1 through 6). The major hemostatic mechanisms involved are the effects of aspirin and salicylates in large doses on prothrombin production and the effects of aspirin in small doses (but not salicylates) on platelet function, which results in an increased bleeding time and possibly other effects such as fibrinolysis (Ref. 7).

(a) *Decrease in prothrombin production.* High doses of aspirin and salicylic acid (6,000 to 10,000 mg daily) taken for several days can cause hypoprothrombinemia, i.e., a decrease in the amount of prothrombin (blood clotting factor II) in the circulating blood (Refs. 1 and 4) which may be reversed by vitamin K (Ref. 5). However, it is important to emphasize that this effect of salicylates does not usually result in clinically significant alteration of the coagulation mechanism except in patients who may be particularly susceptible. Susceptible patients include those receiving anticoagulant therapy; patients consuming high doses of aspirin or salicylates chronically, e.g., patients with rheumatoid arthritis; patients with liver disease which limits the production of prothrombin (blood clotting factor II); and patients with malabsorption syndrome or gastrectomy leading to a deficiency of vitamin K, which is a substance required for prothrombin synthesis (Ref. 8).

As noted above, hypoprothrombinemia is produced by both aspirin and other salicylates when taken in high doses. In one study a daily total dose of 3,200 mg sodium salicylate produced no change in prothrombin time, 6,600 mg produced a slight change and 10,000 mg produced a marked change in prothrombin time (Ref. 6). Aspirin or salicylate-induced hypoprothrombinemia has been implicated in posttonsillectomy bleeding, epistaxis (nose bleed), and postdental extraction bleeding (Refs. 9 and 10), although other mechanisms such as a platelet effect (discussed below) may be involved.

(b) *Increased bleeding time and inhibition of platelet aggregation.* Aspirin increases bleeding time and inhibits the in vivo and in vitro aggregation of platelets.

Bleeding time is defined as the duration of time that bleeding continues after a superficial puncture of about 1 mm is made in the skin. This occurs with doses of aspirin far below those required for a hypoprothrombinemic effect. The effect of aspirin on bleeding time in a patient with bleeding tendencies was noticed many years ago by Frick who attributed it to an effect of aspirin on capillary fragility (Ref. 11). Later, Quick showed that 2 hours after ingestion of 1,300 mg aspirin, but not sodium salicylate, a small but significant increase in the bleeding time occurred in normal subjects. A much greater increase was observed in patients with mild coagulation defects such as von Willebrand's disease and hereditary telangiectasia (Ref. 12). Quick postulated that aspirin, due to the presence of the acetyl group, may interfere with or compete with some vascular factor, such as cholinesterase, involved in the vascular tone of small vessels (Ref. 13). However, the results of a recent study submitted to the Panel, demonstrated, by an in vitro method, that aspirin did not have any effect on cholinesterase inhibition (Ref. 14). In the study, aspirin, salicylic acid and physostigmine (a known inhibitor) were compared. The dosages of aspirin and salicylic acid were correlated to the average amount of nonprotein bound aspirin and salicylic acid found in human plasma up to 2 hours after ingestion of two aspirin (650 mg) tablets. The findings indicated inhibition with physostigmine and none with aspirin or salicylic acid. The investigators concluded that "this information, obtained with dilute enzyme preparations, suggests that in vivo cholinesterase concentrations are too substantial for aspirin doses, at least recommended doses, to have any influence." Still, others have proposed that inhibition of prostaglandin synthesis leads to vasodilation and pooling in the microcirculation (Ref. 5). While, as yet undiscovered, direct effects on the blood vessel or vasoactive mediators may prove to be a factor, it is presently well established that the primary effect of aspirin on bleeding time and hemostasis is due to a potent irreversible effect on platelet function which inhibits the in vivo and in vitro aggregation of platelets.

The effects of aspirin on platelet function were shown almost simultaneously by several independent groups (Refs. 15 through 20). The effect of a single dose of 1,500 mg aspirin on platelets will persist 2 to 3 days and not completely disappear for 4 to 7 days (Ref. 15). Since this is roughly the life span of a platelet, it indicates irreversible damage to platelet function.

Weiss and Aledort reported that bleeding time was increased by a mean value of 3.3 minutes in 10 normal male subjects receiving 350 mg aspirin (Ref. 16). They first reported that aspirin interfered with platelet connective tissue reaction by inhibiting the release of adenosine diphosphate (ADP) which results in prolongation of bleeding time.

Mielke et al. showed the standard Ivy Test to be very reproducible when the wound is standardized ("template bleeding time") (Ref. 21). Aspirin 975 mg (15 gr) increased the mean bleeding time from 5.5 minutes to 9.5 minutes on repeated tests by different investigators (Ref. 19). The population distribution of this trait appeared to be heterogeneous.

Mielke and Britton found that a 300 mg dose of aspirin each day maintained the prolongation of bleeding time and that no greater effect was obtained with higher doses (900 or 2,700 mg) (Ref. 22).

Other analgesic drugs which show marked inhibition of platelet aggregation include indomethacin, ibuprofen, mefenamic acid, and amidopyrine. Less effect was noted with oxyphenbutazone. No effect was noted with sodium salicylate or phenacetin (Ref. 23).

The importance of the platelets as the first line of defense in hemostasis has been established in recent years (Refs. 24 and 25). Platelets adhere to exposed collagen fibers within seconds after damage occurs to small vessels. This interaction results in a release of ADP which facilitates platelet aggregation into a loosely (first phase) and then tightly (second phase) packed plug. The plug formation precedes the formation of a fibrin network which eventually forms a clot. It is now known that aspirin inhibits ADP release in phase one and/or phase two aggregations and also in the initial interaction with collagen fibers. Plug formation may be relatively unimportant when major arteriolar damage occurs because other available mechanisms are more effective; but it is thought to be an extremely important hemostatic mechanism in capillary (oozing) bleeding (Refs. 24 and 26).

This type of bleeding is now believed to be involved in the types of gastrointestinal bleeding that are potentiated by aspirin (Refs. 25, 27, 28, and 29) as well as other sites of bleeding such as the posttonsillectomy tonsillar bed, or surgical wounds, or tooth sockets following dental extractions (Refs. 25 and 30). The demonstrated effect of aspirin on platelet function and the importance of this process in the hemostasis of oozing type of small vessel bleeding provides a consistent mechanism for the wide variety of sites of bleeding that have been associated with aspirin. Some of these types of bleeding are briefly reviewed below.

Nonthrombocytopenic purpura (bleeding in the tissues in a patient with a normal platelet count) associated with aspirin ingestion has been described as a hypersensitivity reaction (Ref. 31). However, idiosyncracy was ruled out in three cases of purpura in children with normal platelet counts who received usual doses of aspirin (Ref. 32). The authors attributed the bleeding to a demonstrated platelet dysfunction due to inhibition of ADP release following aspirin therapy, rather than vascular or hypersensitivity reactions. It is of interest that in two cases with no family history of bleeding disorders, the patients were sisters (9-year-old and 14-month-old). However, the father on two occasions within a 3-year period had experienced severe gastric bleeding after a single intake of 2,000 and 1,000 mg doses of aspirin, respectively.

Buettinghaus and Tenhaeff (1973) stated that 16 of 24 patients taking aspirin developed hematoma (a swelling filled with extravassated blood) in the wound regions following abdominal surgery or hysterectomies (Ref. 33).

De Vries and Ten Cate have suggested that thrombocyte damage may be responsible for many cases of menorrhagia (excessive menstrual discharge), postextraction bleeding in dentistry, and chronic purpura (hemorrhage into the skin resulting in discoloration) (Ref. 34).

Several cases of massive hemorrhage from the tonsillar bed following topical application of aspirin through gargles or aspirin-containing chewing gums have been reported (Ref. 35). Hemorrhage was observed in 8 percent of 100 posttonsillectomy patients medicated with aspirin (Ref. 36). The bleeding occurred on the 6th or 7th postoperative day and could be controlled only with packing and suturing. No hemorrhage occurred in the 100 patients medicated with acetaminophen in an identical manner. Similar results were also reported by Hersh who carried out a controlled study in patients having dental extractions (Ref. 30). Hersh (Ref. 30) conducted a randomized controlled study in patients undergoing dental extraction. Those not taking an aspirin-containing analgesic in the 7 days prior to dental extraction were given either aspirin or acetaminophen for post-tooth extraction pain. Significantly more bleeding was noted among those who received aspirin. Of those patients among the 516 studied who had taken aspirin in the 7 days prior to extraction and who were continued on aspirin, the incidence of postextraction bleeding was the largest of the three groups studied.

A high incidence of posttonsillectomy hemorrhage was also reported by Fox and West (Ref. 37) in children given an aspirin-containing chewing gum. The incidence of bleeding was said to be decreased by 99 percent when use of the gum was discontinued. In view of these reports, the Panel has recommended that all aspirin oral product formulations to be chewed (chewable tablets or gums) should contain the following warning: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician". The Panel has discussed chewable tablets and gums earlier in this document. (See part II. paragraph J.2.a. above—Solid dosage forms.)

The effects of aspirin on hemostasis in the newborn may be particularly hazardous since infants metabolize drugs slowly and are particularly susceptible to central nervous system hemorrhage (Ref. 25). Bleeding episodes in newborns may be higher in those whose mothers have taken aspirin during the 2 weeks prior to delivery. Alteration of platelet function in infants of mothers who ingested aspirin within 2 weeks of delivery has been reported by Bleyer and Breckenridge (Ref. 38), and Corby and Schulman (Ref. 39).

Bleyer and Breckenridge have studied the effects of prenatal administration of aspirin on the blood clotting of newborns. Two potentially serious drug effects were detected in infants born of mothers who had taken ordinary doses of aspirin during the last 2 weeks of pregnancy. They indicated that an aspirin-induced decrease in clotting ability may have clinical relevance particularly during difficult traumatic deliveries or in the presence of other clotting defects (Ref. 38). The effects of aspirin on maternal and newborn hemostatic mechanisms are discussed in more detail later in this document. (See part III. paragraph B.1.a. (2)(iv)(c) below—Effects on maternal and newborn hemostatic mechanisms.)

(c) *Relationship between systemic platelet effects and gastrointestinal bleeding.* Massive gastrointestinal bleeding which is discussed below, is the most frequent serious bleeding problem associated with aspirin. Several authors have recently pointed to the probable role of aspirin-induced platelet dysfunction in gastrointestinal bleeding (Refs. 5, 15, 24, 26, 29, and 40). There is growing evidence that the systemic effect of aspirin on platelets is a significant factor in a causal relationship between aspirin ingestion and subsequent gastrointestinal hemorrhage. Several lines of reasoning and recent experimental evidence support this conclusion.

Aspirin-induced platelet dysfunction will significantly promote bleeding when the platelet plug is the primary factor in hemostasis. This is usually true for the oozing type of bleeding which occurs from capillary beds. An argument against the role of platelet dysfunction in gastrointestinal bleeding has been that bleeding occurs from ulcers which involve extensive tissue and arteriolar damage (Ref. 26). This type of bleeding requires hemostatic mechanisms other than platelet plugs, such as vasoconstriction and fibrin clots, to stop bleeding. Even a significant reduction in the platelet function would not be sufficient to alter the degree of bleeding from these types of sites (Ref. 25). However, recent studies involving direct endoscopic observation of the bleeding lesions have shown that bleeding occurs most often not from ulcers but from inflamed mucosal tissue which is partially denuded of surface epithelium exposing engorged, hyperemic and dilated capillaries in the underlying lamina propria. This histological picture is characteristic of acute gastritis and duodenitis which gastroenterologists state are most often involved in massive gastrointestinal hemorrhage associated with recent aspirin ingestion (Refs. 28 and 41). It is also precisely the vascular condition which many hematologists state is most dependent upon platelet plugs to stop bleeding (Refs. 25, 26, and 29).

Gast (Ref. 42) has pointed out that alteration of platelet function alone is usually not sufficient to initiate bleeding. This is evident in the bleeding episodes due to aspirin described above which usually involve tissues subjected to prior injury, e.g., tonsillectomies. Thus, gastrointestinal bleeding involving platelet dysfunction would generally require other factors to be present to initiate epithelial and capillary damage and perhaps to promote local blood flow (Ref. 43). This is consistent with the relatively infrequent and sporadic incidence of massive gastrointestinal hemorrhage relative to the high incidence of aspirin use and current theories on the multiple factor etiologies of massive gastrointestinal bleeding (Ref. 44). It is also consistent with the difficulty of de-

veloping a suitable animal experimental model or designing adequate epidemiologic studies to define causal relationships. Some experimental evidence to support the role of platelet function in gastrointestinal hemostasis was presented by Schmid et al. (Ref. 31). These authors showed that decreased platelet function produced by aspirin, but not sodium salicylate, correlated with the extent of blood loss following aspirin ingestion. It is perhaps significant that virtually every compound tested thus far (including indomethacin and phenylbutazone), showing a significant deleterious effect on platelet function, has also been demonstrated to cause massive gastrointestinal bleeding. Recently, amidopyrine which has strong deleterious platelet effects was reported to be the cause of massive gastrointestinal bleeding (Ref. 45).

More information is needed on the relationship between gastrointestinal bleeding and platelet function. However, the Panel believes there is convincing evidence that the systemic effects of aspirin on platelet function are quite likely to be a factor in the aspirin-induced gastrointestinal hemorrhage. This systemic effect is independent of the dosage form used.

For the various reasons discussed above, the Panel has concluded that because aspirin can promote or increase bleeding after it has been absorbed into the bloodstream all preparations containing aspirin regardless of formulation should bear the following warning: "*Caution:* Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician". The Panel concludes that this recommended warning should also apply to all salicylates. (See part III. paragraph B.1. below—Category I Labeling.)

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(ii) *Adverse effects on the gastrointestinal tract.* Aspirin has several adverse effects on the gastrointestinal tract. These range from relatively mild effects such as gastric distress (minor stomach pain, heartburn or nausea), superficial mucosal irritation and minor occult (unseen) bleeding, to less frequent but more serious effects such as mucosal erosion, ulceration or life-threatening massive bleeding from a variety of gastrointestinal sites. The Panel concludes that all products containing aspirin should include the labeling warning, "Caution: Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

The direct and indirect roles of aspirin in producing or potentiating these different types of mucosal damage or bleeding in the gastrointestinal tract are complex and have been controversial. Disagreement, in part, has been due to the many interacting variables related to drug use and to the disease processes involved.

Disease variables of interest relative to safety and labeling include the increased incidence, and severity of adverse effects associated with aspirin use, the site and mechanisms involved and whether aspirin causes, potentiates or exacerbates particular types of gastrointestinal conditions. Important drug variables considered by the Panel include the usual dose required to produce these effects, and whether the effects involve acute (1 to 5 days) or chronic (several months) use of aspirin. Particular attention was given to claims that adverse effects may be reduced by a particular type of dosage form such as buffered tablets or highly buffered effervescent solutions. Buffered aspirin can reduce the incidence of minor effects but not serious disorders, such as massive bleeding.

The Panel concludes that aspirin should not be used by individuals with a recent history of peptic ulcers or gastrointestinal bleeding because of the increased incidence of gastrointestinal bleeding in such individuals following acute and chronic aspirin ingestion. Furthermore, because recurrent gastric distress is such a common symptom in upper gastrointestinal tract disease which predisposes individuals who experience massive, life-threatening, gastrointestinal hemorrhage regardless of the presence or absence of ulcers, the Panel recommends that individuals with gastric distress should not take aspirin without the advice of their physician.

There is now sufficient evidence to indicate that some individuals taking aspirin chronically may develop gastric ulcers. Therefore, use of aspirin in chronic conditions such as arthritis is not advised without proper medical supervision and surveillance to avoid development of these untoward effects.

Muir and Cossar (Ref. 1) in 1961 stated that a plethora of information supports the following conclusions: "People with peptic ulcer should not take aspirin; people who have aspirin dyspepsia are in danger of serious gastric hemorrhage under circumstances as yet undefined."

(a) *Gastric distress.* Gastric distress or gastric intolerance including dyspepsia (heartburn), nausea and epigastric pain is a subjective response that can occur after usual doses of aspirin and salicylates in about 2 to 10 percent of the normal population (Refs. 1 through 7). The incidence or severity of gastric distress caused by aspirin is not necessarily related to acute gastric erosion (Refs. 7 and 8) and massive bleeding can occur with no pain (Ref. 9). However, dyspepsia prior to and after aspirin ingestion occurs more frequently in patients with peptic ulcers, gastritis and duodenitis (Refs. 10 and 11).

Buffered aspirin tablets are claimed to reduce the incidence of gastric distress to aspirin which may be true in a small number of normal individuals (Refs. 12 and 13). (See part II paragraph J.2.a. above—Solid dosage forms.) The Panel has discussed a suitable labeling claim for buffered aspirin products which is classified as Category III and discussed elsewhere in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

Gastric distress appears to provide one of the best means of identifying a high percentage of individuals who may be at risk of gastrointestinal hemorrhage after aspirin ingestion. Gastric distress can be categorized according to its cause as follows: Gastric distress caused by an underlying gastrointestinal disease which predisposes a person to bleeding; gastric distress related to recent aspirin ingestion; and gastric distress related to temporary problems unrelated to drug use or serious underlying gastrointestinal disease.

Several studies involving massive bleeding show that most patients experienced gastric distress, usually recurrent epigastric pain prior to their bleeding episode. Gastric distress occurs in 60 to 70 percent of patients with hemorrhagic gastritis (Refs. 14 and 15). In ulcer patients, the incidence of recurrent gastric distress may be 90 percent (Refs. 16 and 17). Patients who develop gastric ulcers because of chronic aspirin use frequently have gastric distress (Refs. 18 and 19).

The incidence of gastric distress after taking aspirin is much higher in patients with severe gastrointestinal disease. Muir and Cossar (Ref. 3) in 1955 stated that dyspepsia after aspirin ingestion is six times greater in patients with peptic ulcer as compared to normal subjects. Roth states that dyspepsia occurs in about 7 percent of normal subjects, 10 percent of rheumatoid arthritis patients and 33 percent of peptic ulcer patients (Ref. 11). Although individuals with an active peptic ulcer are not unusually susceptible to aspirin-induced occult bleeding, they do have an increased susceptibility to dyspeptic symptoms (Refs. 8 and 11).

Vining (Ref. 20) in 1957 reported a higher incidence of gastric distress in rheumatoid arthritics taking aspirin chronically, occurring in about one out of four of this group. However, in a carefully performed study, Stubbe (Ref. 21) in 1958 found no difference in occult bleeding between rheumatoid arthritics and normal subjects indicating as in other studies that there is no correlation between occult bleeding and incidence of gastric distress. (See Part III paragraph B.1.a.(2)(ii)(e) below—Occult bleeding.)

Alvarez and Summerskill (Ref. 22) in 1958 stated that 80 percent of all patients who experienced major gastrointestinal bleeding after aspirin ingestion had proven histories of either duodenal or gastric ulcer, or dyspepsia.

The Panel concludes that by merely identifying those patients with a history of gastrointestinal ulcer or recurrent gastric distress, e.g., dyspepsia, it may be possible to warn as many as 80 percent of the high risk population.

(b) *Direct mucosal damage.* The Panel concludes that aspirin (and salicylic acid) have a direct local irritant effect on all the surface mucosal cells lining the gastrointestinal tract (Refs. 1, 6, 10, 23, and 24). The effect is acute and occurs in most normal individuals (Ref. 10) and has also been demonstrated in several animal species (Refs. 6, 25, and 26). Prolonged contact with aspirin produces direct damage (focal necrosis) and sloughing (desquamation and exfoliation) of surface cells (Refs. 6, 8, and 10). Erosion can occur in the mouth (Refs. 6 and 27), rectum (Refs. 28 and 29) and stomach mucosa (Ref. 6) with concentrated solutions of aspirin (Ref. 26), and with particles of plain, buffered and combination aspirin tablets (Ref. 6).

(1) *Mucosal erosion of the mouth.* Aspirin-containing gum has produced a severe lesion of the inner wall of the cheek which promptly healed upon discontinuation (Refs. 27 and 30). Kawashima et al. (Ref. 30) in 1975 reported that aspirin tablets applied directly to the mucous membranes of the mouth for a local anesthetic effect have resulted in oral lesions on the roof of the mouth. Roth et al. (Ref. 6) found that aspirin preparations (tablet) allowed to remain in contact with mucous membranes of the mouth for 30 minutes produce a white opaque buccal mucosa capable of being peeled off with the slightest manipulation. They placed a quarter of several commercial plain, buffered and combination aspirin tablets between the lower lip or cheek and gums of 26 normal subjects for 30 to 60 minutes. In every case the aspirin produced an irregular opaque lesion with sloughing of cells characteristic of acute superficial necrosis.

(2) *Rectal irritation.* The Panel concludes that aspirin taken rectally in a suppository dosage form may have a direct local irritant effect on surface mucosal cells. The irritating effect of rectally administered aspirin can be alleviated by changes in the composition of the matrix of the suppository vehicle. The adverse effects of aspirin appear to be related to the chemical composition of the suppository base (Refs. 31 and 32) and to the rate of absorption of aspirin from the suppository base (Ref. 33).

Aspirin suppositories (1,300 mg aspirin per suppository) made of a cocoa-butter or a carbowax base were administered to dogs every 4 hours for a total dose of 3,900 mg daily for 3 days (Ref. 31). The experimental dogs in the study all showed signs of mucosal irritation. The irritation ranged from a distinct hyperemia to hemorrhagic ulcerative lesions. Perforations and death also occurred. The four dogs receiving the control suppository bases showed no rectal mucosal changes. The authors concluded that "prolonged rectal administration of aspirin suppositories may be potentially hazardous" and recommended that "additional studies to evaluate the extent of irritation and ulcerative hemorrhagic lesions in the human rectum following repeated administrations of aspirin suppositories seem to be indicated." Serum salicylate determinations in 40 human subjects administered 650 mg aspirin orally (tablets) and rectally (cocoa-butter base suppositories) indicated that the oral route pro-

vided significantly higher blood salicylate levels (p is less than 0.001) than the rectal route (Ref. 31).

In a study reported by Cacchillo and Hassler (Ref. 32), 11 male volunteers were administered 650 mg aspirin in one of three different types of suppository bases on 1 day for 3 successive weeks. On the fourth week, 650 mg aspirin (tablets) was given orally to compare the oral route with the rectal route. The three suppository bases were cocoa butter, Carbowax and glycerinated gelatin. There was virtually no rectal irritation from aspirin suppositories formulated with cocoa butter and Carbowax as the bases. Glycerinated gelatin based suppositories showed a high incidence of prolonged burning and pain, and the subjects evidenced a very strong desire to expel the suppository. There was no statistically significant difference between the absorption of aspirin orally and the absorption of aspirin from the Carbowax base only. The authors state that "individual studies must be undertaken to determine for each drug the base best suited for its absorption." In this study, Carbowax unlike the other two bases, not only showed that "the rectal dosage given is equivalent to the oral, as a high degree of absorption through this vehicle is assured when employed rectally", but also that "little or no irritation" occurred.

The rate of absorption of aspirin rectally was related to the incidence of irritation in a study by Borg, Ekenved, Elofsson and Sjogren (Ref. 33). They formulated suppositories with two neutral triglyceride mixtures as the bases, i.e., Witepsol H15 with a melting range of 33.5° to 35.5° C and Witepsol E75 with a melting range of 37° to 39° C. Male volunteers were administered 750 mg and 1,000 mg aspirin in these formulations in two studies to investigate the absorption of aspirin from the suppositories. In another study, the investigators administered the two aspirin suppository formulations on the first 2 days of the week for 3 consecutive weeks. A dose of two suppositories daily, 8 hours apart, was administered. There was a difference in the rate of absorption of aspirin from the two bases. It was found that a rapid absorption was associated with a high incidence of side effects. Reducing the rate of absorption by changing the suppository base, reduced the intensity and frequency of the side effects. The side effects consisted of burning pain, blood in the feces, diarrhea and tenesmus. The authors point out that with the use of bases giving reduced absorption and reduced side effects, however, the amount of drug absorbed from suppositories "will be highly dependent on the length of time the patient retains the suppository."

(3) *Stomach mucosal damage.* Aspirin has a direct damaging effect on mucosal tissue which is not dependent on the presence of hydrogen ion, bile or other cellular irritants associated with peptic ulcer (Ref. 6). Prolonged contact with aspirin particles or concentrated solution produces lesions in the mucosa of the mouth, stomach, rectum and probably most other mucosal tissue (Refs. 6 and 28). Aspirin tablets placed directly on the gastric mucosa of anesthetized cats initially produced coagulation of mucus and opacification of the adjacent mucosa, similar to the appearance of the buccal (mouth) tissue exposed to aspirin (Ref. 6). These changes were attributed to coagulation of the mucous layer and desquamation (Ref. 8). Multiple small acute lesions showed focal necrosis with underlying secondary capillary damage. The direct mucosal desquamation and focal necrosis produced by aspirin has been observed in man by gastroscopic observations (Refs. 23, 24 and 34), during surgery (Refs. 1, 2, and 6).

The mucous opacity noted after aspirin irritation is related to epithelial exfoliation. Cellular exfoliation can be measured by increased DNA content in the gastric fluids since DNA is found only in cells and therefore reflects sloughed or damaged mucosal cells (Ref. 8). Accumulation of DNA in gastric fluid occurred in about 10 minutes in 9 of 12 subjects receiving aspirin (Ref. 8) which is similar to the percent of subjects showing direct irritation to aspirin in the gastroscopic studies of Douthwaite and Lintott (Ref. 23).

The direct observations by gastroscope of the effects of aspirin on the gastric mucosa by Douthwaite and Lintott in 1938 have provided basic principles which have been substantiated by many investigators during the past 30 years. Specifically, gastroscopic observations of 16 hospital patients demonstrated the following: In 80 percent of the patients, a local inflammatory reaction of the gastric mucosa was observed ranging from slight hyperemia to submucous hemorrhage; and the occurrence and severity of the reaction was not a function of the brand of aspirin, the acidity of the stomach or the prior appearance or condition of the gastric mucosa. Patients with hyperchlorhydria (excessive acid secretion) had both positive and negative direct irritation responses. Responses were seen in patients with atrophic gastritis, hypochlorhydria (hydrochloric acid deficiency) and achlorhydria (absence of hydrochloric acid). Therefore, gastric acidity is not essential for initial direct irritation. Marked hyperemia with submucous hemorrhage (hemorrhagic erosive gastritis) occurred in 1 of the 16 patients. Salicylic acid also caused direct gastric irritation but was less severe. Contact with 20 percent alcohol for 10 minutes did not have a direct effect on the gastric mucosa.

The initial effects of aspirin, such as mucous destruction, epithelial desquamation, and focal mucosal necrosis takes the appearance of small well-demarcated erosions. This phase is not related to vascular damage or bleeding. It is apparently not dependent on the presence of gastric acid. Progression to visible hemorrhage may be dependent on local effects of gastric acid according to Davenport (Refs. 35 and 36) and/or possibly systemic effects (Ref. 6).

Roth found that phenacetin and acetaminophen have no direct irritating effect on the gastric mucosa (Ref. 6). However, phenacetin is claimed (but not proven) to slightly increase occult bleeding (Ref. 37), perhaps indicating that the two events are not necessarily related.

(c) *Acid-mediated erosive gastritis.* In the stomach, the direct effect of aspirin or salicylic acid after being absorbed into the mucosal cell renders the cell more permeable to the hydrogen ions of the gastric acid (Refs. 35, 36, and 38 through 43). Absorption of aspirin or salicylic acid into the mucosal cell causes increased permeability via breakdown of the cell barrier, which normally protects the stomach lining from its own acid secretions. Excessive backflux of hydrogen ion into the cell further damages the cell, causing erosion (acute erosive gastritis). Excess hydrogen ions can also pass into the space just below the surface cell (lamina propria), which contains an extensive network of capillary blood vessels. Hydrogen ions can initiate capillary damage and subsequently, minor bleeding occurs into the lumen of the stomach (Refs. 35 through 41, 44, and 45). This mechanism, referred to as the hydrogen ion mediated effect or the Davenport mechanism has been extensively studied in animals (Refs. 35 through 41, 44, and 45). Many investigators believe that it is a major factor involved in the focal erosion and minor bleeding into the stomach (occult bleeding). This mechanism may contribute in some cases to gastritis and major gastrointestinal bleeding (Refs. 44 and 46).

There are some authors who believe that all gastrointestinal effects of aspirin from occult bleeding to hemorrhagic erosive gastritis to major gastrointestinal hemorrhage are all related to this single mechanism involving the back diffusion of acid (Ref. 46). As a corollary, it has been proposed that any preparation which neutralizes gastric acid during absorption will obviate the danger of severe gastrointestinal damage and massive bleeding (Ref. 47).

The Panel concludes that the acid-mediated gastric erosion induced by aspirin is undoubtedly an important factor in some adverse effects of aspirin on the gastrointestinal tract. It is probably associated with increased occult bleeding following single and multiple doses of aspirin. It may contribute at least in the beginning stages of aspirin-induced gastric ulcer caused by chronic doses of aspirin (Ref. 48). It is also probably a factor in hemorrhagic erosive gastritis directly initiated by multiple doses of aspirin. In this case it may initiate major bleeding. However, as will be noted in subsequent sections, there are other factors which can initiate hemorrhagic erosive gastritis and aspirin has other effects independent of gastric acid which may be of equal or greater significance in contributing to massive gastrointestinal bleeding.

(d) *Other mechanisms of aspirin damage.* The Panel agrees that there is very good evidence in both animals and man that the Davenport mechanism is one important effect of aspirin. However, to conclude that this mechanism is the only effect of aspirin on the gastrointestinal tract and thus the only basis

for aspirin's role in initiating, exacerbating, potentiating or facilitating gastrointestinal pathologies is not consistent with current experimental data and clinical studies.

(1) *Additional factors in the Davenport mechanism.* According to the Davenport theory, the absorption of unionized aspirin or salicylic acid into the cell carries hydrogen ion across the barrier into the cell or interstitial spaces where the pH is higher, where aspirin or salicylic acid are ionized and the hydrogen ion is dissociated. Hydrogen ion is thought to cause the release of vasoactive substances such as histamine, from mast cells, in the lamina propria, which initiates capillary bleeding. If the hydrogen ion flux associated with transport of the acids were the only factor, one would expect salicylic acid to cause greater occult bleeding than aspirin since it is more rapidly absorbed. Leonards and Levy (Ref. 49) have shown that salicylic acid (sodium salt) is more rapidly absorbed than aspirin in man, but it produces significantly less occult bleeding. Mean occult blood loss in 13 subjects was 6.3 ml, 1.9 ml, 1.2 ml and 0.7 ml for aspirin, salicylic acid, salicylic acid with buffer, and control respectively.

An explanation for the differences between aspirin and salicylic acid is that the direct cellular effects of aspirin and salicylic acid interfere at different concentrations with biochemical cellular process (Ref. 50) which affect the hydrogen ion barrier. Lower concentrations of aspirin are needed to initiate cellular dysfunction. Indeed the cellular effects of these agents are consistent with the direct mucosal effects seen in nonacid mucosal cells (mouth).

However, this would not explain why several anti-inflammatory agents cause gastric erosions and massive gastric bleeding but do not affect the hydrogen ion barrier and vice versa.

(2) *Relationship between aspirin damage and bleeding.* Studies using the gastric potential difference which is the most sensitive way to measure changes in the hydrogen ion barrier in man show that phenylbutazone and indomethacin in usual doses do not damage the hydrogen ion barrier (Ref. 51). However, they both produce major gastrointestinal bleeding and gastric ulcer (Refs. 51 and 52). These agents do not generally increase occult bleeding (Refs. 53 and 54) indicating the occult bleeding may involve the Davenport mechanism but not massive bleeding.

Conversely, some agents may affect gastric potential but do not cause bleeding. Indeed this was recognized by Davenport (Ref. 40) who raised the question "why does bleeding occur during back diffusion following salicylate injury and not during comparable diffusion after many other forms of injury." Bile can cause changes in the barrier at neutral pH which is said to be augmented by the effect of aspirin (Refs. 40 and 55). Some discrepancies can be resolved by considering additional direct and indirect effects of aspirin and other agents on mucosal blood flow.

(3) *Vascular effects.* In contrast to the Davenport mechanism which assumes the initial effect of aspirin is on the mucosal cell mediated through hydrogen ion possibly by causing release of histamine with secondary vascular involvement, there is evidence that in some types of hemorrhagic erosive gastritis the reverse occurs where the initial effect is on the mucosal vasculature.

Weiss et al. (Ref. 10) state that the primary local effect is direct vascular injury of the capillaries in the lamina propria followed by capillary hemorrhage and hypoxia (deprivation of oxygen) which produces necrobiosis of the neck cells and exfoliation of the gland.

It is now believed that some types of hemorrhagic erosive gastritis are caused by factors which directly initiate histamine release from the mast cells in the lamina propria as opposed to the hydrogen ion mediated release in the Davenport theory (Ref. 39). These factors may be involved in "stress ulcers", and atrophic gastritis. Thus regardless of the initial mechanism, whether hydrogen ion or stress, the common denominator is initiation of hitamine release from the mast cells in the mucosal capillary region and initial vascular damage or reshunting of blood flow leading to hypoxia and a secondary cellular effect (Ref. 40).

Local capillary blood flow can apparently be affected by many diverse factofs. The mechanism by which vagotomy decreases gastric bleeding may not be a result of decreased gastric acid as commonly stated but reshunting of mucosal blood from the capillaries. Nylander and Olerud (Ref. 56) reported that blood was reshunted from the mucosal capillaries through the direct arteriovenous shunts in the submucosa after vagotomy.

(e) *Occult bleeding.* Occult (unseen) bleeding is a common predictable occurrence related to normal aspirin ingestion. The average person (70 percent of the population) taking one or two tablets of aspirin 3 or 4 times daily will lose from 2 to 5 ml of blood per day into the stools due to the direct effect of aspirin on the gastric mucosa (mucous membrane of the stomach). Some individuals, about 10 percent of the population, may lose as much as 10 ml daily (Ref. 57). Occult blood loss is not decreased by food although aspirin dyspepsia is (Ref. 58).

This minor occult bleeding is not, usually, clinically significant except in those individuals taking aspirin for long periods of time who are anemia-prone or have bleeding tendencies (Refs. 49, 59, and 60).

The Panel has discussed the association of aspirin with iron deficient anemia elsewhere in this document. (See part III. paragraph B.1.a. (2)(ix) below—Adverse effects resulting in iron deficient anemia.)

The mechanisms involved in occult bleeding have been extensively studied in animals (Ref. 26) and to a lesser extent in man (Ref. 61). There is general agreement among most authorities that the primary mechanisms involve first, absorption of aspirin into the cell, followed by the direct effects of aspirin on cellular metabolism and the integrity of the mucous membrane which initiates the subsequent indirect effects of gastric acid through the Davenport mechanism. By interfering with the integrity of the mucous membrane, aspirin increases the permeability of the membrane to the hydrogen ion which either further damages the cell or passes into the underlying space (lamina propria) containing the extensive capillary beds. Hydrogen ion either directly or indirectly through histamine causes capillary damage and small amounts of blood are lost into the lumen of the stomach.

The exact mechanisms involved in occult bleeding are not completely understood, however. Although gastric acid is known to be an important variable, it apparently is not essential since increased occult blood loss following aspirin is small but still greater than control values even in patients with a complete absence of gastric acid (achlorhydria) (Ref. 22).

In some studies there was no correlation between the number of erosions observed and the amount of occult bleeding (Refs. 42 and 62). In fact, carefully done studies (Ref. 62) show that visible erosions are not necessary in order to have increased occult bleeding. This may mean that the effect of aspirin to increase membrane permeability to hydrogen ion may require a lower concentration or require less exposure to aspirin than is needed to produce direct cellular damage and exfoliation. It may also indicate that multiple effects are involved.

Occult bleeding can be readily measured by well-known techniques used for the detection of blood in the feces, such as the use of radioactively-tagged red blood cells (Ref. 57). Therefore, there are many studies and reliable data available on the relationships between occult stomach bleeding and different types and formulations of analgesics (Ref. 58).

There is good evidence that the addition of sufficient buffering to decrease gastric acidity and increase the pH of the gastric contents will significantly reduce, but not necessarily eliminate, occult bleeding. However, highly buffered aspirin preparations will increase occult bleeding in normal subjects if given as multiple doses for 2 to 3 days (Ref. 63). In a few susceptible individuals who are otherwise apparently normal any aspirin preparation including highly buffered aspirin solutions, will greatly increase occult bleeding (Ref. 63).

While these individuals with unusual susceptibilities may provide some insight into the factors related to clinically important massive upper gastrointestinal bleeding, the average occult bleeding following aspirin ingestion in normal individuals or in individuals with peptic ulcer apparently has no relationship to massive bleeding (Refs. 6 and 9).

There appears to be no difference between the average increase in occult bleeding in normal individuals and major bleeders. Correlations between occult bleeding and massive bleeding have

never been shown. Occult bleeding and massive gastrointestinal hemorrhage should be considered as two distinct clinical entities (Refs. 7 and 8). The failure to recognize this difference has been stated to be responsible for much of the confusion in the literature (Ref. 8). Occult bleeding is a predictable occurrence in most normal people. Massive bleeding is relatively rare and unpredictable.

Persons with active peptic ulcer (Refs. 7 and 8) or persons who have recently experienced a massive gastrointestinal hemorrhage (Refs. 7 and 10) do not show greater occult bleeding after small doses of aspirin than normal subjects. These subjects, however, do have a greater propensity for recurrence of massive bleeding (Refs. 7 and 10).

Watson and Pierson (Ref. 64) in 1961 showed that occult bleeding was not greater in persons taking anticoagulants even though prothrombin activity was greatly reduced. Massive bleeding, however, has been associated with hypoprothrombinemia resulting from high doses of aspirin. (See part III, paragraph B.1.a.(2)(i)(*a*) above—Decrease in prothrombin production.) The amount of occult blood loss is less in individuals who have atrophic gastritis (Refs. 8, 61, and 65), and it occurs less frequently than in normals, presumably because these patients have decreased gastric acid. But, patients with atrophic gastritis are often involved in aspirin-induced massive bleeding and are at much greater risk of bleeding following aspirin than the normal population (Refs. 61 and 65).

The Panel concludes that occult bleeding resulting from aspirin ingestion appears to have very little correlative or predictive value in the diagnosis or study of the major clinically important gastrointestinal effects produced by aspirin such as ulceration and massive bleeding.

(*f*) *Gastric ulcers.* The Panel concludes that chronic use of aspirin may directly cause gastric ulcers (Refs. 16 through 19 and 66 through 86). Several types of studies show that chronic aspirin use significantly increases the incidence of gastric ulcers but not duodenal ulcers (Refs. 80, 81, and 82). Chronic use of aspirin is associated with an increased incidence of uncomplicated nonbleeding ulcers, bleeding from ulcers and perforated gastric ulcers (Refs. 18, 86, and 87). Epigastric pain is common in all of these cases. Continued use of aspirin can delay ulcer healing even though ulcer therapy is started (Ref. 18). Discontinuation of aspirin leads to rapid recovery (Refs. 3 and 18). Readministration of aspirin can reactivate gastric ulcer (Ref. 17).

Acute use of aspirin may activate symptoms of both gastric and duodenal ulcers. The symptoms and signs include both epigastric pain and massive gastrointestinal hemorrhage.

The role of acute aspirin use in the exacerbation of existing peptic ulcers has been noted by several authors over the past twenty years (Refs. 16 through 19 and 66 through 86). Evidence that chronic use of aspirin will increase the incidence of gastric ulcers has not been widely appreciated. In the opinion of the Panel a causal role of chronic aspirin use and increased incidence of peptic ulcer is supported by several types of evidence. These include the demonstration that aspirin causes ulcers in animal models; direct observation of isolated cases in man; several recent well-controlled studies (in which disease-induced analgesic ingestion biases were eliminated); demonstration of increased gastric ulcer incidence in a population in which increased chronic use occurred due to abuse; evidence that characteristics of the lesion are different in aspirin users than nonaspirin users; and evidence that the site of the ulcer lesion can be affected by the dosage form used.

The Boston series (Ref. 84) conservatively estimated that 10 out of every 100,000 aspirin users would develop a nonbleeding gastric ulcer requiring hospital admission. This study estimated that one-eighth of all gastric ulcers were related to aspirin and Cameron found one-third of all new non-bleeding gastric ulcers are caused by chronic aspirin ingestion (Ref. 19).

Jorgensen and Gyntelberg (Ref. 88) determined the life incidence of peptic ulcer to be 9.2 percent in a sample of 5,249 men aged 40 to 59 in Copenhagen which is similar to the incidence reported in the U.S. In a one year followup study on 4,753 males the year incidence of peptic ulcer was 1.2 percent. Only 15 percent of these were new (previously diagnosed) ulcer cases and only 24 percent were hospitalized. Thus hospitalized new ulcer cases during the year accounted for only about 3.6 percent (15 percent $\times$0.24) of total cases for the year.

Thirty percent of subjects ingested aspirin regularly compared to 16 percent of controls (p is less than 0.02). In only one of these subjects was aspirin taken for ulcer symptoms.

It can be estimated that 16 percent of the ulcer cases were associated with aspirin which is equivalent to a 19 percent annual incidence rate (19 per 1,000) for men between 50 and 59. However, only 3.6 percent of these (15 percent$\times$0.24) would represent hospitalized new cases. Thus if only hospitalized new cases were used to calculate possible annual cases of aspirin-induced ulcer in 50 to 59-year-old men, one would conclude that the annual incidence associated 0.68 cases per 1,000 or 68 per 100,000 total population in the age group 50 to 59. This is similar to the estimate given by Levy of 10 per 100,000 of all adults taking aspirin since the incidence in women and younger adults would be lower. Thus the total incidence of aspirin related gastric ulcer may be higher than generally assumed.

There appears to be almost universal agreement that aspirin should not be used in persons with peptic ulcer, particularly those with gastric ulcers. Cameron (Ref. 89) states, "* * * the evidence presented suggests that patients with gastric ulcer should be urged to avoid aspirin." Similar warnings have been urged by Roth (Ref. 6), Brown and Mitchell (Ref. 86), Schneider (Ref. 24), Muir and Cossar (Refs. 2 and 3) and Weiss (Ref. 10).

Acute use of aspirin can precipitate massive hemorrhage in gastric and duodenal ulcer patients. The mortality of massive bleeding in peptic ulcer patients is about 8 to 10 percent (Refs. 67 through 70).

The Panel believes that initiation or exacerbation of stomach ulcers, stomach irritation and intestinal inflammation occurs in a significant number of individuals who take aspirin. Particularly at risk are those with a history or symptoms of gastrointestinal problems. Accordingly, a warning should state that individuals who have a history of ulcer, intestinal bleeding and stomach distress should not take aspirin without first consulting a physician.

Peptic ulcer has been estimated to occur in 5 to 10 percent of the general population at one time or another (Ref. 67). In 1967 it was estimated that 3.5 million individuals suffered from gastric ulcer (Ref. 70). Less than 0.5 percent of ulcer patients are hospitalized annually, involving hemorrhage in about 25 to 30 percent of these admissions (Refs. 67 and 68). Duodenal ulcer is about eight to ten times more frequent than gastric ulcer but the annual incidence of new cases per 1,000 adult male population at risk is 3.7 for duodenal ulcers and 1.4 for gastric ulcers. Gastric ulcers occur twice as frequently in men as in women (Ref. 69).

The direct ulcerogenic effect of long term aspirin use and massive bleeding following short term use are not necessarily related to the same factors. Gastric ulcers related to prolonged use of aspirin do not necessarily result in massive bleeding even though aspirin is frequently ingested by these patients (Ref. 15). Furthermore, aspirin is associated with massive bleeding in patients with duodenal ulcers but there is no evidence that aspirin produces duodenal ulcers (Ref. 84).

Kiser (Ref. 18) commented that the role of aspirin in the production of gastric ulcers has been underestimated because most studies have not dealt with the effects of prolonged aspirin ingestion with the exception of the studies by Douglas and Johnson (Ref. 74) and Muir and Cossar (Refs. 2 and 3).

Cameron (Ref. 19) points out that the protocol for a large Veterans Administration cooperative study on gastric ulcer published in 1971 excluded patients taking ulcerogenic compounds such as corticosteroids and phenylbutazone but did not mention aspirin. Patients and physicians in Cameron's study seldom associated aspirin with their ulcers.

(*i*) *Evidence for a causal role in gastric ulcer.* (*i*) *Direct observation in animals and man.* The properties of aspirin that produce direct erosive effects have been discussed earlier relative to acute erosions. Large acute erosions have been observed directly after drug intake in several instances (Ref. 3). Chronic administration of aspirin to animals consistently produces gastric ulcers (Refs. 18 and 66).

(*ii*) *Increased incidence of ulcer in analgesic abuse.* The unusually high incidence of analgesic use in Australia,

particularly in women, provides evidence for a causal relationship between aspirin, usually in combination, and chronic peptic ulcer. This population is significant from an epidemiologic point of view not only because of the very high prevalence of chronic, daily aspirin use but also the significantly greater incidence of daily use by women compared to men, first noted by Billington in 1960 (Refs. 71 and 72). The increased use of analgesics by women who take analgesic compounds is clearly for other than gastro-intestinal symptoms. If increased chronic use of aspirin does result in a higher incidence of gastric ulcer, then this effect should be clearly evident in the Australian population. A correlation between increased analgesic use and increased incidence of ulcer was shown by Douglas and Johnson (Ref. 74) and confirmed by several others (Refs. 16, 17, 19, 76, 77, and 78). It is possible that phenacetin, an ingredient in almost all abused analgesic combinations, contributes to ulcer production. However, phenacetin alone does not have a direct damaging effect on the gastric mucosa (Ref. 6). Furthermore, ulcers are rare in patients taking phenacetin compounds not containing aspirin even though kidney disease continues to develop (Ref. 73).

It is possible, however, that the combined effect of phenacetin and aspirin may be greater than aspirin alone for the same reasons discussed later in the section on the effects of aspirin on the kidney. (See part III. paragraph B.1.a. (2) (vi)—Adverse effects on the kidney.)

Douglas and Johnson of Australia (Ref. 74) reported that 90 percent of 78 chronic gastric ulcer patients took a proprietary compound containing aspirin, phenacetin and caffeine. Most patients were chronic headache sufferers with pain predating the ulcer and were daily users of analgesic compounds containing aspirin. Compounds with phenacetin (or salicylamide) and caffeine were preferred by over 50 percent of this group. The usual reasons for use given by chronic users were chronic headache (41 percent), nerves and tension (31 percent), arthritis (21 percent), and indigestion (7 percent).

Gillies and Skyring (Ref. 77) in an interview study found a statistically significant association between chronic use of high doses of aspirin and the incidence of gastric ulcer. Fifty-seven percent of patients with active gastric ulcer had taken aspirin daily compared to 22 percent of controls. In earlier case-control studies, Gillies and Skyring (Ref. 77) found a significant correlation between high intake of aspirin and gastric ulcer but not intestinal ulcer.

Duggan and Chapman (Refs. 81 and 82) found a correlation between the incidence of gastric ulcer in women and the consumption of large amounts of aspirin, mainly as APC powders taken for headache. No such correlation for duodenal ulcer in either sex or gastric ulcer in males was found. Duggan (Ref. 82) followed all patients with acute perforated peptic ulcer in an Australian hospital over a 4-year period. The proportion of women in this series was very high (24 percent) compared to the usually very low incidence of gastric ulcer in women in British literature. The association between the use of high doses of aspirin over prolonged periods and the incidence of gastric ulcer was highly significant statistically particularly for the women. In men, 28 percent had a heavy intake of aspirin and 45 percent of ulcer patients took no aspirin. In the women, 62.5 percent had a heavy intake and only 25 percent took no aspirin. The authors state that aspirin abuse is the environmental factor responsible for the excess of gastric ulcer in middle-aged Australian women.

In a further study, Duggan (Ref. 90) analyzed the prognostic factors of 1,634 patients with acute gastrointestinal hemorrhage and found 66 percent of the cases had chronic ulcer and 25 percent involved an acute lesion. The total mortality was 11 percent. There was a statistically significant association between gastric ulcer and the incidence of chronic aspirin use. These patients had the worst prognosis. However, the reason for the poor prognosis probably reflects habituation of the individuals to the APC powder which was the usual compound taken by women in Australia. In other series, aspirin-induced gastric ulcers healed rapidly with a good prognosis when aspirin was withdrawn (Ref. 15). In the Duggan study the overall mortality for all forms of major gastrointestinal hemorrhage was 11 percent. The mortality of peptic ulcer patients who had gastrointestinal hemorrhage was 8.5 percent and was not related to whether or not the patients took aspirin.

(iii) Case-control studies with controlled drug intake. There have been three case-control studies in gastric ulcer patients that have been designed to avoid bias due to analgesic drug intake related to gastrointestinal pain.

Cameron (Ref. 19) in a prospective study with matched controls found that chronic aspirin use (15 tablets per week for 1 month or more) was associated with gastric ulcer in 53 percent of 61 patients compared to 10 percent of controls. When patients who took aspirin for their symptoms of ulcer were excluded, 45 percent of 40 ulcer patients took aspirin. The difference between ulcer cases and control subjects was highly significant statistically. When the same correction was applied to duodenal ulcer patients only 16 percent of the remaining 25 duodenal ulcer patients were regular aspirin users which was not statistically different (p is greater than 0.1) from controls.

(iv) Characteristics of aspirin-related gastric ulcer lesions. Aspirin-related gastric ulcer patients have lesions which are generally of the same shape, size and appearance as in nonaspirin ulcer patients. However, the location and distribution of aspirin-induced lesions in the stomach and the condition of the surrounding mucosa appear to be different. Interestingly, the distribution of aspirin lesions is apparently a function of the dosage form as well as the drug.

McDonald (Ref. 91) found that aspirin-related ulcers occurred most frequently on the greater curvature of the antrum. He claimed that only the aspirin-related ulcers were found in this region and were surrounded by normal pyloric gland mucosa. In the Minnesota series of Cameron (Ref. 19), the ulcer was within 1 inch of the pyloric sphincter in 65 percent of patients with gastric ulcer associated with heavy aspirin use, as compared to 21 percent of gastric ulcer patients taking no aspirin (p is less than 0.05). Cameron (Ref. 89) in 1975 noted that 90 percent of the ulcers related to regular aspirin use (15 tablets weekly or more) were in the antral region compared to 50 percent of the ulcers in patients who took less than 15 aspirin tablets per week (occasional and nonusers).

In some parts of Australia, however, where powders rather than tablets are almost exclusively used, aspirin-related ulcers are not located in the antral region and, indeed, Gilles and Skyring (Ref. 78) excluded all antral ulcers from their study. The differences in the peristaltic movement of tablets and powders are considered the reason for the differences in the location of lesions in studies in these two countries (Ref. 19). Other differences have been noted in the patients. The aspirin-related ulcer patient was younger (57.9 years compared to 66.4 years) and included fewer females (53 percent compared to 71 percent) than the nonaspirin ulcer patient. Smoking did not appear to be more frequent than in controls in these aspirin-related ulcer patients in contrast to the nonaspirin related ulcer patients who appeared to have a greater incidence of smoking compared to matched controls.

(v) Acute exacerbation of ulcers. Kiser (Ref. 18) described the effects of continued aspirin administration on five chronic gastric ulcer patients. Two had mild anemia with no overt bleeding. Delayed healing occurred with continued aspirin use. All healed well when aspirin was discontinued. Reoccurrence was observed when aspirin use was reinstated.

Alp et al. (Ref. 17) stated that the ulcer patients who continue to smoke, drink and take aspirin have a much higher incidence, 87 percent compared to 49 percent, (about a two-fold increase) of reactivation of ulcers. Exacerbation or recurrence of ulcer symptoms following aspirin ingestion was demonstrated by Muir and Cossar (Ref. 3) for 14 of 34 gastric ulcer patients who recalled taking aspirin within 24 hours of their symptoms.

Several other authors have shown that activation of ulcers occurs shortly after acute aspirin ingestion (Refs. 12 and 13).

(g) Massive gastrointestinal bleeding. By far the most serious adverse effect of the action of aspirin on the gastrointestinal tract is massive upper gastrointestinal bleeding, which can be life-threatening (Ref. 87), often requiring surgical intervention and which also has a high mortality risk (Ref. 87). The mechanisms and factors involved in massive gastrointestinal bleeding are not completely understood. It is a relatively rare event which in most cases does not ap-

pear to be predictable relative to the dose or frequency of use of aspirin.

Although the incidence of massive bleeding is low, relative to the frequency of aspirin use, the total occurrence is not insignificant. Three different recent reports from the Boston Collaborative Surveillance program and incidence figures supplied by other groups indicate that the number and severity of adverse effects on the gastrointestinal tract produced by aspirin are quite significant (Refs. 28, 92, and 93).

In a recent survey, aspirin was the second most frequent drug involved in adverse effects that were serious enough to require hospitalization. Two out of every 1,000 hospital admissions were attributed to aspirin. Massive bleeding was second only to digitalis intoxication as the most frequent cause of drug-induced hospital admission, and aspirin products were involved in over 60 percent of the cases (Ref. 92). Of greater significance is the fact that the mortality rate associated with this condition is high (Ref. 92). Death occurs in 4 to 10 percent of all patients with gastrointestinal bleeding including those associated with aspirin ingestion (Refs. 15 and 16). Even greater mortality rates are involved in those patients requiring surgery to stop bleeding (Ref. 87).

Miller (Ref. 93) also compared the incidence of adverse reactions in 1,615 hospitalized patients receiving usual doses (300 to 600 mg aspirin in 70 percent of patients). The incidence of gastric distress such as heartburn, indigestion, nausea, vomiting was only 1.9 percent. The incidence of gastrointestinal bleeding, including hematemesis and epistaxis, was 0.7 percent (12 per 1,615) of all patients receiving aspirin (7 per 1,000).

A third report by Levy (Ref. 84) estimated the frequency of major gastrointestinal hemorrhage that was unrelated to any known predisposing factors such as ulcers, gastritis. The incidence of massive bleeding in regular "heavy" aspirin users was estimated at 25 per 100,000 (0.25 per 1,000).

The very low figure in the third study is undoubtedly an underestimate due to the design of the study, which is discussed below.

Numerous clinical studies have indicated that from 30 to 80 percent of all persons (Refs. 4, 22, 85 through 87, and 94 through 101) entering the hospital for massive gastrointestinal bleeding have taken aspirin within the past 24 to 72 hours. Recent epidemiological studies conclusively show that acute use of aspirin is causally related to massive bleeding (Refs. 84 and 95). The Panel believes that aspirin can potentiate bleeding in patients having a variety of gastrointestinal lesions including acute erosive gastritis (Refs. 15 and 102), chronic atrophic gastritis, stress ulcer, gastric ulcer (Refs. 19, 79, 82, and 84), duodenal ulcer (Ref. 84) and duodenitis (Ref. 69).

There are now convincing studies which indicate that aspirin is a definite factor associated with increased incidence of severe gastrointestinal hemorrhage in susceptible individuals. Therefore, the Panel concludes that the labeling should include the warning, "*Caution:* Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

(*i*) *Evidence for aspirin-causation in major bleeding.* Important criteria in establishing a causal relationship between a drug and disease are satisfied when a particular type of lesion associated with the drug can be identified; when a mechanism involving the drug can be established, consistent with all data, or by identification of a particular high risk group.

The possibility of comparing the incidence of aspirin use and the incidence of bleeding from different types of lesions is dependent upon the diagnostic procedures used such as x-ray, laparotomy, gastroscopy and histological examination of biopsies. Radiological (x-ray) methods detect chronic ulcers but not erosions or acute (superficial) ulcer. Detection of erosive gastritis requires gastroscopic examination or, occasionally, observation during surgery. More recently it has been established that acute hemorrhagic gastritis associated with aspirin may be one of several types (incomplete gastritis, atrophic, hyperfunctional etc.) which can only be established if biopsies of mucosa are examined microscopically. Even histological studies involving single biopsies may miss some types of lesions.

(*i*) *Direct observation of bleeding in subjects.* Hemorrhagic erosive gastritis has been directly observed during aspirin studies designed to test other responses. In a few cases, bleeding was severe enough to require surgery. Bleeding erosions containing fragments of aspirin tablets have been reported (Ref. 6). A representative case was described by Roth (Ref. 6) who described an example illustrative of massive hemorrhage secondary to the gastric erosion after acute use of aspirin. Surgical intervention was necessary and revealed two 1-cm round lesions (the size of the tablets). The appearance of the lesions resembled acute focal hemorrhagic gastritis including desquamation of surface epithelium and capillary breakdown in the focal area.

The authors state that there could be no doubt about the causative relation of aspirin to the punched out bleeding erosions but questioned the persistent bleeding from two small erosions involving only capillary breakdown. They concluded that occasional massive bleeding probably requires the local effect to initiate the bleeding but also some undefined effect such as hypersensitivity or a capillary or coagulation defect.

Several other authors have observed mucosal erosions and hemorrhage associated with aspirin particles by gastroscopic examination (Ref. 23) and during surgery (Ref. 3).

(*ii*) *Correlation of individual bleeding response with variable drug intake.* Individual cases showing reversible susceptibility to bleeding when aspirin is increased or withdrawn are given by Weiss (Ref. 10), Hurst (1 case) (Ref. 34), Kelly (3 cases) (Ref. 85), Waterson (Ref. 103) and Brown and Mitchell (Ref. 86).

(*iii*) *Case-control clinical studies.* In the opinion of the Panel, there is sufficient evidence from experimental and clinical studies involving different experimental designs to warrant the conclusion that aspirin ingestion is a contributory factor in increased incidence of major gastrointestinal hemorrhage.

Most clinical evidence involves retrospective case-control studies comparing the incidence of aspirin use in cases compared to a variety of control populations (Refs. 4, 19, 22, 84 through 87, 90, 92, and 94 through 101).

Because aspirin is frequently taken by patients for symptoms of their gastrointestinal disease, it is particularly critical to evaluate this potential bias in all studies showing an increased incidence of aspirin use associated with a particular disease condition. There are several studies, however, in which the available information clearly shows that the drug was not taken for symptoms related to the disease condition and the control group was matched for all important variables except bleeding (Refs. 2, 22, 84, and 95).

Because gastric distress is such a common component of gastrointestinal disease, in some studies all cases of acute upper gastrointestinal hemorrhage in individuals with a known history of gastrointestinal disease, were excluded as possible cases involving aspirin as a causal gastric pain associated with peptic ulcer or contributory factor (Refs. 2 and 84). These studies do not consider the important possibility that aspirin taken either for unrelated reasons or for the chronic gastric pain associated with peptic ulcer or gastritis will initiate bleeding from existing lesions.

(*iv*) *Case-control studies eliminating bias due to drug use for gastrointestinal symptoms.* Langman (Ref. 104) has reviewed several of the case-control studies concluding that a clear association between aspirin and major gastrointestinal hemorrhage was evident but could not be shown to be a causal relationship. A causal relationship could not be shown because it could not be ruled out that aspirin may have been taken for symptoms of massive bleeding. The Panel believes that some of the criticisms of the control groups, made by Langman, were possibly appropriate but also some were arbitrary and not based on any substantive evidence known to the Panel. Furthermore, the fact that the percent of persons taking aspirin in the case group was greater than control in all of the different types of studies is important since it is highly unlikely that a systematic bias would be involved for all groups in all the studies (Refs. 4, 19, 22, 84 through 87, 90, 92, and 94 through 101).

The choice of Alvarez and Summerskill (Ref. 22) in using dyspeptic patients as controls was criticized by Langman (Ref. 104) because these patients may have been warned by their physicians not to take aspirin. In the Panel's opinion this criticism is not valid because the patients

were carefully matched and the "case" group is just as likely to have dyspepsia and be warned by their physician; and dyspeptic patients are probably the best possible control group to assure that the control group would have the same likelihood of taking the drug for symptoms as the case group.

A well-controlled study by Needham et al. (Ref. 95) was designed to meet the criteria described by Langman. They found a definite association between short-term use of aspirin (within 72 hours of hospital admission) and massive upper gastrointestinal bleeding.

A second study also carefully ruled out bias from aspirin being taken for symptoms, a retrospective case-control study of 16,468 patients carried out by the Boston Collaborative Drug Surveillance Program found an association of "heavy" aspirin use (used for 4 or more times a week for 12 weeks) with nonbleeding stomach ulcer and major upper gastrointestinal bleeding in the absence of known predisposing conditions (Ref. 86).

In the Boston study it was estimated that the incidence rate of hospital admissions for major upper gastrointestinal bleeding in individuals without known predisposing conditions, or evidence of intestinal ulcer, and not taking aspirin, to be 11 to 13 per 100,000 per year. The incidence rate in heavy aspirin users was twice as high, being about 28 per 100,000 per year. The yearly incidence rate of new cases of nonbleeding stomach ulcers in individuals not taking aspirin is 3 per 100,000 per year. In heavy aspirin users the rate is about four times higher, 13 per 100,00 per year. Both of these differences were statistically significant. Thus, the increase in admissions for new massive gastrointestinal bleeding, excluding intestinal ulcer, and stomach ulcers that might be attributed to heavy use of aspirin would be about 25 per 100,000 per year. The author concludes that these data are consistent with a causal relationship between regular "heavy" use of aspirin and major upper gastrointestinal bleeding and nonbleeding stomach ulcers. It should be noted that 15 percent of the total patients admitted to the hospitals used aspirin at least once a week for 3 months and 6.3 percent of the total took aspirin four or more times a week for 3 months.

The estimated involvenfent of aspirin is probably conservative in the Boston study since it involved only new cases. It unfortunately does not provide information on a critical point of concern to this Panel, i.e., the possible increased risk of aspirin use in patients with a history of bleeding or peptic ulcer. It also does not provide information regarding the possible role of aspirin effects on the blood clotting mechanism which might potentiate bleeding from existing intestinal ulcers since this group was excluded from the study. The authors state:

> It is worth emphasizing that this study provides no information on the relation of aspirin intake to upper gastrointestinal bleeding in patients who have predisposing conditions such as established chronic peptic ulcer disease. Evaluation of such cases, in a case-control study would be virtually impossible since there would be no satisfactory way to determine the influence of the disease itself on aspirin use.

The Levy study clearly underestimated the true incidence (Ref. 1). It did not study primed subjects. It only studied subjects with chonic use of aspirin. It therefore ignored the largest group. While this may be true in the cited study, other studies have provided controls to eliminate individuals who may have taken aspirin for the gastrointestinal symptom. Even this does not include those individuals who take aspirin for gastric distress which then precipitates bleeding from primed sites.

Of the total number of cases of peptic (stomach) ulcer (517) and upper gastrointestinal bleeding (467) only 242 cases were used in the study. 356 cases were excluded from the study because of a history of stomach ulcer or stomach surgery and an additional 78 cases were excluded because bleeding occurred after admission. Furthermore, this study did not examine the possible effect of one time or short term ingestion of aspirin on massive bleeding since only chronic use of aspirin (3 months) was studied. It is important to realize that while the study does prove that there is a causal relationship between chronic or heavy use that this study does not prove that only chronic use of aspirin will produce ulcer or gastric bleeding. The study was designed such that only chronic aspirin use was studied. Any individual who had taken aspirin less than 3 months was excluded. All other studies of gastric hemorrhage have examined only acute use of aspirin, usually only 24 to 72 hours prior to bleeding. The association between bleeding and "heavy regular" use (more than 3 times per week) may simply reflect the higher probability of aspirin being ingested during the period of gastric susceptibility even though only a few doses were actually necessary to potentiate the bleeding episode.

It is also of possible significance that the Boston Collaborative Drug Surveillance Study found no evidence of an association between aspirin ingestion and newly diagnosed cases of uncomplicated non-bleeding intestinal ulcer. In the study, 7.9 percent of 63 patients were heavy users of aspirin compared to 6.9 percent of controls. In the 43 patients with newly diagnosed duodenal ulcer who had major bleeding 11.6 percent were heavy aspirin users compared to 6.9 percent of controls which was not statistically significant.

However, this trend of an increased incidence of bleeding in duodenal ulcer patients taking aspirin was found to be statistically significant in the study of Needham et al. (Ref. 95). Chapman and Duggan (Ref. 79) in 1969 also found a relationship between chronic aspirin use and the ingestion of a combination product that contained aspirin, phenacetin and caffeine (APC), and the incidence of peptic ulcer but found no association between duodenal ulcer (intestinal ulcer) and analgesic consumption. Prepyloric ulcers (ulcers near the exit valve of the stomach) were found in an abnormally high incidence in aspirin users. The association of aspirin with ulcers was highly significant, supporting the concept that aspirin abuse is a cause of chronic peptic ulcer and is the environmental factor responsible for the excess of peptic ulcers in middle-aged women in eastern Australia (Ref. 89).

(2) *Difference between case and control in the frequency distribution of the time between aspirin ingestion and response.* Unfortunately the details of aspirin consumption in patients with major gastrointestinal bleeding has not been given in most studies. The carefully done prospective study of Alvarez and Summerskill (Ref. 22) does provide some useful information in this regard. These workers carefully noted the exact time and reason for aspirin ingestion in 103 consecutive patients in order to determine if the drug was taken as a result of the bleeding rather than being the precipitating factor. The control group of dyspeptic patients with no bleeding were matched for sex but not age. The differences in age, however, are small and insignificant relative to the study.

Two important conclusions can be drawn from their data. First, the difference in the time distribution provides additional support for aspirin as a causative factor in hemorrhage.

Second, the effect of aspirin in producing hemorrhage is acute. If one plots these data as the cumulative frequency of aspirin use, relative to total use, for bleeders and nonbleeders, it is clear that the probability of aspirin ingestion being associated with gastric bleeding declines exponentially with time. The majority of patients who bleed took aspirin within 1 day prior to bleeding.

(3) *Characteristics of lesions.* (i) *Bleeding in peptic ulcer patients.* Peptic ulcer patients do not show increased occult bleeding after aspirin (Refs. 8 and 9) but aspirin does increase the incidence of massive bleeding in both gastric and duodenal ulcer patients. Weiss (Ref. 10) states that patients with peptic ulcer are two times more likely to show gastrointestinal bleeding.

When bleeding occurs it often occurs from other sites rather than from the healed or active ulcer (Ref. 15) or bleeding may occur from the ulcer directly (Ref. 102).

Gastro-duodenal hemorrhage following the taking of aspirin is more often due to superimposed acute erosive gastritis than to bleeding from the actual ulcer (Ref. 2).

Several recent studies indicate that acute use of aspirin will increase bleeding in both the gastric and duodenal ulcer patient (Refs. 95, 104, and 105). Furthermore, recent studies establish that the gastrointestinal bleeding associated with aspirin is increased by alcohol consumption (Refs. 104 and 105). In these studies the increased effect of alcohol was often statistically demonstrated only in duodenal ulcer patients and not in the gastric ulcer subgroups of massive bleeding patients (Refs. 95 and 104). The fact that aspirin causes only gastric ulcer

but can potentiate bleeding from both gastric and duodenal ulcers suggests that different mechanisms are involved.

It should be noted that the chronic aspirin-related gastric ulcer is not necessarily a bleeding ulcer. Only 3 of the 61 gastric ulcer patients studied by Cameron had hematemesis or melena in the previous 6 months (Ref. 19). The occurrence of acute lesions associated with patients with chronic peptic ulcers is not necessarily dependent upon aspirin ingestion since they are also seen in patients who were not taking aspirin. Furthermore, the nature of the acute lesions depends upon the probable inciting factors such as stress or alcohol. However, the majority of bleeding associated with lesions in acute gastritis involves patients taking aspirin. It appears that aspirin can potentiate bleeding from acute lesions regardless of whether it initiates the lesion. These lesions are usually the type designated as erosive gastritis.

(ii) *Hemorrhagic erosive gastritis.* Hemorrhagic erosive gastritis is characterized by gastric mucosal hemorhage from small superficial discrete lesions. Unlike ulcers they do not penetrate beyond the muscular layer (muscularis mucosa) just below the lamina propria (Ref. 15). These lesions are too small to be seen by radiographic examination and are generally detected only by direct observation with a gastroscope during surgery. In studies in which gastroscopic examinations were not performed this lesion is probably included in the "cause unknown" category. Furthermore, these lesions may not be observed if gastroscopy is performed several days after bleeding as they frequently disappear rapidly (24 to 48 hours).

The incidence of gastric mucosal erosions and hemorrhage have been associated with a variety of diseases, including infections, following gastric and nongastric surgery and trauma (brain injury) (Ref. 15). Although the occurrence of hemorrhagic erosive gastritis has been associated with a variety of disease states, alcohol and aspirin alone or together are most frequently identified as the precipitating agents (Ref. 61).

Sugawa, Lucas and Walt (Ref. 105) followed 132 patients with acute erosive gastritis (84 after sepsis or trauma, 40 after alcohol intake and 8 after aspirin ingestion). They were studied by serial gastroscopy and photography using fiberoptic endoscopes. The color, size, shape and distribution of mucosal changes were recorded during early healing phases, and these changes were correlated with microscopic studies.

Mucosal changes in the trauma-sepsis group (stress "ulcer") with mainly black based erosions, were usually restricted to the parietal cell mucosa and were mainly on the greater curvature near the fundus.

Mucosal changes in the alcohol group were more evenly distributed throughout the stomach. It was found that 17 out of 40 patients had striking antral involvement. Red based erosions were the main lesion in this group. Aspirin erosions were more frequent in the body, but were seen throughout the stomach. An unusual number of patients developed superficial white based ulcerations after aspirin.

Dagradi et al. (Ref. 15) state that the appearance and distribution of lesions in hemorrhagic erosive gastritis are similar regardless of the nature of the inciting agent. They undergo the same course of healing and the clinical spectrum is identical.

There are some differences related to the inciting agent. These differences are exemplified by the series of 106 patients bleeding from hemorrhagic erosive gastritis. The bleeding in 90 percent of the cases was associated with the ingestion of aspirin and/or alcohol just before the bleeding. In 10 percent of the cases, no determinant could be established. In most cases, aspirin was taken acutely, 2 to 3 days prior to bleeding for pain unrelated to gastric condition. Gastric distress was frequently seen in the aspirin-related group and varied from 1 day to several weeks prior to bleeding. Gastric ulcers occurred in 33 percent of the aspirin group but only in 5 percent of the alcohol-related group. Active peptic ulcer was present in 50 percent of the aspirin-related group and only 4 percent of the alcohol group. However, the frequent gastric distress in the aspirin group was unrelated to the presence or absence of ulcers.

Katz and Siegel (Ref. 14) reported that bleeding from acute erosions outnumber acute ulcers as a source of bleeding by 7 to 1, respectively. They described the typical acute gastric lesion as having denudation of superficial epithelium sheared at the neck of the glands with variable hemorrhage in the capillary rich area of the neck. These authors propose that a variety of agents may cause hemorrhagic erosive gastritis through the same mechanism. A variety of inciting agents may cause release of histamine from the mast cells in the lamina propria. They state, "It seems probable that many pathways lead to degranulation of the histamine-laden mast cells in the area about the neck of glands and that capillary injury results whatever the initiating stimulus. Capillary permeability increases, leading to hemorrhage at the neck with tissue anoxia, amputation of superficial epithelium and gross hemorrhage following."

The importance of stress as a precipitating factor for erosive gastritis has been suggested by several authors (Refs. 14, 94, and 96).

The more recent studies of Gelzayd and Gelfand and Gelzayd, Gelfand, and Rinaldo (Refs. 106 and 107) show that aspirin and alcohol may often be involved in duodenitis (inflammation of the intestine) rather than duodenal (intestinal) ulcer. Thirty-two patients had a variable history of epigastric pain (mainly dyspeptic), nausea, vomiting, and hematemesis (passage of blood by vomiting) or melena (passage of blood through the stools). Only three of these people had had a duodenal ulcer. Hemorrhagic duodenitis (bleeding resulting from intestinal inflammation) was present in eight patients with anemia and severe enough in four patients to require transfusion.

These bleeding episodes involve sites of bleeding which would not be decreased by highly buffered aspirin in solution since the primed site is already existing. Thus, there is no rationale for using buffered or highly buffered aspirin for concurrent symptoms of headache and alcoholic gastritis. Indeed, the Panel believes it is contraindicated. The Panel has discussed the labeling of such products elsewhere in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

Those who contend that the systemic effect of aspirin is negligible relative to the association of aspirin to massive bleeding have usually made the assumption that the systemic effect must cause the bleeding rather than potentiate existing bleeding. However, based on current information regarding the effect of aspirin on platelet function, it is clear that aspirin will not initiate bleeding on the basis of the platelet effects and most likely will not potentiate bleeding from all types of bleeding sites. Most authorities agree that reduced platelet function will be important only when there is existing bleeding potential at the capillary level. It is of significance that the unique vasculature of the gastrointestinal tract and the importance of capillary blood flow to the lamina propria is the primary factor in acute hemorrhagic erosive gastritis or duodenitis. It is in these situations that aspirin is most frequently involved, accounting for 50 to 90 percent of all cases of massive bleeding from these sites. There are few situations in the body other than gastrointestinal erosions where extensive existing damage to mucosal tissue would involve extensive capillary networks. The capillary bed in the tonsillar region is one such case, however, and as might be expected, bleeding associated with aspirin does not occur in this region unless trauma and existing tissue damage is present e.g. posttonsillectomy. When existing damage occurs and capillary bleeding does occur, massive bleeding from this site can and does take place following aspirin ingestion. It should be clear that aspirin is not acting through the Davenport (hydrogen ion mediated bleeding) mechanism.

In summary, the Panel finds that massive gastrointestinal bleeding frequently is associated with acute aspirin ingestion by patients who have existing lesions which involve capillary type "oozing" bleeding (Ref. 14), such as weeping types of lesions associated with erosive gastritis regardless of the original cause and the more recently recognized duodenitis (Refs. 106 and 107). The tonsillar bed following surgery or inflammation also presents this picture. These lesions are often multiple superficial areas which would be dependent on platelet function for hemostasis since

they are not under arteriolar control (Ref. 14); massive bleeding is more frequently observed in individuals who have inborn clotting deficiencies. While hemophilia has long been recognized to be a condition which is a contraindication to aspirin use, other clotting deficiencies which are less severe have been detected because of their reaction to aspirin (See part III paragraph B.1.a.(2)(i) above—Adverse effects on the blood.); and large increases of gastrointestinal occult blood loss are frequently associated with individuals who are more likely to have existing mild bleeding sites. The effects of aspirin on platelet function require only small doses. The effect may persist for several days. This dose-time response is consistent with some reports of massive bleeding following one or two aspirin tablets 1 or 2 days before massive bleeding occurs (Ref. 86).

(h) Interaction with alcohol. Another aspect of the gastrointestinal bleeding problem is the evidence in recent studies of a synergism between alcohol and aspirin's ability to cause such gastrointestinal bleeding.

In a study which was also designed to overcome the problems outlined, Needham et al. (Ref. 95) found a definite association between the acute use of aspirin (within 72 hours of hospital admission) and massive upper gastrointestinal bleeding, and evidence of a synergism between alcohol and aspirin in the association with gastric bleeding. It is of significance that of the separate diagnostic groups, i.e., duodenal and gastric ulcer, gastritis etc., only the duodenal group showed a high significance in the synergistic effect of aspirin and alcohol in terms of an increased incidence of bleeding. While this may be because of the low numbers of patients in the other categories, e.g., gastritis, it is important to note that acute ingestion of aspirin had a significant effect on duodenal bleeding and a synergistic effect with alcohol in bleeding from duodenal ulcers even though there is presently no evidence that even chronic aspirin usage is implicated in the incidence of nonbleeding duodenal ulcers (Ref. 86). This gives support to the hypothesis that aspirin may support or potentiate bleeding from gastrointestinal lesions even though aspirin alone may not initiate the lesion.

It is also significant that in this study alcohol alone did not increase the risk of bleeding, but did potentiate the effect of aspirin. It is also of interest to note that 13 percent of the total number of patients took aspirin for stomach pains, and 4 percent for hangover. The authors conclude that there seems to be a good case for warning the public of the dangers of aspirin since the combination of headache and upset stomach are often related to alcohol ingestion and might be a frequent reason for use of aspirin.

(i) Formulation effects. Some authorities claim that the mechanism involved with major gastrointestinal bleeding is the same as occult bleeding, i.e., involving direct cellular damage mediated through, and therefore requiring, available hydrogen ion (Ref. 22). As a corollary to this hypothesis, it has been claimed that highly buffered aspirin solutions which decrease occult bleeding would also obviate major bleeding (Refs. 37 and 47). While the direct acid-mediated gastric erosion may undoubtedly contribute or even in some cases initiate massive bleeding it is clear that this is not the only, and in fact probably not the most important mechanism involved in aspirin-induced massive bleeding.

There are several lines of reasoning to support this conclusion. Mucous membrane damage to the stomach produced by direct contact with aspirin and occult bleeding are responses that are predictable under given experimental conditions. Increased occult bleeding is observed in about 70 percent of the normal population taking normal therapeutic doses (Ref. 108). Massive bleeding has not been simulated in the laboratory and occurs sporadically and unpredictably in the aspirin taking population.

Even though highly buffered aspirin solution decreases the average occult bleeding loss in most studies (Ref. 75), frequently in these studies using highly buffered aspirin, one or two subjects who have taken highly buffered aspirin solution have sporadic, large increases in gastric bleeding. These "atypical responders" or "outliers" have occult bleeding losses which are often significantly greater statistically than the average for all subjects in the study (Ref. 77). Studying occult bleeding without regard to the unusual excessive bleeder or eliminating these "outliers" from the study begs the issue that buffering decreases blood loss and probably ignores the very type of exaggerated responder which is so characteristic of massive gastrointestinal bleeding.

Locally applied aspirin produces massive bleeding from capillary beds of tissues which do not secrete hydrochloric acid such as the tonsillar areas of the throat (See Part III paragraph B.1.a.(2)(ii)(b)(*1*) above—Mucosal erosion of the mouth), particularly following tonsillectomy when abraded oozing tissue is involved.

Enteric-coated aspirin products designed to release aspirin in the intestine where the acidity is low, produce significant increases in occult gastrointestinal bleeding, particularly in individuals who are more prone to such bleeding, e.g., the elderly (Ref. 1).

The Panel recognizes that a direct correlation between a reduction in occult bleeding and a reduction in occasional massive gastrointestinal bleeding has never been demonstrated.

Chronic aspirin ingestion appears to increase the incidence of stomach ulcers to a greater extent than duodenal (intestinal) ulcers presumably due to the hydrochloric acid effect in the gastric mucosa (mucous membrane of the stomach). However, aspirin appears to be implicated in massive bleeding associated with duodenal ulcer patients to the same or greater extent as in patients with stomach ulcers or erosive gastritis (stomach inflammation) (Ref. 79). This supports the hypothesis that the effect of aspirin on massive bleeding may not be dependent on the same factors as those factors related to direct mucosal damage in the stomach.

While the Davenport mechanism may contribute to or even in some cases initiate massive bleeding, it would appear not to be the only mechanism involved.

For the various reasons discussed above, the Panel concludes that because aspirin after it has been absorbed into the blood stream can promote or increase bleeding, all preparations containing aspirin regardless of formulation should bear a warning: "*Caution:* Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

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(iii) *Adverse effects on hypersensitive individuals.* Aspirin has long been recognized to produce allergic type reactions in hypersensitive individuals (Refs. 1 through 9). Hypersensitivity reactions are varied, including the following types: Effects on the respiratory tract ranging from shortness of breath to severe asthma attacks; effects on the skin including urticaria (hives), angioedema (neurotic edema) (giant hives), edema and rash; and anaphylactic shock involving laryngeal swelling, which blocks air pathways, and a precipitous drop in blood pressure (shock) which can result in death if not rapidly treated.

(a) *Incidence of adverse effects.* The incidence of hypersensitivity reactions (dermal and pulmonary) has been estimated to be about 0.2 percent of the general population (Refs. 8 and 9). However, a much higher incidence of hypersensitivity is found in some subgroups. Six to 20 percent of asthmatics are sensitive to aspirin (Refs. 10 through 13). About 20 percent of patients with chronic urticaria will experience exacerbation when given aspirin (Refs. 14 through 16). The Panel concludes that these adverse effects occur in a significant proportion of the population. They can be serious and even life-threatening in some instances (Refs. 4 through 6). Although very rare, death has occurred within minutes following ingestion of only one or two aspirin tablets in individuals who were known to be hypersensitive to aspirin (Refs. 5 and 6).

(b) *Adequate labeling information.* Because of the known risk of a severe aspirin hypersensitivity reaction, the Panel concludes that groups at high risk, such as persons with asthma and persons with a known allergic reaction to aspirin (e.g., shortness of breath, skin rash, hives) should be warned not to ingest the drug without consulting a physician.

The Panel recommends that all products containing aspirin should be labeled with the warning: "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

The Panel also considered the suggestion (Ref. 17) that the warning to asthmatics should be directed only to the asthma subgroup known to be most often involved and that salicylic acid or acetaminophen can be recommended to this and other aspirin sensitive groups as a safe alternative. Evaluation of these and other considerations relating to recommended labeling statements involved assessment of the current information regarding the following: Identification of the mechanism(s) involved and the role(s) that aspirin plays in the pathogenesis of different types of hypersensitivity reactions; characterization of subgroups that can be used to identify individuals that have a significantly higher risk of reaction with aspirin; and identification of other drugs, particularly analgesics, that do or do not have cross-sensitivities with aspirin.

The Panel finds there is still considerable disagreement and there are unresolved questions regarding these important considerations, but some generalizations can be drawn on the probable mechanisms involved and susceptible subgroups. These are complex and exceptions are numerous.

The Panel concludes that aspirin can precipitate hypersensitivity reactions by different mechanisms in different groups of patients who may have entirely different characteristics. The acceptable types of substitute analgesics would also appear to be entirely different for the different groups.

(c) *Major types of hypersensitivity reactions.* Information reviewed by the Panel suggests at least two major types of hypersensitivity reactions to aspirin which differ in mechanism, usual type of response and cross-sensitivities with other agents (Refs. 18 and 19). There may be overlap of individuals in these categories.

It appears that the group usually exhibiting an asthmatic response to aspirin does not usually have atopic characteristics. Rather, they show the usual triad of aspirin hypersensitivity, nasal polyps, and late, abrupt onset of asthma (Refs. 10 through 12). Current evidence suggests this group involves a nonimmunologic hypersensitivity mechanism possibly related to the effects of aspirin on inhibition of prostaglandin synthesis (Refs. 20 and 21). Cross-sensitivity is commonly seen with other prostaglandin synthesis inhibitors including indomethacin, flufenamic acid, mefenamic acid, ibuprofen and phenylbutazone (Refs. 20 and 21). Analgesic agents which do not affect prostaglandin synthesis such as salicylamide, salicylic acid and acetaminophen do not usually show cross-sensitivities in this group (Ref. 20). Exceptions have been noted however (Ref. 13).

The second group are those who usually exhibit dermal reactions, such as urticaria or angioedema (Refs. 14, 15, 16, and 19), but may also have asthma following aspirin ingestion (Ref. 19). They often exhibit typical atopic constitutions (Ref. 19). This group also appears to be susceptible to anaphylaxis (Ref. 19). The mechanism involved in this group is possibly mediated by immunologic response as indicated by a positive rat mast cell reaction (Ref. 19). This group appears to be more susceptible to cross-sensitivities with salicylic acid and acetaminophen (Ref. 19).

Thus, although some generalizations can now be made regarding the type of reactions most likely to occur in a group with particular characteristics, the interrelationships are complex, not precisely defined, and not likely to be under-

stood by the majority of patients. It is sufficient to state that these relationships are not discernible and cannot be self-diagnosed by a lay person. Consequently, at this time, no statement would be any more meaningful to the user of aspirin than the general warning against its use by those known or likely to be hypersensitive to aspirin.

(d) *Asthma.* Asthma may range from mild brief attacks to severe and prolonged attacks and, rarely, deaths. Severe angioedema, bronchial asthma, cyanosis, asphyxia, coma and death within minutes have been reported in hypersensitive individuals (Refs. 1 through 4).

Conflicting figures are given in the literature regarding the incidence of aspirin hypersensitivity in the general population and the asthmatic population, depending on the population studied and the method of assessment (Refs. 8 through 13, 17, 22, and 23). Objective measurement of pulmonary function after oral challenge appears to be an effective means of establishing sensitivity. There is some risk involved in challenge tests because deaths have been reported (Ref. 22). Skin tests have not been found to be an effective means of detection (Ref. 15).

McDonald et al. (Ref. 22) studied 42 asthmatic patients who had no history of asthma after taking aspirin. Patients with an unequivocal history of asthma after taking aspirin (aspirin intolerant) were excluded from the study. Patients who had no history of asthma associated with aspirin were selected for aspirin challenge during a time when the patient's asthma was stable. A dose of 600 mg aspirin was given as two tablets which also contained 150 mg magnesium hydroxide and 150 mg aluminum hydroxide per two tablets. Other tablets, containing 200 mg magnesium hydroxide and 200 mg aluminum hydroxide per tablet and no aspirin, which were similar in size and appearance, were given as a control, in crossover fashion, to the same patients. Respiratory signs were measured by spirometry and a Jones Pulmonor. Eight of 42 (19 percent) challenges were positive. These results, combined with 14 patients with a history of intolerance to aspirin, yield a prevalence of aspirin intolerance of 8 percent in the asthmatic population studied by these investigators. The number of patients who were intolerant to aspirin showed a statistically significant increase in the presence of nasal polyps, sinusitis and steroid dependence when compared to all new asthmatic patients examined during the 2-year period.

Many other authors have noted a particularly high incidence of aspirin sensitivity in asthmatic patients with nasal polyps, chronic sinusitis and eosinophilia. In general, aspirin-induced asthmatics have not fitted the usual characteristics of the typical "allergic" patient. The allergic patient most familiar is one who when exposed to some allergen (reagin), such as pollen or a food, develops "hay fever" watery and itchy eyes, runny nose (allergic rhinitis) and bronchospasm. Secondary symptoms may involve urticaria, allergic asthma and, rarely, anaphylactic shock. Allergy of this type belongs to a subgroup of the so-called "immune" class of disease termed atopy (Type I, reagin-mediated allergic hypersensitivity). In this class of disease an antibody mediates the reaction. The antibody belongs to the IgE class of immunioglobulins which has the peculiarity of attaching itself to a certain type of cell, mast cells in the tissues and basophils in the blood. With the arrival of the allergen (reagin), union between the allergen and the antibody attached to these cells occurs and leads to the release of active substances such as histamine which in turn cause the symptoms we call "allergic."

In contrast to the atopic group, most aspirin-sensitive asthmatics do not have any of the usual indications of an immunological reaction. They have been termed Type II, intrinsic, nonallergic type (Refs. 17 and 24).

Falliers states that aspirin-sensitive asthmatics are usually the Type II, intrinsic, nonallergic type and are quite different from asthmatics not sensitive to the drug (usually Type I atopic asthmatics). Based on his study of 1,298 chronic asthmatics, between the ages of 6 to 16 years, the 25 children sensitive to aspirin were mainly the typical "abrupt-late-onset" intrinsic types with nasal polyps. He states that the majority of the atopic (reagin-mediated or Type I allergic hypersensitivity) are said to carry no greater risk of aspirin sensitivity than the general population. The distinguishing characteristics of the low risk patient are: An early onset of atopic (reagin-mediated) asthma; a family history of allergy; and specifically asthma, atopic eczema, and rhinitis. In contrast to the large number of asthmatic adults who are sensitive to aspirin (approximately 10 to 20 percent), the number of asthmatic children who are allergic to aspirin is only about 2 percent, according to Falliers (Ref. 24). Falliers has recommended to this Panel that the label warning for aspirin should state, "some asthmatics (intrinsic nonallergic type) may react adversely and therefore should not use aspirin without medical advice." One difficulty of this suggestion is that many asthmatics may not know which category they are in and could not self-diagnose their condition. A second more important reason is that some aspirin-sensitive children do in fact have atopic characteristics. For example, in five children with asthma induced by aspirin, Yunginger et al. (Ref. 23) found that four were in the group considered by Falliers to be low risk. These four had no history of nasal polyps and were characterized by atopic constitutions including sensitivities to seasonal pollens, a family history of allergies and positive skin tests.

The mechanism involved in the intrinsic nonallergic aspirin-sensitive asthmatic probably includes the effect of aspirin on prostaglandin synthesis (Refs. 20 and 21).

Polish workers recently demonstrated bronchoconstriction in patients with aspirin hypersensitivity after administration of five drugs which inhibited prostaglandin synthesis (Refs. 20 and 21). Indomethacin produced decreased peak expiratory flow in all 11 patients tested after a dose of 5 mg. Therapeutic doses of mefenamic acid and flufenamic acid, and 200 to 400 mg phenylbutazone produced a bronchoconstrictor effect in most patients. These five drugs all inhibited microsomal prostaglandin synthetase. Salicylamide, acetaminophen, benzydamine and chloroquine did not inhibit prostaglandin synthetase and did not produce bronchoconstriction.

(e) *Urticarial (dermal) hypersensitivity reactions.* Speer states that the most common manifestations of aspirin sensitivity are urticaria (hives) and angioedema (giant hives) rather than asthma (Ref. 15). Urticaral reactions (hives) are generally considered as part of the general aspirin sensitivity syndrome. However, dermal and respiratory reactions frequently occur independently. Different mechanisms may be involved. These patients frequently have other allergies (food, drugs) and do not necessarily exhibit the usual signs of late onset and nasal polyps found in aspirin-induced asthmatics. In 112 patients found sensitive to aspirin (1.5 percent of all patients seen in a 10-year period), there were 74 cases of urticaria and/or angioedema and 38 cases of asthma. Of interest is the fact that four of these patients also reacted to acetaminophen. Of these, three developed urticaria and one asthma.

In contrast to aspirin-induced asthma which is usually precipitated only by aspirin and not salicylic acid, both aspirin and sodium salicylate will exacerbate chronic urticaria in 20 to 25 percent of cases (Refs. 14 through 16).

Phills et al., using the rat mast cell technique, which is thought to detect IgE immunoglobin reactions, were able to distinguish between two groups of patients hypersensitive to aspirin (Ref. 19).

Dermal reactions are not usually life-threatening. There are indications that life-threatening anaphylactic shock is often associated with patients with dermal rather than asthmatic reactions to aspirin. Thus while typical (intrinsic, nonallergic) aspirin hypersensitive patients (Type II) can frequently use salicylic acid or acetaminophen or other analgesics which do not inhibit prostaglandin synthesis without cross-sensitivity, this does not appear to be true with urticarial and possibly anaphylactoid type reactions in the atopic type (Type I) aspirin responders.

The American Academy of Allergy in 1973 (Ref. 25) approved the following resolution:

> While recognizing that acetylsalicylic acid (aspirin) is a valuable drug, the American Academy of Allergy recommends that a formulation containing aspirin and advertisements promoting the formulation should clearly indicate that the preparation contains aspirin and that aspirin can be harmful to some persons.

The Panel is in agreement with this resolution.

In summary, since aspirin has long been recognized to produce allergic type reactions in hypersensitive individuals, the Panel recommends that all products containing aspirin should be labeled with the warning: "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

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(25) News Release, "Aspirin to be Labeled 'Can Be Harmful'," The American Academy of Allergy, February 14, 1973, is included in OTC Volume 030150.

(iv) *Adverse effects during pregnancy.* The Panel has reviewed the effects of aspirin on various aspects of pregnancy as studied and extensively reported in the literature. The investigations on the effects of aspirin ingestion during pregnancy have focused on the following aspects: Teratogenic effects (malformation of offspring); the incidence of stillbirths and neonatal deaths (deaths at or shortly after birth); the effect of aspirin ingestion on the length and duration of pregnancy and parturition time (length of labor and delivery); and the impairment of hemostatic mechanisms by aspirin (but not other salicylates) on the mother as well as on the newborn infant.

In the discussion below, the Panel has elected to separate and review the available data according to the above effects. Teratogenic potential and fetal lethality will be discussed in terms of both animal studies and human retrospective and prospective studies. Secondly, prolongation of the duration of pregnancy and parturition time in animals and in human retrospective studies will then be summarized. Lastly, the effects on maternal and newborn hemostatic mechanisms will be described followed by the Panel's conclusions and recommendations.

(a) *Teratogenic potential and fetal lethality.* (1) *Animal studies.* Warkany and Takacs (Ref. 1) reported for the first time in 1959 that both methyl and sodium salicylate were teratogenic in rats. The drugs were administered to pregnant rats subcutaneously from days 9 to 11 of pregnancy. However, the doses used were, on a weight basis, much greater than the therapeutic doses used in man. Females received either single subcutaneous injections of methyl salicylate in doses of from 0.1 to 0.5 ml (the mg/kg dose was not specified) or sodium salicylate in doses of 60 to 180 mg (maximum 900 mg/kg based on the assumption of a 0.2 kg rat). In addition, the teratogenic doses (doses which caused malformations) were found to be quite close to doses lethal to the embryo (developing offspring) and toxic to the mother (Ref. 1).

Larsson, Bostrom and Eriksson (Ref. 2) in 1963 showed that large doses of salicylates, 10 mg (maximum 500 mg/kg based on the assumption of a 0.02 kg mouse) sodium salicylate, administered intramuscularly to pregnant mice induced malformation in the embryos. A feature of particular interest was that these malformations occurred either in vascular (blood vessel) or skeletal tissues both know to contain acid mucopolysaccharides. The authors hypothesized that the teratogenic effects of salicylates in mice were related to the inhibition of mucopolysaccharide synthesis and suggested that the embryos seemed to be most sensitive when the injections were given on the 12th and 13th day of gestation.

Larsson and Eriksson (Ref. 3) in 1966 investigated the effects of time of administration of salicylates to pregnant mice on the incidence of fetal death and fetal resorption. They compared two mouse strains identified as A/Jax and CBA strains and found that they had different teratogenic susceptibility. Sodium salicylate, 500 mg/kg of body weight, was given intramuscularly in a single dose on one specific gestation day (either day 9, 11, 13, 15 or 17) to pregnant primiparous mice of A/Jax and CBA strains and to their reciprocal crossings. It was found that the fetal resorption rate increased steadily the later in pregnancy sodium salicylate was given to the A/Jax strains and to hybrids from A/Jax females crossed with CBA males. In contrast, in the CBA strain, and to the progeny from CBA females crossed with A/Jax males, the resorption rate was low even after injection of sodium salicylate in late pregnancy. Vascular anomalies were studied and it was noted that the highest incidence of vascular anomalies occurred after injection of sodium salicylate on the 15th day of gestation, whereas anomalies of the ribs and vertebrae showed the highest incidence after injection on the 9th day. Again, the A/Jax strain, and the progeny from A/Jax females crossed with CBA males were shown to be the most susceptible. The authors suggested that in drug tests for teratogenic potential the drug should also be given after the period of organogenesis and that special attention should be focused on fetal lethality.

Eriksson (Ref. 4) in 1970 studied the role of dosage and frequency of administration of sodium salicylate on fetal mouse damage as well as a possible protection against such damage when pentobarbital was given as a pretreatment. There was little or no effect on the fetus when a dose of 150 mg/kg of body weight was administered to the mother on day 17 of pregnancy. At a dose of 500 mg/kg of body weight given to the mother on day 16, death occurred in 70 percent of the fetuses. Subcutaneous and subcapsular liver hemorrhages were found in 39 and 13 percent of the living fetuses, respectively. Macroscopically visible submucosal hemorrhage in the stomach was seen in 22 percent of the surviving fetuses. When a dose of 750 mg/kg was administered, four out of ten pregnant females died within 24 hours. Five of the remaining six pregnant females gave birth before being sacrifificed and the fetal lethality in one litter was 100 percent. When 75 mg/kg pentobarbital was

administered on days 15 and 16 of gestation followed by 500 mg/kg salicylate on day 17, fetal death was significantly decreased. Although these observations are interesting, it must be noted that here again extremely high doses were used since the LD_{50} for females of the strain used (A/Jax) was determined to be 760 mg/kg of body weight.

Studies in rhesus monkeys by Wilson (Ref. 5) have shown that doses of aspirin five to six times higher than the teratogenic doses used in rodents produced embyrotoxicity and fetal malformations in this species. It should be emphasized that the daily dose of 500 mg/kg was considerably in excess of that likely to be used therapeutically in pregnant women.

According to Wilson (Ref. 6), this "margin of safety" has been made less secure by the observation of Kimmel, Wilson and Schumacher (Ref. 7) that the teratogenic potential of a given dose of aspirin in rats can be appreciably increased by the concurrent administration of benzoic acid, a widely used food preservative. Levy, Amsel and Elliott (Ref. 8) have shown that benzoic acid elevates salicylate blood levels in man by inhibiting salicyluric acid formation, but whether such interaction could raise the salicylate concentration in maternal blood sufficiently to cause embryotoxicity still remains an open question. The Panel has further discussed the role of benzoic acid-containing ingredients later in this document. (See part VI. paragraph B.2. below—Benzoic acid-containing ingredients.)

Since these and other reports have appeared, questions are sometimes raised about the possible embryotoxicity of salicylates, particularly aspirin, in view of its widespread use as an analgesic and the high doses used in arthritis. For purposes of comparison, it should be noted that the use in the average adult female of the recommended maximum daily dosage of 3,900 mg aspirin would be equivalent to 70 mg/kg for an average 55 kg (120 lb) woman.

Recently, Beall and Klein (Ref. 9) have reported a study in rats using a dose of 250 mg/kg (administered on days 7 through 10 of pregnancy) with and without food restrictions. They found that the controls (group I) (food ad libitum, no drug administration) had 2.6 percent of abnormal progeny. Group II (250 mg/kg aspirin and food ad libitum) had 23.8 percent of abnormal fetuses. Group III animals on a restricted diet (6 g daily) had an incidence of abnormal fetuses of 5.3 percent. However, Group IV receiving 250 mg/kg aspirin plus food restriction had an incidence of 95.8 percent malformed fetuses.

The types of anomalies observed included rib anomalies, craniorachischisis, umbilical hernia, scoliosis, anophthalnia, cleft lip and palate, etc.

The data also show a significantly increased number of resorptions in group IV when compared to groups I, II, and III (p is less than 0.05). The litter size of control group I was 11.6 ± 1.54, for group II it was 9.4 ± 1.45, for group III it was 13.1 ± 0.56 and in group IV it was 6.4 ± 1.51. This seems a marked decrease in litter size in group IV when compared to other groups, although the authors do not mention the significance of this factor. These data indicate that, in rats, the combination of food restriction and aspirin affected fetal development more than did aspirin alone.

In summarizing the animal studies as they might be related to humans, several important points should be noted. As has already been emphasized, on a weight basis the doses used in the animal studies were excessively high and approached or were at lethal levels in comparison to the usual human adult dosage. Not only were these doses at lethal levels for the animals, but considering that the lethal dose for man ranges from 400 to 600 mg/kg, the animal doses were also at levels that would be lethal to humans (equivalent to 84 to 96 aspirin 325 mg (5 gr) tablets). When pregnant mice were given lower doses, such as a dose of 150 mg/kg, there was little or no adverse reaction. As noted above, the total maximum daily dose of aspirin recommended by the Panel for an average woman is approximately 70 mg/kg, about one-half the dose in mice of 150 mg/kg. However, extrapolation from animal data to humans is not always a matter of simple arithmetic and conversion of doses on a mg/kg basis. It is a well-known fact in toxicological assessment that species vary in the susceptibility to toxic agents and often it is required by government agencies that doses 10 or 50-fold of those intended for human use be used in animals for the assessment of toxic potential.

This interspecies variation could be due to susceptibility of the target organ (or growing embryo) or to differences in absorption, metabolism, distribution or excretion. Interspecies differences in metabolism are extremely common.

(2) *Human studies.* Studies related to the use of salicylates by pregnant women were reviewed by the Panel to make an assessment of the risks involved. Obviously, ethical and moral reasons preclude specially designed randomized studies that would examine the effects of salicylates on pregnancy. The Panel has therefore had to rely mainly on retrospective studies, i.e., previous clinical experience or statistical records which are subject to many valid criticisms and from which conclusive evidence cannot be definitively drawn. Several retrospective studies in humans attempting to determine if a correlation exists between aspirin ingestion and fetal malformations have been reported in the literature.

A retrospective survey of malformed infants resulting from 833 pregnancies during the period between 1964 to 1966 was performed in Wales by Richards (Ref. 10). The mothers of the malformed infants were matched with an equal number of controls, women who had given birth to normal infants. The findings were based on interviews in the homes of each mother of a malformed infant and her matched control. In addition to the retrospective nature of the study, the dosages of salicylates, the duration of treatment, and the medical histories of the mothers were not given. Richards reported that a very highly significant greater (p is less than 0.001) percentage of women (22.3 percent) delivering malformed babies, had taken salicylates during the first trimester of pregnancy than had women who had not taken salicylates and delivered normal babies (14.4 percent). It is interesting that in these populations of women following pregnancy, the incidence of salicylate ingestion was relatively low, i.e., only 36.7 percent of the 833 subjects had taken salicylates.

The author concluded that the results of the investigation "suggest that either salicylates have a teratogenic effect or that the conditions for which they are given have such an action." It should be noted that in addition to salicylates, other drugs had been taken by some of the women during pregnancy such as antibiotics, sulfonamides, steroids, sedatives, iron, oral contraceptives, antiemetics, etc. However, the women taking salicylates did not all take these various drugs.

The retrospective study included a statistical evaluation of each drug administered to the mothers to determine whether there was a statistically significant relationship between the drug and the malformation found in the infants. The author acknowledged that there are several limitations to a retrospective study that cannot be overlooked, and that "a large number of tests of significance were performed and many of these apparently significant differences could have arisen merely by chance." The author performed a total of 1,025 tests of significance and indicated that of the 101 tests that showed statistical significance, he considered that 51 of these statistically significant results could have occurred merely by chance.

In reviewing the study, the Panel finds several limitations which prevent a valid interpretation of the findings. Even the author acknowledges limitations to a retrospecive study including the fact that the results may be affected by bias on the part of the interviewer or the mother; events, drugs and dosages may have been forgotten; emphasis was placed on the whole of the first trimester, whereas the critical periods of development are short and occur at different times for different organs; and lastly that since a large number of tests of significance had been performed, many of these apparently significant differences could have arisen mainly by chance. The Panel recognizes these deficiencies and especially the fact that the statistical analyses were not planned in advance of the study. It is also important to note that the study was not designed specifically to evaluate the effects of salicylates or other drugs but to evaluate congenital malformations and environmental influences in pregnancy. Many factors besides drugs were evaluated such as illnesses during first trimester, smoking and diet habits, employment, accommodations, water supply, etc.

Nevertheless, the Panel concludes that regardless of the circumstances, the Panel views the summary conclusions of the authors as very important. Namely, the fact that Richards found many statistically significant differences between cases and controls, those of greatest interest (and possible importance) being: (i) Use of salicylates, (ii) certain other drugs (antiemetics) and (iii) the effects of diet in the first trimester considered to be unbalanced or doubtful. Of importance to this Panel, the author found that the taking of salicylates in the first trimester resulted in the following significant differences: Defects on the central nervous system (p is less than 0.05), of the alimentary tract (p is less than 0.01), miscellaneous defects (p is less than 0.05) and talipes (club foot) (p is less than 0.01) (for all organ systems p is less than 0.001).

In another retrospective study by Nelson and Forfar (Ref. 11) reported in 1971, the effects of drugs administered during pregnancy and their possible association with congenital abnormalities of the fetus were compared. Virtually all 1,369 of these women (1,333 out of 1,369) had taken one or more drugs during pregnancy. Only 2.1 percent of mothers in the abnormal group and 2.9 percent of mothers in the control group had not taken any drug. Most mothers who had taken analgesics delivered normal infants. In the study 97 percent of the mothers took prescribed drugs and 65 percent OTC drugs. Aspirin was one of the drugs included. More specifically, the aspirin ingestion during pregnancy of 458 mothers of malformed infants was compared with the ingestion of aspirin by 911 mothers of normal infants. Of mothers delivering normal infants, 54.3 percent took aspirin during the entire period of pregnancy as compared with 62.2 percent of mothers delivering malformed infants. This was reported to be a statistically "highly" significant difference (p is less than 0.01).

Approximately 50 to 60 percent of the mothers of the malformed infants and also the mothers of the normal infants had taken two to five different drugs during pregnancy. Approximately 15 to 20 percent of both groups of mothers had taken 6 to more than 10 drugs during pregnancy. The drugs consisted of analgesics, antacids, antiemetics, antibiotics, appetite suppressants, barbiturates, bronchodilators, cough medicines, diuretics, hormones, hypnotics and tranquilizers, iron, sulfonamides and vitamins. Tests for significance had to be done for each class of drugs for the same groups of mothers. In the case of some drugs, the actual numbers were too small to show significant results which could not alone exonerate a drug from possible teratogenic effects. In other instances, although a greater number of mothers of malformed infants took a particular drug than the control mothers, it might not necessarily mean that the drug had a teratogenic effect.

Twenty-three different analgesic preparations had been used by the women. Statistical comparisons were made between the analgesics used during the whole of pregnancy, the first trimester and the first 14 and 56 days and all abnormalities observed (which were further divided into major and minor abnormalities). The data showed that analgesics were used by a significantly high proportion of mothers of infants with "all and minor" abnormalities during the whole of pregnancy and "all" abnormalities during the first 56 days of pregnancy. The authors specifically note that "aspirin was taken by a significantly higher proportion of mothers of all abnormal infants and of infants with major abnormalities in the whole of pregnancy and of infants with all abnormalities in the first trimester." It was specifically concluded that the increased occurrence of congenital abnormalities associated with analgesics appeared to be related to the aspirin content.

The data further showed no significant differences for aspirin for the first 14 and 56 days. However, there was a significant difference for the first 28 day period where 8 out of 458 mothers (1.75 percent) in the "all" abnormalities group had taken aspirin compared to 3 out of 911 mothers (0.33 percent) in the control group (p is less than 0.05). The abnormalities included achondroplasia, hydrocephalus, congenital heart disease, mongolism, congenital dislocation of the hip, hydrocele, talipes, and papilloma of the forehead. It should be noted that Richards (Ref. 10) also observed talipes. Since the average dose of aspirin per mother in the study group was reported to be a little over half that in the control group, this indicates a woman does not necessarily have to be an abuser or take large quantities of the drug to have the fetus at risk.

The authors' summary comments emphasize the need for caution in presuming teratogenic effects on the basis of the associations found in the study. They do recommend that any drug which carries a suspicion of teratogenicity should be avoided during pregnancy unless specifically prescribed. More interestingly, they recommend that OTC drugs such as aspirin should be avoided.

A retrospective study in Finland reported by Saxen (Ref. 12) in 1975 investigated the association between oral clefts in infants and drugs taken by their mothers during pregnancy. Five hundred ninety-nine cases of oral clefts (cleft lips and cleft palates) reported to the Finnish Register of Congenital Malformation in the years 1967 to 1971 were used in the study. The mothers of these malformed infants were compared with matched controls, i.e., mothers of normal infants, for salicylate ingestion during pregnancy. In considering the results, it should be kept in mind that this study was partially prospective and partially retrospective. The information concerning intake of drugs was obtained from welfare center records (prospective) whereas questionnaires were completed by the mothers during their first visit after delivery (retrospective). Although it was reported that in the first trimester of pregnancy 14.9 percent of the mothers of the malformed infants took salicylates as compared to 5.6 percent of the controls (p is less than 0.001), approximately the same percentage of mothers of malformed infants and of the controls (18.4 and 16.9, respectively) did not remember exactly when during pregnancy they took salicylates. Since a correlation with the intake of other drugs during pregnancy was also studied, the author cautions that when a large number of significant tests are performed, the possibility of chance correlations must be taken into account; but the fact that the significant differences were mostly confined to the first trimester, lessens the probability that these differences arose by chance. Saxen also points out that other drugs administered simultaneously may alter the response to a drug.

A survey in England by Crombie et al. (Ref. 13) reported in 1970, compared the number of aspirin prescriptions issued by physicians to women in early pregnancy who had eventually delivered a congenitally malformed baby, with the number of aspirin prescriptions issued to women who had delivered a normal baby. There was no statistically significant difference between the two sets of mothers. The authors concluded that any relationship between "drug consumption and a congenital abnormality is indirect and possibly more directly related to the morbid conditions for which the drugs were given." This survey included the records of approximately 10,000 women.

In another study by Turner and Collins (Ref. 14) reported in 1975, the infants of 144 mothers who took salicylates regularly during pregnancy were studied with respect to birth weight, perinatal mortality and the incidence of congenital malformations. Since salicylates cross the placental barrier freely and go into the fetal circulation, the study was initiated in an attempt to assess the effects of increased levels of blood salicylate on infants whose mothers regularly took salicylates during pregnancy. After delivery, the babies were divided into groups, i.e., Group I (64 infants) where the mothers had taken salicylates daily and Group II (82 infants) where the mothers had taken salicylates at least once a week. Mothers in Group I were matched with controls for age, parity, gravity, ethnic group and social class. Blood salicylate level determinations showed that when the maternal blood level was high so was the cord-blood level. The mean birth weight of the infants of mothers who took salicylates daily was significantly lower than the mean control birth weight (p is less than 0.005). The birth weight was also found to decrease in relation to the length of time (in years) that mothers had been taking salicylates which suggested that it may not be solely an effect of salicylates on fetal growth but rather a cumulative secondary effect from some maternal factor. When the present and past pregnancies of the women were combined, it was found that the stillbirth rate and the perinatal mortality rate were significantly increased in infants born to the Group I mothers (p is less than 0.01 and 0.005, respectively).

With regard to teratogenicity, there was no significant increase in malformed infants as compared to controls.

The authors concurred with the suggestions of Richards (Ref. 10) and Nelson and Forfar (Ref. 11), stating that it may well be as suggested by those investigators "that teratogenicity is related to the illness for which salicylates were taken rather than a direct effect of the salicylates themselves." Turner and Collins (Ref. 14) did find that babies of mothers taking salicylates had a significantly reduced birth weight compared with controls. In addition, some babies were born with an elevated cord-blood level of salicylates but this was not associated with hypoglycemia, bleeding or any other obvious clinical disturbance. It is interesting to note that there were more anomalies in the group of women who took salicylates intermittently rather than constantly which suggested to the authors that if there is any teratogenic effect it may be more related to fluctuating levels of salicylate than a constantly elevated level. Turner and Collins concluded, "Our findings do not support the suggestion that salicylates are teratogenic, but they do suggest that chronic salicylate ingestion is associated with an increase in perinatal mortality and with decreased intrauterine growth."

In a recent study reported by Slone et al. (Ref. 15), the results of a prospective study suggest that aspirin is not teratogenic. In the study, which was conducted in 12 hospitals throughout the U.S., 50,282 mother-child pairs were selected for evaluation. Prior to delivery, data were collected on drugs taken, maternal illnesses, complications, etc. However, full details of dosages were not recorded but the heaviest use of aspirin, which was recorded, was for 8 or more days in any lunar month. Aspirin had been the most commonly used drug which was taken by 32,164 women during pregnancy. With regard to evaluating congenital malformations, the first 4 lunar months of pregnancy were studied in which aspirin had been taken by 14,864 women. In fact, during this period, 5,128 women (heavy users) had taken aspirin for at least 8 days during at least 1 of the first 4 lunar months. To fully evaluate the data, the authors developed risk factors for each of the outcomes identified. These included comparisons of the children (with and without each of the outcomes) in terms of such factors as antenatal visits, personal characteristics of mother and offspring, age, illnesses, genetic factors (prior malformed siblings), etc.

The findings of the study in terms of malformations according to aspirin exposure during the first 4 months of pregnancy are as follows:

CONGENITAL MALFORMATIONS FOLLOWING ASPIRIN EXPOSURE IN EARLY PREGNANCY

GROUPS EVALUATED

Group I: Containing 5,128 "heavily" aspirin-exposed mother-child pairs. (See description of heavy users above.)

Group II: Containing 9,736 aspirin-exposed mother-child pairs.

Group III: Containing 35,418 non-aspirin-exposed mother-child pairs.

Findings of study

Parameter measured	Group I	Group II	Group III
Number malformed children	343	663	2,242
Percent of group	6.7	6.8	6.3
Relative risk	1.06	1.08	1.0

When the children were further divided according to outcome, i.e., uniform malformations (CNS, cardiovascular, etc.) and nonuniform malformations (inguinal hernia and clubfoot), the data show that both aspirin exposure groups were similar to the unexposed group. The standardized relative risk approximated unity. The upper approximate limits (p value less than 0.05) for uniform and major malformations in children who were heavily exposed to aspirin (Group I) were 1.08 and 1.11, respectively. The authors stated that "With regard to any exposure to aspirin (whether heavy or not), the standardized relative risks of uniform and major malformations were 1.00 and 1.01, respectively, with approximate upper 95 percent confidence limits of 1.06 and 1.09."

As with other studies, criticisms were raised which could have obscured possible teratogenic effects. The authors commented in their discussion:

First, chance may explain failure to detect relationships with some of the less common outcomes. Second, even though multiple logistic risk function analysis was used to simultaneously control a wide range of potential confounding factors, the possibility of negative confounding by undetected factors could not be ruled out. Third, a systemic bias in the data collection could have obscured an association. Certainly, observer bias was unlikely in this study because the information on drug exposure was collected before delivery. Fourth, some degree of underestimation of aspirin use was undoubtedly present, since the median time of entry into the study was 21.6 weeks: some women may not have recalled taking aspirin during early pregnancy. However, there was less likelihood of underestimation among heavy users. In addition, misclassification of aspirin users as non-users would have had to be very common to completely obscure an actual association, because the non-exposed group was extremely large.

The data presented here are not in accord with two previous studies (Refs. 14 and 16).

The striking differences between the study of Slone et al. and those of Collins and Turner (Ref. 16) and Turner and Collins (Ref. 14) are not as dramatic as it may appear at first sight. The studies in the American and Australian papers were widely different and probably the main difference lies in the definition of "heavy user" given in the U.S. study. The term "heavy user" as described by Slone et al. appears to be a misnomer as these authors were really studying three non-abusing populations and the outcome could have easily been predicted. A person who has taken eight aspirin or therapeutic dosages in any lunar month or in any of the first 4 lunar months can hardly be called a heavy user.

However, it is noteworthy that Slone et al. (Ref. 15) concluded that the study gave no evidence that aspirin ingestion during pregancy is associated with congenital malformations. They pointed out that from the statistical analysis the relative risk estimates for uniform malformations and for major malformations make it unlikely that substantial teratogenic effects would have escaped detection. Nevertheless, they were of the opinion that the possibility still remains that grossly excessive exposure to aspirin may be teratogenic. However, they referred to the study of Turner and Collins (Ref. 14) which in their view showed no effect. More importantly, Slone et al. concluded: "Based on a larger body of data, more conventional doses of aspirin as used by pregnant American women do not appear to cause malformations in their offspring."

(b) *Prolongation of the duration of pregnancy and parturition (labor and delivery) time.* Tuchmann-Duplessis et al. (Ref. 17) have recently reported that the administration of 200 mg/kg/day to rats during the last 6 days of pregnancy resulted in a prolongation of the duration of pregnancy, a prolongation of parturition time and the appearance of dystocia (abnormal labor) in some animals resulting in possible secondary death of fetuses in utero. Seventy percent of control dams delivered during day 21 of pregnancy while only 18 percent of the treated dams did (p is less than 0.05). Fetal deaths occurred undoubtedly during but not before parturition and were the result of prolonged parturition and not the result of the toxic effect of aspirin on the fetus in utero.

Lewis and Schulman (Ref. 17) reported a 20 year retrospective study of 103 patients, most of whom had nonspecific collagen disease or degenerative musculoskeletal disease, taking doses of aspirin greater than 3,250 mg/day during the last 6 months of pregnancy in which comparisons were made with two control populations. The control populations were chosen as follows: The first control group consisted of 52 pregnant patients with rheumatoid arthritis, "nonspecific collagen disease", or degenerative musculoskeletal disease who were not taking aspirin or other compounds known to affect prostaglandin synthesis; and the second control group contained 50 pregnant women without known disease who were not taking therapeutic doses of aspirin or related drugs. The patients taking aspirin had an average gestation period of over 1 week longer than either control group. These differences were significant (p is less than 0.025). The two control groups did not differ from each other. The change in the mean length of gestation which occurred in the group taking aspirin was associated with increases (42 percent vs 3 percent in controls) in gestation periods lasting more than 42 weeks

(15 days postmature). Patients taking aspirin had a longer length of labor than either of the 2 control groups (12 hours vs 7 hours; p is less than 0.005). Further analysis showed that there were no statistical differences in mean age, parity or growth.

The Panel has summarized some of the findings of the authors in the following table:

INFLUENCE OF ASPIRIN ON DURATION OF HUMAN GESTATION AND LABOR

COMPARISONS OF STUDY GROUPS

Group I: Patients with rheumatic diseases taking therapeutic dosages of aspirin with daily consumption greater than 3,250 mg for at least the last 6 months of gestation (103 patients).

Group II: Control patients with rheumatic diseases not taking aspirin (52 patients).

Group III: Control healthy women not taking aspirin (50 women).

Results of study groups

Parameter measured	Group I	Group II	Group III
Length of gestation (days)	286.1±13.3	275.2±10.6	278.6±6.91
Length of labor (hours)	12.1±10.6	7.3±4.11	6.96±4.96
Birth weight (g)	3,077.0±597.0	2,972.0±538.0	3,379.0±499.0
Estimated blood loss (ml)	340.0±155.0	244.0±114.0	235.0±97.0

The purpose of the study was to evaluate the influence of aspirin, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labor. Prostaglandins are known to be capable of initiating uterine contractions. Lewis and Schulman indicate that their results support the view that prostaglandin metabolism may be an important determinant of the timing of the onset of spontaneous labor and of its duration. Patients taking aspirin had labors averaging 70 percent longer than those in the control populations.

Collins and Turner (Ref. 16) in an Australian study compared two groups of pregnant women who self-medicated with analgesics regularly, with a group of matched controls. One group of self-medicated women took analgesics in a powder daily (constant takers). A combination of aspirin, salicylamide, and caffeine was taken by 58 percent; 36 percent took a combination of aspirin, phenacetin, and caffeine; and 6 percent used either powder. The second group of self-medicated women admitted taking analgesics at least once a week throughout pregnancy (intermittent takers). Many of the constant takers had self-medicated with analgesics for many years and were "habituated" to analgesics. After the delivery of each patient in Group I (constant takers), the next Australian-born clinic patient to deliver a baby, who was matched for age, parity and gravity and after assurance that the patient had not taken analgesics, was used as a control. There were 63 patients in Group I, the same number in the control group and 81 patients in Group II. The major effects of regular salicylate consumption in pregnancy were found to be an increased frequency of anemia during pregnancy, a prolonged gestation, an increased incidence of complicated deliveries, a high incidence of antepartum and postpartum hemorrhage and transfusion at delivery and an increased perinatal mortality. The mechanism of the prolongation of gestation and labor by salicylates have been found to be related to the inhibition of the release of prostaglandins.Since one of the actions of prostaglandins is to stimulate uterine contractions, salicylates might be expected to delay the onset of labor and increase the length of labor. The Panel has summarized some of the findings of the authors in the following table:

INCIDENCE OF MAIN CLINICAL FEATURES FROM REGULAR SALICYLATE INGESTION DURING PREGNANCY

COMPARISONS OF STUDY GROUPS

Group I: Constant takers—analgesics taken 2 to 12 times daily during entire pregnancy.

Group II: Intermittent takers—analgesics taken at least once weekly during entire pregnancy.

Group III: Controls—no analgesics taken during entire pregnancy.

Results of study groups

	Group I	Group II	Control
Anemia in pregnancy ..... percent	[1] 41	[1] 22	[1] 20
Antepartum hemorrhage ..... do	14	7	4
Postpartum hemorrhage ..... do	12	5	2
Transfusion at delivery ..... do	12	6	0
Mean duration of pregnancy ..... weeks	39.7	39.8	38.7
Duration 36 weeks or less ..... percent	5.6	5.6	8.6
Duration 42 weeks or more ..... do	[2] 16.9	[2] 16.9	[2] 4.9
Mean duration of labor ..... hours	5.6	5.5	4.8
Complicated delivery	30	27	11
Cesarian section	12	6	2
Stillbirths	4/57	1/81	0

[1] P is less than 0.025.
[2] P is less than 0.050.

Because the numbers in the survey were small, the findings in present and past pregnancies of the women in the study were combined when assessing the antepartum hemorrhage, postpartum hemorrhage and transfusion at delivery, and all of these were found to be significantly increased in the constant takers group (p is less than 0.001). The stillbirths and perinatal death rates of the combined pregnancies of this group were also much greater than in the controls (p is less than 0.01 and less than 0.005, respectively).

In another recent study reported by Shapiro et al. (Ref. 19), the results showed no evidence that aspirin taken during pregnancy is a cause of stillbirth, neonatal death, or reduced birth weight. In this study, the collaborative perinatal project previously described by Slone et al. (Ref. 15) was used. The 50,282 mother-child pairs previously described were reduced to 41,337 mother-child pairs by the following modification:

When a mother was enrolled in the study more than once, a random pregnancy was selected. This was done because perinatal deaths in prior siblings may increase the risk of subsequent perinatal death. Pregnancies lasting less than 7 lunar months were excluded, since as explained below, the definition of heavy aspirin exposure used here was partly dependent upon the duration of pregnancy.

As in the previous study, women were divided into those who were not exposed to aspirin (14,956), those with intermediate exposure but poorly defined (24,866) and those who were heavily exposed (1,515). Heavy exposure was defined for pregnancies lasting at least 8 lunar months, as aspirin taken for at least 8 days per lunar month in at least 6 lunar months. For pregnancies of 7 lunar months duration, the drug had to be taken for at least 8 days in each of at least 5 lunar months.

The findings of the study in terms of stillbirths and neonatal deaths according to aspirin exposure during pregnancy are as follows:

STILLBIRTHS, NEONATAL DEATHS, AND MEAN BIRTH WEIGHTS FOLLOWING ASPIRIN EXPOSURE DURING PREGNANCY

GROUPS EVALUATED

Group I: Containing 1,515 heavily aspirin-exposed mother-child pairs.

Group II: Containing 24,866 intermediate aspirin-exposed mother-child pairs.

Group III: Containing 14,956 non-aspirin-exposed mother-child pairs.

Findngs of study

Parameter measured	Group I	Group II	Group III
Number stillbirths	21	296	203
Percent of group	1.4	1.2	1.4
Number of neonatal deaths	17	232	168
Percent of group	1.7	1.0	1.1
Mean birth weight (g) [Standardized (±S.E.M.)]:			
White	3,223(±30.4)	3,268(±4.6)	3,268(±6.1)
Black	3,074(±17.0)	3,047(±4.6)	3,046(±6.2)

The findings demonstrate that in this study there is no evidence that aspirin taken during pregnancy is a cause of stillbirths, neonatal deaths or reduced birth weight. The fact that white children were associated with slightly reduced birth weight and for that matter neonatal deaths could have been in the authors' views due to chance. Opposite trends were evident in black children.

Criticisms of the study by Slone et al. (Ref. 15) discussed above are equally valid here. However, it is the conclusion of Shapiro, et al. that "based on our data, we find no evidence that aspirin as used by pregnant women in the United States is related to perinatal mortality or low birth weight."

(c) *Effects on maternal and newborn hemostatic mechanisms.* (1) *Interference with maternal hemostatic mechanisms.*—In the study of Lewis and Schulman previously mentioned (Ref. 18), the average blood loss at delivery in patients in Group I, patients taking large doses of aspirin for at least 6 months of gestation, was 340±155 ml compared to 244±114 ml and 235±97 ml in the two control groups. This difference was found to be significant (p is less than 0.025) when the results were assessed using Student's t-test.

Collins and Turner (Ref. 16) also found that the incidence of antepartum hemorrhage defined by the authors as "bleeding greater than a show, after 28 weeks gestation," and postpartum hemorrhage defined by the authors as "a blood loss of 600 ml of blood or more in the first 24 hours after delivery," was significantly increased (p is less than 0.001) when group I (constant takers) was compared to controls. In the same study, the authors also found that the incidence of patients requiring transfusions at delivery was markedly increased when groups I and II (constant and intermittent takers) were compared to the control group (12 percent (6 percent versus 0 percent, respectively)).

(2) *Effect of aspirin on newborn hemostasis.* Bleyer and Breckenridge (Ref. 20) studied the effects of prenatal administration of aspirin on newborn hemostasis. Fourteen newborn babies who had been exposed to aspirin during the week prior to birth were compared to 17 children whose mothers had not taken aspirin. The two potentially adverse drug reactions detected were platelet dysfunction and diminished factor XII (Hageman Factor) in neonates born of mothers who had taken ordinary doses of aspirin during the last week of pregnancy. Aspirin-induced platelet dysfunction may have clinical relevance particularly during difficult traumatic deliveries or in the presence of other hemostatic defects. The authors conclude that "until the clinical significance of these findings is more fully evaluated, it would seem prudent to restrict aspirin during the last month of pregnancy."

Preliminary studies of premature infants whose mothers have ingested aspirin during the week preceding delivery suggest that this drug might be a risk factor to these infants and produce clinical bleeding (Ref. 21). Studies are now in progress to confirm this preliminary finding.

Haslam, Ekert and Gillman (Ref. 22) have reported one case of a "life-threatening gastrointestinal hemorrhage" requiring two transfusions in one infant whose mother had taken calcium aspirin (3 tablets of 300 mg on each of the last 3 days of pregnancy, making a total of 2,700 mg). The baby required a transfer to a children's hospital because of vomiting blood at 4, 9 and 10 hours of age as well as rectal hemorrhage (30 ml of blood). Platelet function studies showed that platelet aggregation was impaired. Three weeks after the transfusions, the platelet function had returned to normal.

On the other hand, Turner and Collins (Ref. 14) examined the infants born to mothers who took salicylates regularly during pregnancy and found that although these infants had raised cord-blood levels of salicylate, they did not show signs of clinical bleeding.

(3) *Salicylate exposure in the perinate.* Studies demonstrating the presence of salicyluric acid in neonatal urine specimens have shown intrauterine fetal exposure to aspirin or other salicylates. Umbilical cord sera from 272 consecutively delivered infants were examined for salicylate by Palmisano and Cassady (Ref. 23). Salicylate levels were unexpectedly found to be above 1 mg/100 ml in 26 of the sera (9.5 percent). The degree of fetal exposure to salicylate was indicated by a mean concentration of 3.3 mg/100 ml with a range of 1.2 to 10.9 mg/100 ml in this group. The mean reserve albumin binding capacity in these infants was significantly depressed (p is less than 0.03). The authors reported that unrecognized fetal exposure to salicylate was surprisingly common during late pregnancy. In view of comparable serum protein concentrations, the depression in the mean reserve albumin binding capacity is unlikely to be related to different albumin concentrations between the positive sera and control sera samples. Since salicylates displace bilirubin from its albumin binding sites (Refs. 24 and 25), this could pose problems in neonatal hyperbilirubinemia. The problem seems to be of such importance that Palmisano and Cassady have proposed that blood salicylic acid measurements should be included in the clinical assessment and management of neonatal hyperbilirubinemia (Ref. 23).

Turner and Collins (Ref. 14) had shown that the babies of 144 mothers who took salicylates regularly during pregnancy had increased cord-blood salicylate concentrations. Although maternal blood was not always collected immediately after delivery it was always taken while the mother was still in the labor ward and, as expected, when the maternal blood salicylates concentrations were high, so were the cord-blood concentrations. Unfortunately, because of the timing it was not possible to compare maternal and cord-blood levels directly but in most cases the cord-blood concentrations were higher than the maternal concentrations.

It has been previously shown that the concentration of salicylate in the blood of the infant is usually higher than that of the mother (Refs. 26 and 27). This has been interpreted as an indication that the fetus near birth has the pharmacokinetics of a "deep" compartment with respect to salicylate (Ref. 28).

Furthermore, another factor to consider is that the apparent volume of distribution for salicylates is higher in the neonate (300 to 350 ml/kg) than that for similar doses, on a body weight basis, in older children and adults, namely 200 ml/kg (Refs. 29 and 30).

In a recent report Garrettson, Prockal and Levy (Ref. 29) have described the placental transfer and kinetics of elimination of salicylates in an infant whose arthritic mother took 6.5 g/day aspirin during her entire pregnancy. The baby was born with a salicylic acid concentration of 25 mg/100 ml plasma. While salicylate elimination was slower than in normal adults, it was more rapid than in the newborn whose mother had taken only one small dose of aspirin shortly before delivery. The slower rate of elimination in this infant when compared to adults was described as due to immaturity of the glucuronidation pathway and immaturity of the renal excretory mechanism.

(d) *Conclusions and recommendations.* Any relationship regarding the possibility of any teratogenic effect of salicylates in pregnant women has come from retrospective studies which are indirect and are possessed with obvious shortcomings. As conducted, they do not unequivocally demonstrate a teratogenic effect. Some limitations of the study, as indicated by the authors themselves, are that they cannot distinguish between the effect of the salicylates and the effect of the condition for which the salicylates were taken. In those specific studies (Refs. 14, 15, 18, and 19), in which the delivery of women who had taken salicylates during pregnancy was directly observed, no relationship between salicylates and teratogenicity was found. Even in a survey in which a comparison could be made between mothers of normal infants who

had taken salicylates by prescription during pregnancy and mothers of malformed infants who had taken salicylates by prescription, no difference was found that would demonstrate any relationship between salicylates and malformation in the offspring. Of particular significance in these retrospective studies, is the fact that the women in the study who had delivered malformed infants had taken several drugs other than salicylates, either alone or in addition to salicylates. This meant that many tests for significance had to be done during the statistical analysis to determine whether an association existed between the ingestion of a drug and the development of a malformation in an infant. The authors of the retrospective studies recognize these factors as limitations in the studies, and they state that because so many tests of significance were necessary some of the results of the tests may be due to chance.

Most of the studies relating to pregnancy did show that in those women taking salicylates, adverse effects to the mother and the fetus were significantly increased. High levels of salicylates in cord-blood were correlated with high levels of salicylates in maternal blood. In cases where such correlations were found, adverse effects were significantly increased in the mother and in the infant at delivery. In the mother the adverse effects consisted of an increase in the length of pregnancy and labor, and bleeding before and after delivery (Ref. 16). The fetus was adversely affected as evidenced by a decreased birth weight, and an increase in the stillbirth rate, perinatal mortality rate and decreased albumin binding capacity (Ref. 14).

The Panel is particularly concerned with the effects of chronic aspirin ingestion on the fetus, i.e., decreased birth weight, increased stillbirth rate, perinatal mortality and prolonged parturition. As for the acute administration of aspirin, the Panel is concerned with its effects on increasing duration of labor, changing hemostatic mechanisms in the newborn and increasing maternal blood loss. The latter may be a hazard particularly in premature labor and thus at any time during the last 3 months of pregnancy.

For the reasons detailed in the above paragraphs, the Panel concludes that there is a potential hazard to the use of aspirin during pregnancy and recommends the following warning on all aspirin-containing products "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

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(v) *Adverse effects on the central nervous system.* The lethal dose of aspirin or other salicylates probably is between 20 to 30 g for adults (Ref. 1) but doses of 200 to 300 mg/kg in children usually require hospital treatment (Ref. 2). The major toxic signs and symptoms arise from stimulation followed by depression of the central nervous system. Stimulation reveals itself in many ways including tinnitus (ringing in the ears), rapid breathing, confusion, unusual or bizarre behavior, vomiting, mania and even generalized convulsions. In severe poisoning, the stimulation is followed by depression as shown by respiratory failure, collapse of the cardiovascular system and coma. Tinnitus has been studied recently in man (with rheumatoid arthritis) by Mongan et al. (Ref. 3). In 59 subjects they noted tinnitus to be present in two individuals taking 12 aspirin tablets (3,900 mg) daily. The highest incidence of tinnitus was reported by those patients (14) taking 16 tablets per day. They found the serum salicylate level was invariably greater than 19.6 mg/100 ml when tinnitus was reported. They also observed a lack of correlation between the total daily aspirin ingestion and serum salicylate concentration. The authors emphasize the fact that patients with preexisting hearing loss will not report tinnitus as plasma salicylate concentrations increase.

It has been known for some time that salicylates produce a reversible ototoxicity manifested by deafness (Ref. 4). This was discussed recently by Jick et al. (Ref. 5) who studied drug-induced deafness in 11,526 hospitalized patients. Following aspirin, deafness was noted in 11 per 1,000 patients exposed. It is important for physicians to monitor patients receiving aspirin regularly at higher dosages for hearing loss as well as the presence of tinnitus. Because tinnitus or ringing in the ears is an early and frequent sign of aspirin or salicylate overdosage and the other symptoms mentioned may vary and be misinterpreted, the Panel believes that the labeling of aspirin and other salicylates should contain the following warning: "Stop taking this product if ringing in the ears or other symptoms occur". This built-in

"early warning system" of overdosage is advantageous in that it alerts users to a potential hazard and thereby contributes to the safe use of aspirin.

However, it should be noted that approximately 100 deaths per year result from accidental poisoning by salicylates and congeners (Ref. 6). Until recently, over one-half the deaths have been of children under 5 years of age. This figure has recently declined to approximately one-fourth probably as a result of the introduction of safety closures for medicine containers and educational campaigns.

The Panel has included the following table which summarizes the total number of deaths of children under 5 years and the total number of deaths for all ages from accidental poisonings due to salicylates and congeners for the years 1968 to 1974 (Ref. 3):

Deaths from accidental poisonings due to salicylates and congeners

	1968	1969	1970	1971	1972	1973	1974
Total deaths of children under 5 yr	61	58	48	44	46	26	25
Total deaths for all ages	120	104	107	105	122	95	88

Thus, salicylate poisoning can result in death and these drugs should not be viewed as harmless household remedies. Some authorities (Ref. 7) feel that the toxicity of the salicylates is underestimated by both the general public and physicians resulting in a higher than necessary incidence of toxic reactions most of which, fortunately, are mild and inconsequential.

However, with the consumption of aspirin exceeding 19 billion doses annually in the U.S. the relatively small number of accidental deaths attests to the safety of the salicylates under present conditions of use. The Panel believes that continued education of the public regarding the proper use and the potential dangers of misuse of these valuable OTC remedies and more informative labeling will result in a progressive decrease in the incidence of toxic reactions to aspirin and related drugs.

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(vi) *Adverse effects on the kidney.* Aspirin has been suggested as a contributing factor in analgesic-induced kidney disease. Studies of many animal species and a few individual cases in man have been reported which suggest that aspirin may cause kidney disease or may increase existing kidney disease (Refs. 1 and 2). However, studies in other species of animals have shown no adverse effects (Ref. 3).

In rats, aspirin in combination with phenacetin may augment the nephrotoxic effect of phenacetin through synergistic renal effects (Refs. 3 and 4) producing a greater effect than either aspirin or phenacetin alone. The effects of phenacetin in producing nephropathy are discussed elsewhere in this document. (See part III. paragraph B.2.d. (2) (ii) (*b*) (2) below—Mechanism of action producing nephropathy.) In view of the much higher incidence of the use of aspirin than of phenacetin and the very few reports implicating products containing aspirin alone with renal papillary necrosis, the principal lesions associated with analgesic renal disease, the Panel finds that it is unlikely that aspirin alone is an initiator of analgesic nephropathies. This view is supported by recent epidemiologic studies which show that aspirin alone is not a cause of permanent (irreversible) kidney disease in man even when taken in high doses for prolonged periods of time (Refs. 4 through 8).

There are some indications that long term (chronic) aspirin consumption even in the absence of phenacetin may cause renal dysfunction in a small number of long term aspirin users (Refs. 9 and 10). The majority of these cases involved abuse of analgesic compounds or treatment of rheumatoid arthritis. It is the Panel's opinion that long-term abuse of aspirin, used alone, is infrequent. Almost all nontherapeutic chronic use has been as a component in a mixture containing another ingredient with greater potential to produce dependence (codeine, caffeine, phenacetin). The other major group involved in long-term use are patients with rheumatoid or osteoarthritis. It is the Panel's contention that for this and other reasons elaborated elsewhere in this document that arthritic patients should not be self-medicating without medical supervision. (See part V. paragraph A. below—General Discussion.) In addition, it is the Panel's recommendation that professional labeling to health professionals adequately alert physicians to the need for periodic renal function tests for their patients taking large amounts of aspirin. An OTC kidney warning labeling is therefore not necessary.

The Panel concludes that although prolonged use of high doses of aspirin may produce kidney disease in rare instances, the risk involved is insignificant in the recommended target populations when aspirin alone is involved. In the opinion of the Panel, a warning regarding aspirin causing kidney disease is not warranted for OTC use. However, physicians should be alerted that substitution of aspirin alone or in combination, for phenacetin, in patients with existing analgesic kidney disease, may be tolerated in low doses in some patients but contribute to continued renal deterioration in others.

Furthermore, recent evidence discussed below showing acute effects of aspirin on renal glomerular filtration, indicates that perhaps short term use of aspirin may contribute to or exacerbate other types of chronic or acute renal disease. Although a warning label regarding the use of aspirin in patients with existing renal disease would be premature now, this is only because the definitive studies have not been performed to the Panel's knowledge.

(*a*) *Acute effects (short-term use).* Prescott found that aspirin produces a transient increase in urinary excretion of tubular epithelial cells (Ref. 1). The effect of aspirin was greater than that obtained with phenacetin. The effect does not persist during continued dosing. Two very recent studies have demonstrated that aspirin produces an acute decrease in glomerular filtration rate (Refs. 11 and 12). A mean 10.5 percent decrease in glomerular filtration rate was observed in patients receiving oral doses of 20 mg/kg aspirin (Ref. 10). In another independent study, an intravenous dose of aspirin produced a 30 percent fall in glomerular filtration rate (Ref. 12). This effect is significant since the usual decrease in glomerular filtration rate is only about 20 percent from 25 to 65 years of age (Ref. 13).

It is not known whether these acute effects of aspirin on the kidney contribute to long term analgesic nephropathy. Some authors believe this is unlikely (Ref. 14). The significance of these findings relative to the short-term use of aspirin in patients with acute or chronic renal disease is also not yet known.

(*b*) *Analgesic nephropathy.* A large number of studies in rats have shown that, in this species, aspirin alone can produce renal papillary necrosis, the primary kidney lesion associated with analgesic kidney disease (Refs. 1, 2, 15, and 16). Combinations of aspirin and phenacetin produced renal papillary necrosis more frequently than aspirin alone. In rats, aspirin alone produced renal papillary necrosis in a generally greater number of cases than phenacetin alone (Ref. 15).

Renal papillary necrosis has also been induced in the dog. However, most animal studies have been carried out in the rat.

The rat kidney is different than that of man. Being unilobular and having a long slender papilla, it has been suggested that the rat kidney may be much more susceptible to papillary damage (Ref. 17). The pig was selected as a more suitable test animal because it has a multilobular kidney similar to that of man and is thought to metabolize salicylate similarly to man. McIver and Hobbs fed aspirin to 11 pigs for 10 months at a dose higher than that usually used by abusers without any evidence of renal injury to any of the animals (Ref. 13).

(c) *Clinical studies.* In spite of the extensive use of aspirin and numerous attempts to show correlation between chronic aspirin use and renal papillary necrosis, there are less than 10 cases of renal papillary necrosis reported in the world literature that are associated with the use of aspirin only (Refs. 1, 6, 9, 10, 18, and 19). The possibility of a causative role of aspirin when used alone in large long term doses has been the subject of several epidemiologic studies.

A recent study of the Boston Collaborative Drug Surveillance program reported by Lawson (Ref. 20) examined a possible correlation between analgesic use and renal function in 6,407 patients and found no correlation. As discussed elsewhere in this document, the negative results of this study are inconclusive because the study design (error due to drug, dose, time) is such that real associations are unlikely to be detected. (See part III, paragraph B.2.d.(ii)(*b*)(*1*) below—Epidemiological studies.) This study also could not show any association between renal dysfunction and ingestion of phenacetin compounds.

The better controlled long-term prospective study of Dubach clearly showed an association between analgesic abuse of phenacetin combinations and decreased renal function (Ref. 4). No such correlation could be demonstrated in those patients taking preparations containing only aspirin.

In a recent study by Emkey and Mills (Ref. 5), it was shown that prolonged high doses of aspirin given to patients with rheumatoid arthritis do not cause significant kidney damage. They studied all patients with rheumatoid arthritis followed at the Massachusetts General Hospital Arthritis Clinic who had been taking aspirin for 10 or more years. There were 36 patients whose average age was 60.5 years, mean duration of therapy was 23 years, and mean daily ingestion was 5 g aspirin. The average total amount of aspirin ingested was 42 kg. Studies of renal function and urinary abnormalities revealed that although minor histological or functional renal abnormalities could not be ruled out, no permanent kidney damage could be demonstrated in these patients.

Macklon and coworkers (Ref. 6) initially studied renal function in 17 patients with rheumatoid arthritis who had ingested 5 to 20 kg aspirin. Renal function was assessed by measuring serum creatinine, creatinine clearance and proteinuria. Fourteen of these patients were followed up after 2 years. No evidence of permanent renal damage was found.

The New Zealand Rheumatism Association Survey in 1974 (Ref. 8) of 763 patients with rheumatoid arthritis and 145 patients with osteoarthritis, showed no association between aspirin (alone) intake and a renal score designed to identify analgesic nephropathy. Analgesic nephropathy was detected in three patients taking APC (aspirin, phenacetin and caffeine) compounds, one taking aspirin and phenylbutazone and one taking aspirin and acetaminophen. The New Zealand Rheumatism Association concluded that there is risk from APC compounds but not aspirin alone. However, aspirin may have an additive or potentiating effect with other analgesics.

Bulger (Ref. 7) found a correlation between the total dose of aspirin ingested and the depression of creatinine clearance in rheumatoid arthritis. These findings were not corrected for age of the patients, and none had a creatinine clearance less than 50 even though one patient took a total dose of 40 kg aspirin.

The Panel concludes, that in view of the much higher incidence of the use of aspirin than phenacetin and the very few reports implicating products containing aspirin alone with renal papillary necrosis, it is unlikely that aspirin is an initiator of serious kidney disease. However, it has been suggested that products containing aspirin, alone, can exacerbate and/or perpetuate the progression of papillary necrosis and renal dysfunction (Refs. 1 and 2). Aspirin may contribute to the nephrotoxic effect of phenacetin through the impairment of renal concentrating mechanisms (Ref. 15) or other possible mechanisms. Burry (Ref. 21) speculates that the initial damage occurs in the ascending limb of the loops of Henle. Ischemia may be caused by inhibition of prostaglandin E, synthesis by aspirin. Phenacetin and its metabolites have a profound oxidative effect on cells with salicylate-induced suppression of the hexose monophosphate shunt. Burry and others have suggested that aspirin may contribute to renal papillary necrosis through an additive effect even though aspirin alone is rarely associated with renal papillary necrosis (Refs. 8 and 21).

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(vii) *Adverse effects on the liver.* Several recent studies have confirmed that aspirin causes a reversible hepatotoxicity (Refs. 1 through 9). Increased hepatic dysfunction after aspirin ingestion has been identified by increased serum activity of transaminase (Refs. 1 through 4), serum glutamic oxaloacetic transaminase (SGOT) (Ref. 2), serum glutamic pyruvic transaminase (SGPT) (Ref. 2) and decreased activity of aspirin esterase (Ref. 9).

The increased incidence of hepatotoxicity has generally been observed in children (Ref. 2) and adults (Refs. 7 and 8) of both sexes treated for systemic lupus erythematosus or rheumatoid arthritis requiring moderate doses over a period of several weeks. The effect is apparently a function of dose (Refs. 2 and 10), plasma salicylate level (Ref. 10), the disease state and preexisting liver disease (Ref. 9).

In children treated for juvenile rheumatoid arthritis requiring high plasma

salicylate levels, over 65 percent experience elevated transaminase activity (Ref. 2).

Seaman and Plotz gave aspirin four times daily at a dose sufficient to obtain a serum salicylate level of 25 to 30 mg/100 ml (Ref. 6). They observed increased transaminase activity in 3 of 18 rheumatoid arthritis patients. Patients with systemic lupus erythematosus required lower salicylate plasma concentrations to produce hepatitis. Some patients experienced a fall in elevated transaminase activity even though the multiple aspirin dosing was continued. Others maintained high transaminase activity until aspirin therapy was stopped or the dose reduced.

Rich and Johnson reported dose-related hepatotoxicity of salicylates in six children with severe rheumatoid arthritis (Ref. 2). Elevated SGOT and SGPT activities were observed in all patients and occurred only when serum salicylate levels were above 25 mg/100 ml. The effects occurred with sodium and choline salicylic acid salts as well as aspirin. A reduction of the dose reversed the effect indicating that the effect is primarily a function of salicylic acid level, rather than aspirin per se and is a reversible process. Clinical symptoms were also manifest in four patients. Liver biopsies were done in two patients which showed histological evidence of liver damage with scattered cell necrosis evident in one case.

Aramaki et al, studied 42 patients with various diseases given 2 g aspirin daily for 3 to 4 weeks (Ref. 9). They concluded that aspirin caused liver damage only in adult patients with impaired liver function. They found aspirin esterase enzyme activities decreased after aspirin administration in 8 of 14 patients with liver damage but slightly increased in those patients without liver disease. The decrease in aspirin esterase correlated with elevated transaminase in six of the eight patients with liver disease.

In view of the recent findings which have confirmed that aspirin causes a reversible hepatitis, especially in children and adults with systemic lupus erythematosus or rheumatoid arthritis and for other reasons elaborated elsewhere in this document, the Panel concludes that arthritic patients should not be self-medicating without medical supervision. (See part V. paragraph A. below—General Discussion.) In addition, it is the Panel's recommendation that professional labeling to health professionals adequately alert physicians to the need for periodic liver function tests. An OTC liver warning labeling for this group is therefore not necessary.

The Panel concludes that although prolonged use of high doses of aspirin may produce hepatotoxicity, the effect is dose related, dependent upon the disease state for which aspirin is indicated, and is a function of any preexisting liver disease. In the opinion of the Panel, a warning that aspirin may cause liver disease is not warranted.

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(viii) *Adverse effects of concomitant use with other drugs or by persons with certain disease states.* The Panel has earlier briefly discussed the need for caution in the use of salicylates, especially aspirin, in the presence of serious illness and medical conditions for which prescription drugs are indicated. (See part II. paragraph H. above—Drug Interactions with Analgesic, Antipyretic and Antirheumatic Agents.) Reports have indicated possible drug interactions between the salicylates and other drugs (Refs. 1 through 7). Individuals who are taking prescription drugs may also use OTC analgesics, antipyretics or antirheumatics containing salicylates to relieve pain, fever or headache without consulting a physician. Therefore, to alert such individuals that a drug interaction may occur between their prescription drugs and salicylates, the Panel recommends that the labeling of these OTC products contains a general warning against the concurrent use of salicylate-containing products and certain prescription drugs. The warning on products containing salicylates should read *"Caution:* Do not take this product if you are presently taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout or arthritis except under the advice and supervision of a physician".

The effects of a drug may be modified by prior or concurrent administration of salicylates. Such modifications or drug interactions may alter the effectiveness or toxicity of a drug by several mechanisms. Pharmacokinetic interactions and pharmacologic interactions are the two best understood mechanisms by which salicylates may modify the actions of drugs. In pharmacokinetic interactions, salicylates affect the absorption, metabolism, distribution or excretion of other drugs. Salicylates may also alter the pharmacologic effects of other drugs by producing an additive, synergistic or antagonistic pharmacologic effect. In the interaction of prescription drugs with salicylates, both of these mechanisms operate to modify the effectiveness and/or toxicity of prescription drugs.

Salicylates may interfere with or modify the effect of drugs that are taken for therapeutic use in the following disease conditions:

(a) *Anticoagulants used in the treatment of blood diseases.* As the Panel has noted above, high doses of aspirin and salicylic acid taken for several days can increase prothrombin time significantly. (See part III. paragraph B.1.a.(2)(i)(a) above—Decrease in prothrombin production.) Aspirin in doses below those required for a hypoprothrombonemic effect may also increase bleeding time by inhibiting aggregation of platelets. (See part III. paragraph B.1.a.(2)(i)(b) above—Increased bleeding time and inhibition of platelet aggregation.) Aspirin, particularly, should be avoided when oral anticoagulants (especially the coumarins) are taken. Anticoagulants are prescribed for thrombophlebitic and thromboembolic states including postoperative thrombophlebitis, pulmonary embolism and coronary thrombosis.

Aspirin has an additive effect on the action of anticoagulant drugs. Coumarin anticoagulants [coumadin (warfarin sodium), dicumarol (bishydroxycoumarin), acenocoumarol, ethyl biscoumacetate, and phenprocoumon] as well as indandione anticoagulants (anisindione, diphenadione, and phenindione) would all be expected to act in a similar manner (Ref. 6). The inhibition of platelet aggregation by which aspirin can significantly increase bleeding time, may preclude its concurrent use with heparin.

The available clinical data actually provides conflicting reports with regard to the effects of aspirin on the prothrombin time response to warfarin and other oral anticoagulants. Nevertheless, in view of aspirin's effect on gastric erosion, its inhibition of platelet activity, and its possible direct inhibition of the prothrombin complex, the possibility of inducing a clinically significant problem in patients receiving oral anticoagulants needs to be recognized (Ref. 6). The concurrent use of large doses of salicylates and anticoagulants may lead to severe hemorrhage unless the dosage of the anticoagulant is reduced or the individual stops taking the OTC salicylate (Ref. 2).

The Panel recommends that nonsalicylate analgesics be used in patients requiring oral anticoagulants of the coumarin type. Since documented adverse effects with salicylates have been shown to be directly related to oral anticoagu-

lants, and since the use of anticoagulants must be closely monitored by a physician, the Panel concludes that the term "anticoagulant drug" should be included in the general warning statement. It is the Panel's view that patients currently taking such prescription drugs are under the close supervision of a physician. These patients will be aware that they are taking anticoagulant drugs, and it is important that they be immediately alerted through adequate labeling not to take salicylates concurrently.

(b) *Hypoglycemic effect with antidiabetic drugs.* The hypoglycemic (low blood sugar) activity of the oral antidiabetics (sulfonylureas) may be enhanced by the concurrent administration of salicylates. It should be noted that salicylates, themselves, were among the first compounds used for their hypoglycemic effect. The exact mechanism of the hypoglycemic effect of salicylates is not completely understood. Several mechanisms by which aspirin may decrease plasma glucose levels have been postulated, among which are hepatic glycogen depletion and increased glucose utilization.

It has been reported that the hypoglycemic activity of the antidiabetic drug, chlorpropamide, may be enhanced by the concurrent administration of aspirin (Ref. 6). Chlorpropamide is chemically related to other hypoglycemic agents such as tolbutamide, acetohexamide and tolazamide and a similar interaction with aspirin may possibly occur. The interaction between salicylates and oral antidiabetic drugs would result in a prolonged and protracted fall in plasma glucose levels. The mechanism by which this effect is brought about has been attributed to salicylate displacing the antidiabetic agent from its binding sites rather than to any intrinsic hypoglycemic activity of the salicylates. The displacement would increase the amount of free (pharmacologically active) antidiabetic drug in circulation and increased hypoglycemia would result. The interaction would result in poor control of diabetes (Ref. 5). The only alternative, if both drugs were required, would be to decrease the dosage of the antidiabetic drug during salicylate intake and then to increase the dosage when salicylates were discontinued. This would need to be accomplished under the direct supervision of a physician.

There have been no controlled clinical trials demonstrating a direct relationship between chlorpropamide and aspirin. However, as has been pointed out, the literature does indicate that the hypoglycemic activity of chlorpropamide may be enhanced with use of aspirin, but maybe only at uricosuric doses. Nevertheless, because of this possibility and because salicylates do have hypoglycemic properties, the Panel recommends that the general warning advise against the use of salicylates concurrently with prescription drugs used in the treatment of diabetes.

(c) *Uricosuric inhibition in gout.* Individuals with gout have high serum uric acid levels. Several prescription drugs are prescribed for gout to decrease uric acid blood levels by increasing the renal excretion of uric acid (uricosuria). These drugs include probenecid, the sulfinpyrazones and phenylbutazone. Aspirin has been reported to specifically interfere with the uricosuric action of sulfinpyrazone. High serum uric acid levels and mutual suppression of uricosuria occur in humans when both drugs are used concurrently (Ref. 6).

The concurrent use of salicylates with uricosuric drugs results in the inhibition of the excretion of uric acid in the urine (uricosuria inhibition) and thereby results, in effect, in the antagonism of the activity of these drugs (Ref. 5). Uric acid is normally reabsorbed into the body and not excreted by the kidney. The uricosuric agents used in gout block the reabsorption of uric acid from the urine to the plasma and thus increase the excretion of uric acid. It is interesting to note that salicylates alone have a pronounced uricosuric effect in high doses and can be used to reduce high uric acid levels in gout, but in OTC doses, aspirin causes retention of uric acid. Hence in the latter instance the uricosuric effect of the uricosuric agents may be counteracted. This interaction in low OTC doses may cause a suppression of uricosuria which results in uric acid retention in the body; uricosuria is prevented and the therapeutic action of the drug is negated.

Salicylates and uricosuric agents compete for common binding sites on plasma proteins and for active tubular transport in the kidneys. Concurrent administration decreases the binding of the uricosuric agents. The salicylate binding remains unaltered, reducing the excretion of the salicylates.

The Panel concludes that individuals with gout should avoid salicylates. Because salicylates have been shown to antagonize the effects of uricosuric agents, the Panel recommends that the general warning advise against the use of salicylates concurrently with prescription drugs used in the treatment of gout.

(d) *Ulcerogenic enhancement in arthritis.* Almost all anti-inflammatory agents commonly used in rheumatic diseases can cause gastric ulcers. These agents include aspirin, corticosteroids, phenylbutazone and indomethacin. Although the mechanisms by which the ulcerogenic effect is produced by these agents are not definitely established, the possibility of an increased incidence of gastric ulceration when aspirin is used concomitantly with other ulcerogenic anti-inflammatory agents must be considered.

When corticosteroids and salicylates are taken concurrently, the ulcer-producing effect in the stomach is additive. An increased ulceration hazard occurs. In addition, the corticosteroids may increase the excretion of salicylates so that to achieve a therapeutic anti-inflammatory and/or analgesic effect, the dose of the salicylates must be increased. If the steroids are then withdrawn, the continuing high dose salicylate medication may lead to signs of salicylate toxicity (Ref. 5).

The combined use of indomethacin and salicylates also poses an increased potential for gastric ulceration since both indomethacin and salicylates have an ulcer-producing effect on the mucous membrane of the stomach (Refs. 1 and 5). The use of aspirin with indomethacin is particularly hazardous since aspirin appears to have some inhibitory effect on the gastrointestinal absorption of indomethacin. Aspirin decreases and delays the gastrointestinal absorption of indomethacin causing a decrease in the indomethacin serum level and urinary excretion, and a rise in the fecal excretion of indomethacin (Ref. 6). The concurrent use of the two drugs does not produce an additive therapeutic effect but may increase gastric ulceration.

The Panel concludes that individuals taking antirheumatic agents for the treatment of arthritis should not self-medicate with salicylates. Because salicylates increase the potential for gastric ulceration and because aspirin has been shown to decrease and delay the gastrointestinal absorption of a commonly used antirheumatic agent, e.g., indomethacin, the Panel recommends that the general warning advise against the use of salicylates concurrently with prescription drugs used in the treatment of arthritis.

(e) *Other drug interactions of varying significance.* The Panel has considered several other interactions between salicylates and prescription drugs which the Panel does not consider warrant inclusion of a warning in the labeling of salicylates. The clinical significance of these interactions is not sufficiently urgent, either because individuals taking these prescription drugs are under close medical supervision, are not taking these drugs chronically or because there is little likelihood of toxicity.

An example of an interaction with a prescription drug that is closely supervised by a physician, is methotrexate. This drug is a highly potent and very toxic drug which is prescribed for individuals with cancer or extensive psoriasis or psoriatic arthritis. Salicylates potentiate the therapeutic as well as the toxic effects of this drug (Ref. 5). The Panel is cognizant of the severity of this interaction, particularly of its immunosuppressive effect. However, because of the severe toxicity of methotrexate, physicians always carefully control the patient's use of all other medications, thereby negating the need for a warning.

Sulfonamides are antibacterials employed primarily in the treatment of urinary tract infections. It has been suggested that the increased antibacterial activity resulting from the interaction with salicylates is due to the ability of salicylates to decrease the serum protein binding of sulfonamides, thus increasing the amount of free drug (pharmacologically active) (Ref. 6). Even though this interaction can be potentially serious, sulfonamides are usually used for treatment of active infections, not for chronic conditions, and thereby do not merit inclusion in a warning.

An interaction which the Panel does not consider enough of a hazard to justify inclusion in the warning concerns the concurrent use of salicylates with drugs that result in changing the pH of the urine. Some substances, such as ascorbic acid (vitamin C), increase the acidity of the urine. The acidification of the urine increases the renal tubular reabsorption of salicylates, thus decreasing the excretion of the salicylates and increasing the salicylate level in the blood (Ref. 5). On the other hand, when substances, such as sodium bicarbonate, are taken, the urine becomes alkaline. Under alkaline conditions, the excretion rate of salicylates is increased, decreasing salicylate levels in the blood (Ref. 3). For salicylates to reach toxic levels in the blood when urine acidifiers are taken concurrently, high doses of salicylates would have to be ingested. The Panel does not believe that this interaction is important since in the usual OTC use of salicylates, it is unlikely that an ascorbic acid salicylate type of interaction would result in toxic salicylate levels in the blood.

For patients with disease conditions that require prescription drugs but which do not require the constant or daily supervision of a physician, the Panel recommends that a warning on the labeling of OTC salicylates is necessary, to warn the patient against serious potential interaction with salicylates. The Panel has therefore concluded that the warning against the use of salicylates with drugs prescribed for specific kinds of disease conditions, i.e., anticoagulants and drugs used in the treatment of gout, diabetes and arthritis, is adequate for the labeling of OTC salicylates.

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(ix) *Adverse effects resulting in iron deficient anemia.* Occult blood loss is usually not clinically significant (Refs. 1 and 2), but prolonged use of aspirin can result in greater occult bleeding in some patients and cause a persistent, otherwise inexplicable, iron deficient anemia (Refs. 3 through 4). This has been observed in adults, particularly in some studies in rheumatoid arthritis (Ref. 5). At the same time it is known that anemia associated with some rheumatoid diseases will improve when the disease is brought under control with therapeutic doses of aspirin. Aspirin has been recently re-emphasized as an important consideration in the diagnosis of anemia in children (Ref. 6).

Aspirin causes occult blood loss from the gastrointestinal tract. This has been discussed extensively elsewhere in this document. (See part III. paragraph B.1.a.(2)(ii)(e) above—Occult bleeding.)

Stubbe (Ref. 1), in a study on the presence of occult blood in the feces due to aspirin ingestion, stated that:

> It has been demonstrated that the loss of blood (produced by aspirin) may not always be ignored; this applies especially to the extent to which the patient is already anaemic and in a bad state generally. The taking of aspirin over a long period is most common in the case of persons suffering from rheumatoid arthritis. Many such patients are anaemic, a state of which has always been regarded as a consequence of the rheumatic process. Now that we know that aspirin can cause bleeding, it may be asked whether this has not likewise often played a more or less important part in bringing about anaemia.

Holt (Ref. 2), in a study in which gastrointestinal blood loss was measured after aspirin ingestion, found that 69 percent of 35 subjects who were ingesting 40 gr of aspirin (8 tablets daily) were losing blood and that 17 percent lost more than 6 ml (an average of 20-fold over control values). Ten of the 35 were "healthy" volunteers tested at the same doses, all 10 bled with an average blood loss of 5.7 ml daily. Fourteen out of the remaining 25 subjects who bled had an average blood loss of 3.3 ml daily. These latter subjects were patients with negative histories of gastrointestinal bleeding. This difference was found not to be statistically significant. Holt concluded that "This suggests that alimentary bleeding represents a very frequent side effect of aspirin therapy, and in some patients chronic ingestion of salicylates may be accompanied by sufficient blood loss to induce iron deficiency over a prolonged period."

The first report directly linking the consumption of aspirin with anemia appeared in 1958 (Ref. 3). The authors described two cases of patients with severe anemia due to the ingestion of salicylates. The first, a 39-year-old man, complained of fatigue and exertional dyspnea. For 7 years he had suffered from migraine headaches and had taken an average of 8 to 10 tablets of aspirin weekly. His hemoglobin was 8.4 g/100 ml and there were hematological features of iron deficiency. A history failed to reveal the cause of the anemia, and after responding to intravenous iron therapy he was discharged to the outpatient department where he was followed with oral iron treatment. Six months later he was readmitted to the hospital with severe anemia (hemoglobin 4.2 g/100 ml). He again responded favorably to intravenous iron therapy and then continued iron injections as an outpatient.

The clinical and hematological findings were compatible with iron deficiency anemia due to chronic hemorrhage. Occult blood tests in the stools were negative while the patient was hospitalized. It was difficult to diagnose the reason for the anemia.

Then, on two occasions aspirin (10 gr) was administered three times daily and the occult blood tests showed strongly positive results. Confirmation of the relationship between salicylate consumption and the anemia was obtained when the patient was advised to discontinue the intake of aspirin. Iron therapy could soon be discontinued and at the time of publication there was no recurrence of the anemia.

The other case described in this report was that of a 29-year-old woman who was admitted to the hospital for the treatment of anemia. She also complained from fatigue and exertional dyspnea, as well as epigastric pain and "acid-regurgitation". She had had severe headaches for a year for which she took up to "30 salicylate tablets" weekly. Her history also included a complication of hemorrhage during her "fourth confinement" (fourth child delivery) for which she had received a blood transfusion and iron tablets. Examination revealed severe anemia (hemoglobin of 5.6 g/100 ml) apparently due to iron deficiency. She responded well to oral iron therapy. After leaving the hospital she regularly attended the outpatient clinic. The anemia recurred and required continuous iron therapy which had to be supplemented on two occasions with intravenous iron. She had a dilatation and curetage and then a total hysterectomy. She still remained anemic and did not respond to a 6-month course of oral iron. Her anemia worsened to 4.2 g of hemoglobin per 100 ml and she was again hospitalized. Her serial stool occult blood tests were negative. The diagnosis for the cause of the anemia in this case was again very difficult. The patient was experimentally administered 10 gr aspirin four times daily which was followed by strong occult blood reactions in the stools.

This patient again was advised against salicylate ingestion and an alternative analgesic was suggested. The patient started to take salicylates after having recovered from the anemia and again her hemoglobin decreased from 14.6 to 11.2 g/100 ml. Eventually, after repeated exhortations the patient stopped taking salicylates and recovered. This latter case has been described in what may seem excessive detail; however, the purpose is to illustrate that in this case, because of the failure to obtain an early correct diagnosis, this woman had to undergo not only anemia of long time duration but dilatation and curetage and eventually even hysterectomy at the age of 29 years.

Stubbe has described 16 cases of severe iron deficiency anemia due to blood loss associated with aspirin ingestion (Ref. 4). Stubbe comments:

In every patient the use of aspirin, even if not the sole cause, played an important role in the development of the condition. There were no indications of peptic ulcer, profuse menses or haemorrhagic diathesis in any of these patients. It appears that the use of aspirin certainly does not need to be extravagant to play a predominant role. The main feature of these 16 patients, all of whom developed strongly positive benzidine reactions after the administration of aspirin, were:

(i) reason for taking aspirin: rheumatic complaints, 4; headache, 12 (patients);

(ii) daily dose of aspirin 0.5–3 g in 15 (patients);

(iii) Age less than 25 years in 9;

(iv) Sex: 15 females

(v) Hemoglobin less than 9.0 g/100 ml in 15.

He then commented on the difficulties of diagnosing this type of anemia: "As a rule aspirin is no longer given after admission, and so the role of this drug will often be masked and will therefore not be found unless one is conscious of this process."

All the patients reported by Stubbe had also a low serum iron and a high iron binding capacity.

Menguy in a review of the clinical, pathological and pathogenetic aspects of gastric mucosal injury induced by aspirin described two other cases of aspirin-induced anemia (Ref. 5). The first case was that of a 60-year-old retired pharmacist with severe iron deficiency anemia. His hematocrit had never risen over 30 percent except immediately after each of the many transfusions he had received. When the attending physician, to whom the patient had been referred, inquired about aspirin ingestion, which had never been explored before, the patient confided he had been taking 2 g aspirin daily over the past 2 to 3 years. Initially, he had taken them for headaches, then it became a "habit." Tests for fecal blood were carried out using ^{51}Cr-tagged red blood cells during and after the administration of 2 g aspirin daily. After the results of the tests were disclosed to the patient he stopped taking salicylates, and without any transfusion his hematocrit rose from 19 percent upon admission to 25 percent 2 weeks later a month later it was 34 percent and 3 months later it was normal.

The second case described in this report was that of a 40-year-old woman who was admitted with severe anemia after an episode of melena.

The patient later admitted taking an aspirin-containing preparation (an average of 100 tablets weekly) over the previous 6 months. This one is the only case in the literature reviewed where the anemia was due to excessive doses of an aspirin-containing analgesic preparation.

More recently five cases of aspirin-induced anemia have been reported to occur in children (Ref. 6). The first case was that of a 3-year-old child who had received 150 mg aspirin nightly as a "sedative". His hemoglobin was 5.2 g/100 ml and his blood showed an iron deficiency anemia pattern. After he stopped taking aspirin, the anemia did not recur. The second case involved another 3-year-old child with a hemoglobin of 4.3 g/100 ml and his blood again showed an iron deficiency anemia pattern. The results of occult blood tests in the stool were positive on the first 3 days after admission. From repeated history-taking, it was found that the boy had been taking two to three 300 mg aspirin tablets daily for many months as a "sedative". The third case was that of a 14-year-old boy with a hemoglobin of 5.8 g/100 ml and the blood film was classical of iron deficiency anemia. The occult blood tests were positive for the first 5 days after admission. After repeated questioning the boy disclosed that he had been taking 600 mg aspirin daily and often 600 mg at night for 6 months "to relieve mild tooth aches, headaches and sleeplessness."

Case 4 involved a 12-year-old girl with a hemoglobin of 7.1 g/100 ml and again the blood film showed iron deficiency anemia. She eventually admitted having taken 600–1,200 mg aspirin daily for 4 months before admission to the hospital.

Case 5 was a 8-month-old infant who had a hemoglobin of 7.4 g/100 ml and the blood film showed iron deficiency anemia. Stool occult blood tests gave positive results. On closer questioning the parents admitted that the baby had received 2 "junior" 150 mg aspirin daily for the previous 6 to 8 weeks for febrile episodes, teething and as a "sedative". Aspirin was stopped, the anemia responded to iron therapy and the baby remained well thereafter.

The similar pattern in all five children and the complete recovery when aspirin ingestion was stopped suggests strongly that the aspirin ingestion caused the anemia.

All of the cases in this review of the literature suggest that caution should be exerted during aspirin therapy and that when pallor, fatigue and easy exertion are the symptoms the possibility of aspirin-induced anemia should be investigated.

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(3) *Dosage.* (i) *For products containing 325 mg (5 gr) per dosage unit.* (*a*) *Standard schedule.* Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg (7.5 gr) every 4 hours while symptoms persist not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while symptoms persist not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while symptoms persist not to exceed 1,625 mg (25 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg (3.75 gr) every 4 hours while symptoms persist not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while symptoms persist not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(*b*) *Nonstandard schedule.* Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *For products containing 80 mg (1.23 gr) per dosage unit.* Children 11 to under 12 years oral dosage is 480 mg (7.38 gr) every 4 hours while symptoms persist not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while symptoms persist not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while symptoms persist not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while symptoms persist not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 160 mg (2.46 gr) every 4 hours while symptoms persist not to exceed 800 mg (12.3 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(iii) *For products containing more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) per dosage unit.* Adult oral dosage is more than 325 mg (5 gr) but not more than 842 mg (12.96 gr) initially, followed by more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) every 3 hours while symptoms persist not to exceed 3,789 mg (58.32 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(iv) *For products containing more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) per dosage unit.* Adult oral dosage is more than 421 mg (6.48

gr) but not more than 970 mg (14.92 gr) initially, followed by more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) every 4 hours or 842 mg (12.86 gr) but not more than 970 mg (14.92 gr) every 6 hours while symptoms persist not to exceed 3,880 mg (59.68 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(v) *For products containing more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) per dosage unit.* Adult oral dosage is more than 485 mg (7.46 gr) but not more than 1,000 mg (15.38 gr) initially, followed by more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) every 3 hours or 970 mg (14.92 gr) but not more than 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(vi) *For products containing more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) per dosage unit.* Adult oral dosage is more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (*a*) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

(*b*) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(*c*) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(ii) *Standard aspirin dosage unit.* In the previous discussion on "standard strength" dosage forms, the Panel made clear the need to indicate both the quantity of aspirin per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing aspirin differs per dosage unit from the established standard of 325 mg (5 gr) aspirin per dosage unit. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that all products containing aspirin be clearly labeled as containing aspirin on the principal display panel. In addition, labeling shall state in metric units and secondarily in apothecary units the quantity of aspirin per dosage unit. As previously stated, such labeling will not only benefit all consumers but will alert those individuals having sensitivity to aspirin.

(*a*) *Products containing the standard aspirin dosage unit.* The Panel recommends that products containing only 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) aspirin per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(*b*) *Products containing aspirin in an amount different than the standard aspirin dosage unit.* While the Panel recommends that products contain only 325 mg (5 gr) aspirin per dosage unit, if the Food and Drug Administration is unable to implement this recommendation, the Panel recommends that products containing an amount of aspirin other than 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg (X gr) aspirin per dosage unit compared to the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount "X" of aspirin for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

b. *Acetaminophen.* The Panel concludes that acetaminophen is a safe and effective OTC analgesic when taken in the recommended dosage of 325 to 650 mg every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* This drug belongs to a group of drugs which were introduced into therapeutic use before the era of well-controlled clinical trials. Acetaminophen (N-acetyl-p-aminophenol) was first used by von Mering in 1893 (Ref. 1). Yet, as Beaver has observed, there have been a number of suitably controlled studies of its analgesic effect in man in the past few decades as noted below.

While acetanilid and phenacetin have been used extensively since the time of their introduction, acetaminophen was used very little until Brodie and Axelrod demonstrated that in man, both acetanilid and phenacetin are converted into acetaminophen and proposed that acetaminophen may be the "active" metabolite through which both precursors exerted their pain relieving and fever reducing effects (Refs. 2, 3, and 4).

Flinn and Brodie in 1948 evaluated the effect of 325 mg of acetaminophen in 12 normal healthy females subjected to experimental pain by means of heat radiation. They found that within 30 minutes following administration the pain threshold rose significantly. The analgesic activity was maximal at approximately 2.5 hours and was terminated at about 4 hours after administration. They also showed that the analgesic effect obtained with acetaminophen was significantly superior to that of placebo (Ref. 5).

Zelvelder administered repeated doses of 500 mg acetaminophen, 500 mg aspirin and placebo in a crossover study in patients with chronic pain of different causes and found both analgesics superior to placebo (Ref. 6).

Batterman and Grossman evaluated the analgesic activity of acetaminophen in 234 patients with musculoskeletal pain using doses of 300 or 600 mg 4 times daily for up to 25 weeks. They concluded that with the exception of inflammatory pathological situations acetaminophen was superior to aspirin for the treatment of musculoskeletal pain (Ref. 7).

In a double-blind study Wallenstein and Houde compared aspirin, acetaminophen and salicylamide, all at a dose of 600 mg, against placebo in a population of hospitalized cancer patients. The time-effect curves were similar for acetaminophen and aspirin and both were greater in peak effect and in duration than those for salicylamide and placebo (Ref. 8).

Lasagna, Davis and Pearson (Ref. 9) carried out a double-blind study in 373 patients who had just undergone childbirth. Acetaminophen, phenacetin and aspirin, 600 mg of each, were compared against placebo. They concluded that "in agreement with the findings of other workers, our data show that acetaminophen is, in commonly recommended doses, an effective analgesic which can be satisfactorily substituted for acetylsalicyclic acid."

Kantor et al. compared aspirin at two dose levels, 600 and 1,200 mg, acetaminophen at 600 mg, and placebo in patients who had just undergone childbirth and found the three drug treatments were all significantly superior to placebo but not significantly different from each other (Refs. 10 and 11).

Parkhouse and Hallinon (Ref. 12) in a double-blind study in post-operative orthopedic patients, in which a nurse-observer and the patient assessed the pain, found that both 600 mg aspirin and 1 g acetaminophen were easily distinguishable from placebo.

In the study of Moertel, Ahmann, Taylor and Schwartau (Ref. 13) acetaminophen rated fourth after aspirin, mefenamic acid and phenacetin in the patients' ratings which were from 1 to 10 and it rated third in a mean percentage relief of pain. They concluded that acetaminophen or phenacetin would be a reasonable alternative in case of aspirin intolerance.

In *AMA Drug Evaluations* (Ref. 14), acetaminophen effectiveness is described as follows: "The analgesic and antipyretic efficacy of phenacetin and acetaminophen is equal to that of aspirin; however, unlike aspirin, these two analgesics do not have anti-inflammatory or uricosuric effects and thus are not as useful in the treatment of rheumatic diseases."

The Panel reviewed unpublished well-controlled double-blind studies where acetaminophen was studied in patients with headache (Refs. 15 and 16). Acetaminophen 650 mg, was shown to be effective in the treatment of headache. Additionally, in another double-blind crossover study of patients with migraine headache (Ref. 17) patients received (a)

a combination of 65 mg isometheptene, 325 mg acetaminophen and 100 mg dichloralphenazone, (b) 325 mg acetaminophen and (c) placebo. Only the combination showed to be superior to placebo in this type of headache.

In another study, not controlled, a combination of acetaminophen and Vitamin C was studied in 45 patients with pain of different etiology (Ref. 18). The doses used were four to six tablets (containing 330 mg acetaminophen) per 24 hours. Nine of these patients had headache, and positive, favorable results were obtained in all of them. Four of these patients had pain described as neuralgia and all four obtained relief using this dose.

In another uncontrolled study by Perrin (Ref. 19) acetaminophen in combination with Vitamin C (doses not given) was evaluated in 1,000 patients with pain of different etiology. Of these, 96 patients were admitted into the study for headache. The results are mostly analyzed in global form for all patients included. However, the following statement is made: "patients with headache reacted well and were alleviated rapidly." Unfortunately, the doses and dosage regimen are not specified for these patients. An additional 66 patients in the study are identified as having "neuralgias and neuritis" but the response of this group of patients is not stated.

In another single-blind study (Ref. 20), 500 mg acetaminophen was compared with a combination of 300 mg acetaminophen, 5 mg hydroxyzine, 30 mg propoxyphene hydrochloride and 30 mg caffeine. One to two tablets of each preparation were given to patients suffering from tension headache. The results showed that 45 percent success was obtained with acetaminophen alone and 90 percent with the combination. This superiority was attributed to the "potentiation of the analgesic agents by hydroxyzine."

The Panel concludes that acetaminophen is effective in relieving the pain of headache, and that it is a general analgesic of proven efficacy as shown by clinical testing. Thus, acetaminophen is considered to be equivalent to aspirin in its analgesic effects, although the lack of anti-inflammatory action might make it less useful in conditions having an inflammatory component (Ref. 21).

(2) *Safety.* Numerous clinical studies have shown that acetaminophen, when taken in recommended doses, is relatively free of adverse effects in most age groups, even in the presence of a variety of disease states. There was no increase in fecal blood loss (Ref. 22). There were no stomach mucous membrane reactions in patients with gastrointestinal illnesses (Ref 23) There was no interference with the action of drugs which promote uric acid excretion in the urine (Ref. 24). No effects on clotting were seen in hemophiliacs (Ref. 25). However, several studies have shown small increases in blood clotting time in patients using acetaminophen, but concurrent anticoagulant therapy was considered manageable with conventional precautions (Ref. 26). Larger than normal doses were required to produce a mild methemoglobinemia (a reversible blood disorder) (Ref. 27). The safety of acetaminophen is discussed in detail below. The metabolism of acetaminophen was considered and has been reviewed by the Panel elsewhere in this document. (See part II. paragraph L. above—Absorption, Distribution, Biotransformation (Metabolism) and Excretion of Acetaminophen.)

A few cases of hypersensitivity to acetaminophen have been reported, as manifested by skin rashes (Ref. 28), thrombocytopenic purpura (characterized by "black and blue" patches on skin and mucous membranes) (Ref. 29), rarely hemolytic anemia (anemia due to red blood cell destruction) and the very serious blood disorder agranulocytosis (Ref. 30). Occasional individuals respond to ordinary doses with nausea and vomiting or diarrhea.

The only contraindications to the use of acetaminophen presently well-established are known hypersensitivities to the drug. Definitive studies are not available on whether or not acetaminophen should be used in patients with certain preexisting liver diseases. The Panel concludes that increased risk may be a possibility in these individuals and recommends that high priority be given to well-designed studies to resolve this issue.

(i) *Animal toxicity.* With regard to the acute toxicity of acetaminophen, the large doses of acetaminophen required to evoke toxic reactions in the studies cited below are considered by the Panel to reflect a wide range of safety. This is especially true when those dosages are compared to the Panel's recommended single dose and daily intake.

The single-dose oral LD_{50} (dose that kills 50 percent of the animals) of acetaminophen in male rats was reported to be 3,710 mg/kg (Ref. 31), as compared to the previously reported LD_{50} of 1,650 mg/kg for phenacetin in the female rat (Ref. 32). The LD_{50} of acetaminophen in the rat is about 300 to 400 times the usual single dose in 50 to 70 kg (110 to 150 lb) adult humans.

In an acute toxicity study by Boyd and Bereczky (Ref. 31), acetaminophen produced early pathologic effects in the rats similar to those seen in the same laboratory in an earlier study (Ref. 32) with phenacetin. Rats dying in 24 hours showed extensive capillary-venous congestion, tubular nephritis and centrilobular hepatitis (kidney and liver inflammatory conditions, respectively). When deaths occurred later with acetaminophen the hepatitis had progressed into hepatic necrosis.

A 100-day LD_{50} of acetaminophen in the rat was found to be 770 mg/kg daily; the 100-day LD_{50} was estimated to be 400 mg/kg daily (Ref. 33) Extrapolating to humans ranging in weight from 50 to 70 kg (110 to 150 lb) the latter dose represents about 5 to 7 times the usual maximum recommended daily dose of 3,900 mg.

Boyd further found that his 100-day LD_{50} in the rat produced atrophy of the testes and inhibition of the production of sperm in rats and guinea pigs as well (Ref. 34). The sex organs of females were affected to a lesser degree. Other effects noted by Boyd and Hogan (Ref. 33), in rats receiving the 100-day LD_{50} dose, included kidney and liver damage.

(ii) *Acute toxicity in man.* Several recent reports have also described numerous cases of poisoning in man by large single doses of acetaminophen, apparently usually taken for suicidal purposes. Prescott, Roscoe, Wright and Brown (Ref. 35) observed liver damage in 17 of 30 patients who had taken at least 15 g; one went into a coma induced by liver degeneration and died. In this report, no estimate was given of the lowest dose thought to have caused liver damage. Clark et al. (Ref. 36) studied a series of 60 patients who took doses of acetaminophen claimed to range from 13 to 100 g. Forty-nine developed liver damage, 17 progressed to hepatic encephalopathy (brain damage), and 12 died from fulminant liver failure. Death occurred in 4 to 18 days after the ingestion of the drug. Proudfoot and Wright (Ref. 37) studied 41 cases of acute acetaminophen poisoning, 17 of which showed liver damage. One patient died, 3 developed jaundice and the others showed only biochemical evidence of liver dysfunction. These authors stated that "liver damage is a toxic effect which is present in most patients who ingest more than 15 g of paracetamol" (acetaminophen). In all these series it was noted that other drugs were, or may have been, also taken.

In the U.S. in 1972, 61 cases of acetaminophen overdosage were reported to the National Clearinghouse for Poison Control Centers, Food and Drug Administration (Ref. 38). Of these, 15 reported the ingestion of less than 3.5 g, 23 between 3.5 and 15 g, and 7 ingested more than 15 g. Two of the latter developed toxic hepatitis. No effects of this nature were reported from doses lower than 15 g. In 1971 there were only 3 cases reported in which more than 15 g were ingested. One of these had no symptoms, another experienced some lethargy, and the other experienced nausea, vomiting and abdominal pain. The Panel concludes that single doses less than 15 g are not usually associated with serious liver damage. The much lower incidence of reported acetaminophen hepatotoxicity in the U.S.A. compared to England has been attributed to the well known axiom, if the diagnosis is not suspected, it is not seen, since one investigator reported 156 cases with 4 fatalities in one city alone (Ref. 39).

A dose of 15 g is 23 times the usual recommended single dosage of acetaminophen (650 mg) and about 4 times the maximum recommended daily intake. In estimating the range of safety, the single dosage comparison is probably more appropriate than the comparison of the single toxic dose with the daily divided therapeutic dose. The toxic effect of acetaminophen on the liver is related to glutathione depletion (Ref. 40).

Since acetaminophen is metabolized by the liver the question of the safety of its use in the presence of liver disease should be considered.

In a study of 72 patients with various forms of liver disease given 10 mg/kg of acetaminophen, Fevery and de Groote (Ref. 41) found an increase in both the serum levels and urinary excretion of unconjugated acetaminophen in the presence of certain liver diseases (parenchymal disease with hyperbilirubinemia or obstructive jaundice). Patients with cirrhosis exhibited plasma levels 2 to 3 times higher than those observed in subjects with no liver damage indicating decreased rates of metabolism. No decrease in the blood levels of conjugated acetaminophen or total urinary excretion of the drug could be demonstrated indicating that these two types of observations would not be expected to show differences in metabolism of free drug as would be expected from the pharmacokinetic characteristics of this drug. Vest and Fritz (Ref. 42) observed a lowered ability of the liver to conjugate acetaminophen in six children with infectious hepatitis given 10 or 20 mg/kg of the drug intravenously. In the acute phase of the hepatitis the excretion of conjugated acetaminophen was decreased. However, urinary excretion of free drug or excretion of total conjugated acetaminophen is an insensitive method to observe changes in metabolism of acetaminophen. Direct comparison of blood levels of unchanged drug indicates that the relative rate of conjugation can be decreased significantly without significant differences in urinary excretion of total conjugates. Free acetaminophen disappeared more slowly from the blood. The effects on excretion and blood levels of the conjugates and free acetaminophen reflected a partial inhibition of the conjugation of the drug to its glucuronide and the sulfate resulting in a moderate delay in the total elimination of the drug from the body. In 33 patients with liver cirrhosis, Jirsa and Hykes (Ref. 43) found no effect on the excretion of conjugated acetaminophen but did find a significant decrease in diabetics. Schmid and Hammaker (Ref. 44) observed no significant reduction in the formation of conjugated acetaminophen in five patients with Gilbert's disease (congenital liver disorder) after the administration of 30 mg/kg of acetaminophen but did not study blood levels of unchanged drug. In studies on infants prior to the development of their ability to metabolize this drug, no significant hematologic or other toxic effect were produced by single oral doses of acetaminophen up to 16.6 mg/kg (Ref. 45), or by 100 mg 3 times daily rectally for 3 days (Ref. 46).

There have been no clinical studies of the effect of liver disorders on metabolic pathways other than the glucuronide and sulfate conjugation pathways through which acetaminophen may be metabolized. In this connection Mitchell et al. (Ref. 40) have postulated that a minor but as yet unidentified highly reactive metabolite formed by nonconjugating enzymes (mixed oxidase) is responsible for the liver toxicity of acetaminophen. In normal subjects the concentration of this metabolite is low, and it is further conjugated with glutathione to a nontoxic metabolite. At high doses glutathione stores may be overwhelmed and the reactive metabolite reacts chemically with other compounds in the cell which results in necrosis. It is pertinent to know whether liver disease might affect the liver toxicity of acetaminophen by interfering with the production of this toxic metabolite by nonconjugating pathways and further conjugation with cysteine to a nontoxic substance.

There is evidence in the results of the above studies that in some forms of liver disease there is a decrease in the conjugation of acetaminophen. This effect significantly increases the half-life of acetaminophen to 3 to 4 hours in some cases. It is perhaps significant that in toxic reactions to overdoses of acetaminophen the half-life is usually increased to 4 hours (Ref. 35).

Decreased metabolism of acetaminophen by normal conjugation mechanisms (glucuronide and sulfate) observed in some patients with chronic liver disease, could potentially increase toxicity of acetaminophen by increasing the relative fraction metabolized through nonconjugating pathways to the toxic metabolite. Decreased conjugation could also indicate decreased capacity of the liver to further conjugate the toxic metabolites with gluthathione to a less toxic conjugate.

An alternative explanation for the increased susceptibility of chronic alcoholics to the hepatotoxicity of acetaminophen (Ref. 47) is the induction of the microsomal enzyme systems (nonconjugating) by chronic use of alcohol (Ref. 48). However, recent evidence suggests that the overall elimination by conjugation is decreased in alcoholics similar to that observed in other cases of decreased liver function.

Shamszad et al. found that preexisting liver disease significantly decreases the rate of elimination of drug (as evidenced by the increased half-life of unchanged drug in the plasma in patients with cirrhosis (half-life 3.5±1.3 hours) and active alcoholic hepatitis (4.5±1.5 hours) compared to chronic alcoholics with normal liver function (2.2±.039 hours) and chronic alcoholics off alcohol for 7 days (2.8±0.7 hours)) (Ref. 49).

Thus several types of liver disease result in prolonged half-lives of unchanged drug which are about the same increase (about 4 hours) observed in patients who suffer liver damage after acetaminophen overdosage.

One cannot conclude that because an increased acetaminophen half-life occurs in association with acute liver damage caused by acetaminophen, that increased acetaminophen half-life caused by preexisting liver disease will increase the potential or severity of acetaminophen hepatoxicity. Well designed studies to answer this question are needed. Although the Panel does not have evidence to warrant a warning to persons with liver disorders at this time, it is noted that there is no evidence to exclude this possibility and the considerations discussed above require that this possibility not be dismissed.

Although the Panel concludes that additional studies are needed to determine if a warning is required for normal doses in adults or infants with liver disease, overdose may result in such severe liver damage that a label warning regarding this effect is obligatory. The basis for such a warning is well documented in several recent reviews of the hazards of acetaminophen overdosage, especially with respect to the harmful effects on the liver (Refs. 39, 48, and 50 through 52).

The warning should state: "Do not exceed recommended dosage because severe liver damage may occur".

Kidney damage has been described in numerous cases in which the liver injury has been of primary concern in acute poisoning by acetaminophen, as previously discussed. The nature of the injury to the kidney observed in such acute cases is apparently not related to the type of injury (papillary necrosis) which typically results from long-term abuse of analgesic drugs.

One case of the papillary necrosis type of kidney injury has been reported (Ref. 53) following prolonged use of acetaminophen at a dose of 11 to 18 g daily for 6 months in combination with proportionately large doses of chlormezanone. Two other cases, though questionably attributed to acetaminophen (Ref. 54), involved in one case this type of kidney injury which continued after switching to acetaminophen after the consumption of phenacetin-containing analgesics for 14 years. In the other case, the kidney damage developed after 5 years of intake of 1.5 g acetaminophen daily along with other drugs including some drugs containing phenacetin. Master (Ref. 55) reported a case of analgesic-induced kidney injury in a woman who took an average of 1.5 g acetaminophen daily for 10 years, though other analgesics were consumed previously or concurrently. Nanra (Ref. 56) mentioned two other cases of analgesic-induced kidney injury occurring in Australia. He attributed these to acetaminophen alone but he described no details. In none of the above six cases, in which the consumption of acetaminophen was involved, is it clear that this drug was the sole cause of the analgesic-induced kidney damage or that it was the primary drug of abuse.

Abel (Ref. 57) and the Royal Australasian College of Physicians (Ref. 58) have stated that patients fail to recover from kidney injury when their intake of phenacetin combinations is replaced by acetaminophen either alone or in combinations.

In studies on healthy adult human subjects, Prescott (Ref. 59) and Prescott, Sansur, Leven and Conney (Ref. 60) observed a slight increase in the excretion of kidney tubule cells in the urine following the intake of 3.6 g acetaminophen daily for 5 days. In the latter

study the increase was significant in one of eight subjects on acetaminophen and two of nine subjects on the same dosage schedule of phenacetin. This effect was considerably less than that seen in subjects taking similar doses of aspirin.

Edwards, Edwards, Huskisson and Taylor (Ref. 61) found only a minor impairment of urine concentrating ability in 6 of 13 patients after their intake of 2 to 30 kg acetaminophen over a period of 2 years. Batterman and Grossman (Ref. 7) noted no blood, liver or kidney disturbances in human subjects receiving 3.6 g daily for up to 116 weeks.

In an experiment on dehydrated dogs, Bluemle and Goldberg (Ref. 62) found a high concentration of acetaminophen in the papillae of the kidney after a single dose of phenacetin, and a similar concentration of the drug in the renal papillae was observed after a single dose of acetaminophen. However, in this study, no concentration of acetaminophen was found in nondehydrated dogs.

Acetaminophen has not been reported to produce effects on the central nervous system like those produced by phenacetin, variously described as euphoria, stimulation, sedation, depression, etc. These effects of phenacetin are considered to constitute the basis of the potential for abuse of analgesic preparations containing this drug. In comparing the subjective effects of phenacetin and acetaminophen in 20 healthy male volunteers, Eade and Lasagna (Ref. 63) found that phenacetin "depressed mood, energy and mentation," while acetaminophen in the same dose, 28 mg/kg, had no such effects and did not differ from aspirin or placebo. However, Nakra et al. recently reported that some patients, especially housewives, have used acetaminophen as a "pick-me-up" and raises the possibility that some will abuse it (Ref. 64).

No comparison has yet been made with regard to the relative abuse potential of analgesic mixtures of phenacetin and similar mixtures of acetaminophen. A longer history of use of acetaminophen combinations, especially those with aspirin, will be required before this question can be answered. However, considering the lack of effects of acetaminophen on the sensorium similar to those of phenacetin it is justifiable to conclude that acetaminophen, as a single entity or in analgesic mixtures, does not have the abuse potential demonstrated for analgesic mixtures containing phenacetin. Reports from Australia (Ref. 59) showing that established abusers of phenacetin-containing drugs continued to abuse acetaminophen combinations after the removal of phenacetin from proprietary products, do not indicate a primary abuse potential of acetaminophen or of its analgesic mixtures.

The Panel concludes from observations reviewed above that acetaminophen may be taken in recommended doses without undue risk.

The Panel has examined the regulations of the Poison Prevention Packaging Act of 1970 as set forth in 21 CFR 1700.15 (a), (b) and (c), that provide for poison prevention packaging standards for aspirin-containing products in a dosage form intended for oral administration. The standards for child-resistant safety closures required on the containers of these products are intended to protect children from intentional or accidental ingestion without hampering the adult use effectiveness of the products. The Panel concurs with these standards and is of the opinion that the standards for child-resistant safety closures should apply to the containers in which acetaminophen oral products are packaged as well as to aspirin-containing products.

The Panel further concludes that the restrictions on the maximum number of tablets permitted in containers of aspirin products for child use should also apply to acetaminophen products formulated for use in children only. Therefore, acetaminophen products containing 80 mg (1.23 gr) tablets intended for oral use in children should contain no more than 36 tablets to reduce the hazard of accidental poisoning, as set forth in 21 CFR 201.314(c)(2) for products containing 80 mg (1.23 gr) tablets of aspirin for pediatric use.

The Panel concludes that the OTC packaging requirements for safety closures and the restriction on the maximum number of tablets in the containers of aspirin products for pediatric use should also apply to acetaminophen products for use in children.

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(3) *Dosage.* (i) *For products containing 325 mg (5 gr) per dosage unit.* (*a*) *Standard schedule.* Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg (7.5 gr) every 4 hours while symptoms persist not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while symptoms persist not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while symptoms persist not to exceed 1,625 mg (25 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg (3.75 gr) every 4 hours while symptoms persist not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while symptoms persist not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervison of a physician.

(*b*) *Nonstandard schedule.* Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *For products containing 80 mg (1.23 gr) per dosage unit.* Children 11 to under 12 years oral dosage is 480 mg (7.38 gr) every 4 hours while symptoms persist not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while symptoms persist not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while symptoms persist not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while symptoms persist not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 160 mg (2.46 gr) every 4 hours while symptoms persist not to exceed 800 mg (12.3 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(iii) *For products containing 500 mg (7.69 gr) per dosage unit.* Adult oral dosage is 500 mg (7.69 gr) to 1,000 mg (15.38 gr) initially, followed by 500 mg (7.69 gr) every 3 hours or 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (*a*) "Do not exceed recommended dosage because severe liver damage may occur".

(*b*) "Do not take this product for the treatment of arthritis except under the advice and supervision of a physician".

(ii) *Standard acetaminophen dosage unit.* In the previous discussion on "standard strength" dosage forms, the Panel made clear the need to indicate both the quantity of acetaminophen per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing acetaminophen differs per dosage unit from the established standard of 325 mg (5 gr) acetaminophen per dosage unit. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that all products containing acetaminophen be clearly labeled as containing acetaminophen on the principal display panel. In addition, labeling shall state in metric units and secondarily in apothecary units the quantity of acetaminophen per dosage unit.

(*a*) *Products containing the standard acetaminophen dosage unit.* The Panel recommends that products containing only 325 mg (5 gr) acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(*b*) *Products containing acetaminophen in an amount different than the standard acetaminophen dosage unit.* While the Panel recommends that products contain only 325 mg (5 gr) aceta-

minophen per dosage unit, if the Food and Drug Administration is unable to implement this recommendation the Panel recommends that only nonstandard dosage units of 500 mg (7.69 gr) be recognized for acetaminophen in addition to the standard dosage unit of 325 mg (5 gr). The Panel recommends that products containing 500 mg (7.69 gr) of acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of 500 mg (7.69 gr) acetaminophen per dosage unit compared to the established standard of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

c. *Calcium carbaspirin.* The Panel concludes that calcium carbaspirin is a safe and effective OTC analgesic when taken in the recommended dosage of 414 to 828 mg every 4 hours while symptoms persist not to exceed 4,968 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* Calcium carbaspirin is a complex of calcium acetylsalicylate and urea (Ref. 1). This compound is also frequently called soluble calcium aspirin. This nomenclature has produced some confusion with another preparation which consists of aspirin, calcium carbonate, and citric acid, which occasionally is also referred to as "soluble" calcium aspirin. Because calcium carbaspirin is a larger molecule than aspirin, a larger amount (414 mg) will be required to produce the same pharmacological effect as that produced by 325 mg of aspirin. Levy and Hayes have reported that the dissolution rate for this compound is faster than that for aspirin (Ref. 2). However, Beaver noted that the rate of absorption into the bloodstream was similar to that of aspirin (Ref. 3). Bonica and Allen have reported that "there is no evidence that it offers a clinically significant advantage (over aspirin) in the rate in which analgesic effects are achieved" (Ref. 4).

The previous discussion in this document with regard to effectiveness of aspirin including the limitations on maximum daily and total intake are applicable here with a slight modification based upon potency (414 mg instead of 325 mg). In addition, the previous discussion on aspirin dose-response relationship regarding the lack of correlation between blood levels and threshold levels of analgesia, rapidity of onset of analgesic action, intensity of analgesia, and duration of pain relief, are equally applicable to calcium carbaspirin. (See part III. paragraph B.1.a.(1) above—Effectiveness.)

(2) *Safety.* Evidence indicates that calcium carbaspirin is as safe as aspirin when taken in equivalent doses (Ref. 5). It is a complex of urea and calcium acetylsalicylate which is hydrolyzed (broken down) in the gastrointestinal tract to aspirin, calcium and urea. While calcium carbaspirin has a more rapid dissolution rate than aspirin, the amounts of calcium and urea formed from the breakdown of therapeutic doses of calcium carbaspirin would not be expected to have any pharmacological effects. It is assumed that calcium and urea are not absorbed in significant quantities. Thus the severity and incidence of adverse reactions either prior to or after absorption of calcium carbaspirin would be comparable to the incidence of adverse reactions discussed previously in this document for aspirin. (See part III. paragraph B.1.a.(2) above—Safety.)

The only studies which show that the side effects of calcium carbaspirin may be different from those of aspirin are the following: Muir and Cossar (Ref. 6) in a study with patients undergoing gastrectomy summarized their finding as follows: "Soluble calcium aspirin has shown no significant signs of gastric irritation in 95 gastrectomy specimens. Standard aspirin has shown potentially serious gastric lesions in 8 out of 102." These authors also found that calcium carbaspirin produced significantly less gastric bleeding than aspirin in 20 patients (aspirin 65 percent with bleeding, calcium carbaspirin 5 percent with bleeding) with no previous history of dyspepsia.

One article reported a series of studies using radioactive labeled chromate to determine gastrointestinal blood loss when aspirin and calcium carbaspirin were ingested (Ref. 7). The authors concluded that gastrointestinal bleeding occurred for both drugs, but the quantities of blood lost were less with calcium carbaspirin than with aspirin preparations for the same subjects (Ref. 7), and this difference was highly significant (p is less than 0.01).

In an unpublished study submitted by the manufacturer (Ref. 5), 20 patients with known intestinal ulcers and 20 patients with arthritis were followed for 9 months. Stool tests for blood using the testing reagent guaiac were used. A comparison between aspirin, placebo and calcium carbaspirin revealed guaiac reagent-positive stools in all three situations, and no difference could be observed between the three treatments. The data are difficult to assess; the results were not presented in tabulated form and the data were not statistically analyzed.

The Panel concludes that while slightly less gastrointestinal bleeding may result from the use of calcium carbaspirin, not enough evidence exists to differentiate this effect quantitatively from that of aspirin. Consequently, all cautions required for aspirin should be required for calicum carbaspirin.

(3) *Dosage.* Adult oral dosage is 414 to 828 mg every 4 hours while symptoms persist not to exceed 4,968 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 621 mg every 4 hours while symptoms persist not to exceed 3,105 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 517.5 mg every 4 hours while symptoms persist not to exceed 2,587.5 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 414 mg every 4 hours while symptoms persist not to exceed 2,070 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 310.5 mg every 4 hours while symptoms persist not to exceed 1,552.5 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 207 mg every 4 hours while symptoms persist not to exceed 1,035 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (*a*) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

(*b*) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(*c*) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(ii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of calcium carbaspirin per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing calcium carbaspirin differs per dosage unit from the established standard of 325 mg (5 gr) aspirin. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing calcium carbaspirin be clearly labeled on the principal display panel: "Equivalent to X mg (X gr) per dosage unit of the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 414 mg calcium carbaspirin per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg (5 gr) per tablet of the established standard of 325 mg (5 gr) aspirin per tablet".

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d. *Choline salicylate.* The Panel concludes that choline salicylate is a safe and effective OTC analgesic when taken in the recommended dosage of 435 to 870 mg every 4 hours while symptoms persist not to exceed 5,220 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* Choline salicylate is one of several nonacetylated salicylates reviewed by the Panel. Choline salicylate is highly soluble and may be administered as a stable, palatable liquid. It should be noted that an advantage of this drug is that it is the only liquid salicylate preparation that is currently available on the OTC drug market. It is said to be absorbed 5 times faster than aspirin (Ref. 1). Beaver (Ref. 2) has stated that "While choline salicylate may prove more palatable than an equivalent dose of aspirin, the analgesic effectiveness of the two drugs has never been adequately compared, and experience with sodium salicylate suggests that from the standpoint of analgesia at least, simple salicylates are less than equianalgesic when compared with equivalent doses of aspirin."

While no well-controlled clinical studies for the assessment of the analgesic activity of choline salicylate have been found, the Panel's review of the scientific literature has produced sufficient evidence of its analgesic activity. Broh-Kahn (Ref. 3) conducted a study in which 80 physicians throughout the U.S. and Canada gave this drug to 1,200 patients. Attempts were made to compare the effectiveness of choline salicylate to that of aspirin. This was accomplished in several ways. In some cases, patients had been treated with aspirin, and when its effect was assessed, it was discontinued and replaced with choline salicylate. In other cases in which the effect of aspirin was not previously ascertained, a crossover study was performed. Physical differences in the appearance of both drugs precluded the use of a double-blind technique. Finally, in some cases the physician compared the effects of choline saliyclate in some patients with the known effects of aspirin in his patient population at large. The author concluded that "choline salicylate displayed a more favorable effect than aspirin." No adequate statistical analysis is presented to support this conclusion.

Leary (Ref. 1) has also reported that salicylate concentration in the blood of man rises faster and to a considerably higher level after the administration of choline salicylate than after the administration of aspirin.

Levy, Gumtow and Rutowski (Ref. 4), in a study with 12 healthy male volunteers, assessed the blood plasma levels obtained after the administration of a solution of choline salicylate with those of two product formulations of aspirin tablets, aspirin tablets combined with aluminum glycinate and magnesium carbonate and an aqueous solution of sodium salicylate. The authors concluded that the two aspirin formulations produced significantly lower absorption rates than choline salicylate solution. There was no difference in absorption between the several types of salicylates administered in solution (Ref. 4).

Wolf and Aboody (Ref. 5) have also shown that choline salicylate is more rapidly absorbed than aspirin.

Broh-Kahn (Ref. 6) in a study with normal volunteers who acted as their own controls has shown that choline salicylate is absorbed approximately 5 times more rapidly than aspirin.

The significance of faster absorption has not been determined, since there is no evidence that faster absorption also indicates a faster onset of analgesic effect. Besides, as stated by Beckman (Ref. 7), "it is absurd to claim advantages for compounds that may at best advance the advent of relief no more than a few minutes."

2 *Safety.* The Panel finds that choline salicylate is about as safe as aspirin, because the side effects are similar to aspirin and those of the other salicylates. Yet unlike aspirin and the other acetylated salicylates, choline salicylate has not been reported to be associated with reactions causing asthmatic attacks in susceptible people. In addition, choline salicylate, as well as the other nonacetylated salicylates, do not affect the platelet adhesiveness involved in the clotting mechanism. However, choline salicylate in large doses does have an effect on another aspect of the clotting mechanism, an hypoprothrombinemic effect. Therefore, the caution concerning bleeding should be addressed to that population which is exposed to large doses of choline salicylate.

There have been many reports assessing the occurrence of gastrointestinal bleeding associated with the use of choline salicylate. Watson and Pierson (Ref. 8) measured gastrointestinal bleeding in 90 normal volunteers who had ingested various salicylate compounds. The subjects were injected with radioactively labeled red blood cells and the daily stools were checked for blood loss. The average loss was 4.8 ml for the patients taking aspirin. Ten percent showed a loss of over 10 ml daily for aspirin. Choline salicylate resulted in an average daily loss of 0.5 ml.

Lange (Ref. 9) selected 19 patients who had shown signs of occult (unseen) or manifest (noticeable) bleeding under ordinary salicylate treatment. He concluded that there was less incidence of blood in the stool with the use of choline salicylate. In a crossover study 73 percent of patients who took aspirin versus 36 percent of those using choline salicylate showed occult blood loss.

Rider et al. (Ref. 10), using the gastroscope studied 30 patients soon after ingestion of choline salicylate. He found no evidence of irritation of the mucous membrane of the stomach, hyperemia, hemorrhage, or ulcer.

In another study using radioactive Chromium-51 tagging of cells, Pierson, Holt, Watson and Keating (Ref. 11) demonstrated that 73 percent of 148 patients had significant bleeding with aspirin. When choline salicylate was used, no intestinal bleeding was noted. Croft, Cuddigan and Sweetland (Ref. 12) using Chromium-51 labeled red blood cells reported the same amount of bleeding after choline salicylate or soluble aspirin administration.

A submission summarizes ten uncontrolled or partially controlled clinical studies involving approximately 1,500 patients (Ref. 13). There were no serious untoward reactions reported. The most significant of these reports was that of Broh-Kahn (Ref. 2) which included a collection of the results of a cooperative study by 80 physicians of 1,200 patients using aspirin as a reference standard. The conclusion was stated in general terms. There evidently was a lower incidence of gastrointestinal distress, and choline salicylate was better tolerated in higher doses than aspirin.

The labeling in this submission (Ref. 13) includes claims for choline salicylate such as "Taken on an Empty Stomach, Starts Acting 5 Times Faster Than Aspirin" and "Provides Gentle-To-The-Stomach Action". Other claims made for this product have been discussed by the Panel elsewhere in this document. (See part III. paragraph B.2. below—Category II Labeling.) As for the claims mentioned above, the Panel concludes that its remarks regarding the claims of rapid absorption and the consequent rapid onset of analgesia made for highly buffered aspirin products also apply to choline salicylate products. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

In the case of choline salicylate, the Panel notes that although choline salicylate may not contain buffering ingredients as highly buffered aspirin does, it is, like highly buffered aspirin, taken in a solution dosage form and therefore may, for this reason, have similar performance action. In addition, the Panel concludes that regarding the claims for choline salicylate and its effect on the stomach, further testing is required to substantiate such claims, and therefore, will only permit the following claim which may be included in the principal display panel and which it classifies as Category III labeling: "May be taken on an empty stomach and may prevent the stomach distress that aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label". The Panel further concludes that any other statement(s) are classified as Category II.

(3) *Dosage.* Adult oral dosage is 435 to 870 mg every 4 hours while symptoms persist not to exceed 5,220 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 652.5 mg every 4 hours while symptoms persist

not to exceed 3,262.5 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 543.8 mg every 4 hours while symptoms persist not to exceed 2,719 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 435 mg every 4 hours while symptoms persist not to exceed 2,175 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 326.5 mg every 4 hours while symptoms persist not to exceed 1,632.5 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 217.5 mg every 4 hours while symptoms persist not to exceed 1,087.5 mg in 24 hours for not more than 5 days. Children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(ii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of choline salicylate per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing choline salicylate differs per dosage unit from the established standard of 325 mg sodium salicylate per dosage unit. (See Part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing choline salicylate be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 435 mg choline salicylate per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg per tablet of the established standard of 325 mg sodium salicylate per tablet".

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(13) OTC Volume 030077.

e. *Magnesium salicylate.* The Panel concludes that magnesium salicylate is a safe and effective OTC analgesic when taken in the recommended dosage of 325 to 650 mg every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* This ingredient has been used since 1888 when it was first cited in an editorial of *Pharmazeutische Post* and was used for therapy of typhoid fever (Ref. 1). The same year Caldwell (Ref. 2) in a review article reported on its use as an "intestinal antiseptic" and therefore useful in typhoid fever. This product was still found in the *Merck Index*, 1930 Ed., where it was described as antiseptic, antirheumatic and antidiarrheic and still listed among its uses "typhoid fevers and typhus" (Ref. 3).

In a report published in the late 1930's, analgesia is mentioned for the first time by Joseph (Ref. 4). That report consists of the experience of a single physician with ten of his patients in which magnesium salicylate produced a marked analgesic effect. In 1967, Stern (Ref. 5) compared aspirin with magnesium salicylate and found no statistically significant differences in the levels of analgesia using these two agents. This study was double-blind and analgesia was evaluated in 22 patients with several types of arthritis. They concluded that magnesium salicylate was preferable to aspirin in conditions requiring long term therapy since it produced less gastrointestinal irritation than aspirin.

In an unpublished study performed by F. W. McCoy (Ref. 6) in 1964, aspirin, magnesium salicylate and aspirin plus magnesium aluminum hydroxide were compared on the basis of salicylate blood levels. Although it is known that salicylate blood levels do not directly correlate with analgesic effects it is interesting to note that magnesium salicylate, in spite of a greater solubility than aspirin, gave "somehow" lower blood levels of salicylate than aspirin. The blood levels of salicylate obtained with magnesium salicylate were greater than those obtained with aspirin plus aluminum and magnesium hydroxides. This is most likely due to the buffering of the aspirin formulations by aluminum and magnesium hydroxides. In another unpublished study, the analgesic effectiveness of magnesium salicylate was evaluated in 42 elderly patients with degenerative bone disease. In this double-blind crossover study, magnesium salicylate was compared to aspirin and placebo. The data were analyzed statistically, and the conclusions obtained from this study were that magnesium salicylate and aspirin were equally effective in relieving the pain of patients with osteoarthritis and that both drugs were superior to placebo (Ref. 7).

Batterman (Ref. 8) reported the use of magnesium salicylate in 34 patients with rheumatoid arthritis and 27 patients with degenerative joint disease. In this study, analgesic and not antirheumatic effect was assessed. The data suggest the effective value of this drug as an analgesic in the patients tested.

The Panel concludes that while the number of well-controlled clinical studies are few and mostly unpublished, the studies and the other data reviewed by the Panel indicate that magnesium salicylate is an effective analgesic and that it is comparable to aspirin. However, the claim that magnesium salicylate might be indicated when aspirin cannot be tolerated, remains to be proven.

(2) *Safety.* At the present time, there is evidence which indicates that magnesium salicylate is as safe as aspirin, although it has side effects similar to aspirin and the other salicylates. Unlike aspirin and the other acetylated salicylates, magnesium salicylate has not been associated with reactions causing asthmatic attacks in susceptible people. In addition, magnesium salicylate, as well as the other nonacetylated salicylates, are not known to affect the platelet adhesiveness involved in the clotting mechanism. However, magnesium salicylate in large doses does have an effect on another aspect of the clotting mechanism, an hypoprothrombinemic effect. There is evidence of gastric mucosal bleeding and irritation similar to aspirin.

Unpublished studies on magnesium salicylate, utilizing the gastrocamera, revealed some variation between aspirin and magnesium salicylate when irritation of the stomach walls was assessed. Irritation to the mucous membranes of the stomach did occur in the presence of both drugs (Ref. 9). Other submitted studies used radioactively-labeled sodium chromate Cr_{51}. These studies indicated that bleeding also took place in a significant number of subjects. There was evidence that the amount of bleeding might be less with magnesium salicylate than with aspirin (Ref. 10). One study that determined magnesium concentrations in the blood indicated considerable individual variations which were neither consistent nor significant (Ref. 11).

The Panel has reviewed the possible systemic toxicity of magnesium ions with

recommended doses of magnesium salicylate. Unless renal insufficiency is present, toxicity due to the absorption of magnesium is unlikely in the recommended dosages of 325 to 650 mg magnesium salicylate every 4 hours not to exceed 3,900 mg in 24 hours for not more than 10 days (Ref. 12). Absorbed magnesium is rapidly excreted, so that hypermagnesemia is difficult to achieve by the oral route in the presence of normal renal function. In renal dysfunction, however, hypermagnesemia toxicity may occur and a warning is therefore necessary (Ref. 13). The Panel concludes, based on the available evidence, that a restriction on the intake of magnesium salicylate for normal persons in the recommended daily dosage is not necessary because there is no evidence of possible systemic toxic effects due to magnesium. The amount of magnesium in the recommended maximum daily dosage of 3,900 mg magnesium salicylate is 26.2 mEq magnesium which does not pose any safety problem. However, for any product containing magnesium in which the maximum daily dosage exceeds 50 mEq of magnesium, the labeling should contain the warning: "Do not take this product if you have kidney disease except under the advice and supervision of a physician".

(3) *Dosage.* Adult oral dosage is 325 to 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while symptoms persist not to exceed 2,437.5 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while symptoms persist not to exceed 2,031.5 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while symptoms persist not to exceed 1,625 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while symptoms persist not to exceed 1,219 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while symptoms persist not to exceed 812.5 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(ii) *For products containing more than 50 mEq of magnesium in the recommended daily dosage. Warning.* "Do not take this product if you have kidney disease except under the advice and supervision of a physician".

(iii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of magnesium salicylate per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing magnesium salicylate differs per dosage unit from the established standard of 325 mg sodium salicylate per dosage unit. (See Part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing magnesium salicylate be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 325 mg magnesium salicylate per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg per teaspoon of the established standard of 325 mg sodium salicylate per tablet".

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f. Sodium salicylate. The Panel concludes that sodium salicylate is a safe and effective OTC analgesic when used in the recommended dosage of 325 to 650 mg every 4 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* Sodium salicylate had already been in use for about 25 years when aspirin was introduced into therapy in 1899. Aspirin was introduced on the basis that it was more palatable and caused less gastrointestinal disturbances than sodium salicylate (Ref. 1).

It has been demonstrated that aspirin (acetylsalicylic acid) is hydrolyzed to salicylic acid. It has been suggested that the latter is the active compound (Ref. 2). However, the therapeutic effect of aspirin as an a analgesic is generally recognized as being superior to an equal dose of sodium salicylate (Refs. 1 and 2).

Some researchers using patients with cancer pain as well as post partum patients, have found aspirin superior to sodium salicylate when given in equimolar doses (Refs. 3 and 4).

Frey has reported that aspirin was more effective than sodium salicylate in the treatment of the common headache (Ref. 5).

The *AMA Drug Evaluations* (Ref. 6) mentions sodium salicylate as an analgesic and states that "* * * it is less effective than equal doses of aspirin in relieving pain and reducing fever * * *"

Woodbury (Ref. 7) cites sodium salicylate as one of the two most commonly used preparations for analgesic effects, the other one being aspirin.

The Panel concludes that the few well-controlled clinical studies, the long clinical history of this ingredient's use and acceptance in most basic medical and pharmacology texts, indicate that sodium salicylate is an effective analgesic.

(2) *Safety.* The Panel concludes that sodium salicylate is as safe as aspirin, although it has side effects similar to aspirin and the other salicylates. Yet unlike aspirin and the other acetylated salicylates, sodium salicylate has not been associated with reactions causing asthmatic attacks in susceptible people. In addition, sodium salicylate, as well as the other nonacetylated salicylates, are not known to affect the platelet adhesiveness involved in the clotting mechanism. However, sodium salicylate in large doses does have an effect on another aspect of the clotting mechanism, an hypoprothrombinemic effect.

Comparison between aspirin preparations and sodium salicylate in various studies reveals some differences of opinion in the conclusions drawn by the authors. However, it would seem that some bleeding from the gastrointestinal tract does indeed take place.

Grossman et al. reported that sodium salicylate, aspirin, and calcium aspirin all gave a significant increase of blood in the stools as compared to the controls. This was determined using the radioactively-labeled red blood cell technique (Ref. 8). Stubbe, Pietersen and Van Heulen after studying 130 patients found that there was much less blood found in the stools when using sodium salicylate as compared to aspirin (Ref. 9). Scott et al. in 1961 also reported decreased bleeding with sodium salicylate as compared to aspirin (Ref. 10).

Leonards and Levy (Ref. 11) have shown that 325 mg sodium salicylate

tablets caused a gastrointestinal blood loss of 1.2 ml daily above control values but the blood loss produced by 325 mg aspirin tablets was appreciably greater, 5.6 ml daily above control values.

Furthermore, the effects of prolonged salicylate administration on the carbohydrate metabolism of rheumatic fever patients ranging in age from 5 to 18 years have been studied. Glucose or other carbohydrates were given orally at a dose of 1 g/kg after measuring the fasting blood sugar. It was found that although the fasting blood sugar was lower than normal, sugar concentrations determined 30 and 60 minutes after the carbohydrate administration remained abnormally high. The single ingestion of 0.6 g of sodium salicylate did not produce these changes in glucose metabolism (Ref. 12).

These latter reports are not sufficiently clear to permit any definitive conclusion to warrant a labeling warning.

The Panel has reviewed the relationship between sodium intake and hypertension and found that it is generally accepted that sodium intake is one of several factors contributing to the pathophysiology of hypertension. In experimental animals, sodium salts may precipitate marked hypertension in the presence of certain endocrine and/or renal disturbances. Even in the absence of abnormalities, blood pressure increases with sodium intake. However, in the presence of normal renal function, the rise in pressure is moderate (Ref. 13). The doubling of salt and water intake raises the mean blood pressure in man by 10 mm Hg (Ref. 13). Apart from hypertension, edema may develop in persons with occult heart failure or renal disease with high salt intake. The prevalence of these conditions increases with age (Refs. 14, 15, and 16). The recommended maximum daily dosage of 4,000 mg sodium salicylate contains 25 mEq sodium which is sufficiently high to warrant a warning in the labeling. Therefore, the Panel concludes that the labeling for sodium salicylate shall contain the warning: "Do not take this product if you are on a sodium restricted diet except under the advice and supervison of a physician" (Ref. 17). It would seem prudent for individuals on sodium restricted diets to take another Category I OTC analgesic, antipyretic or antirheumatic product instead of sodium salicylate to avoid any increase in sodium intake.

(3) *Dosage.* (i) *For products containing 325 mg per dosage unit.* (*a*) *Standard schedule.* Adult oral dosage is 325 to 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while symptoms persist not to exceed 2,437.5 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while symptoms persist not to exceed 2,031.5 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while symptoms persit not to exceed 1,625 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while symptoms persist not to exceed 1,219 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while symptoms persist not to exceed 812.5 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(*b*) *Nonstandard schedule.* Adult oral dosage is 325 mg to 975 mg initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *For products containing more than 325 mg but not more than 421 mg per dosage unit.* Adult oral dosage is more than 325 mg but not more than 842 mg initially, followed by more than 325 mg but not more than 421 mg every 3 hours while symptoms persist not to exceed 3,789 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(iii) *For products containing more than 421 mg but not more than 485 mg per dosage unit.* Adult oral dosage is more than 421 mg but not more than 970 mg initially, followed by more than 421 mg but not more than 485 mg every 4 hours or 842 mg but not more than 970 mg every 6 hours while symptoms persist not to exceed 3,880 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(iv) *For products containing more than 485 mg but not more than 500 mg per dosage unit.* Adult oral dosage is more than 485 mg but not more than 1,000 mg initially, followed by more than 485 mg but not more than 500 mg every 3 hours or 970 mg but not more than 1,000 mg every 6 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(v) *For products containing more than 500 mg but not more than 650 mg per dosage unit.* Adult oral dosage is more than 500 mg but not more than 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III, paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(ii) *For products containing 0.2 mEq (5 mg) or higher of sodium per dosage unit.* The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq (5 mg) or higher.

(iii) *For products containing more than 5 mEq (125 mg) sodium in the maximum recommended daily dosage. Warning.* "Do not take this product if you are on a sodium restricted diet except under the advice and supervision of a physician".

The Panel recommends that all products containing sodium salicylate be clearly labeled as containing sodium salicylate on the principal display panel.

(*a*) *Products containing the standard sodium salicylate dosage unit.* The Panel recommends that products containing only 325 mg sodium salicylate per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg sodium salicylate per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(*b*) *Products containing sodium salicylate in an amount different from the standard sodium salicylate dosage unit.* While the Panel recommends that products contain only 325 mg sodium salicylate per dosage unit, if the Food and Drug Administration is unable to implement this recommendation, the Panel recommends that products containing an amount of sodium salicylate other than 325 mg sodium salicylate per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg sodium salicylate per dosage unit compared to the established standard of 325 mg sodium salicylate per dosage unit". The actual amount "X" of sodium salicylate for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

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CATEGORY I LABELING

The Panel recommends the following Category I labeling for analgesic active ingredients to be generally recognized as safe and effective and not misbranded as well as any specific labeling discussed in the individual ingredient statements.

a. *Indications.* "For the temporary relief of occasional minor aches, pains and headache".

b. *Warnings.* (1) *For products containing any analgesic ingredient.* (i) "Adults: Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician".

(ii) "Children under 12 years: Do not take this product for more than 5 days. If symptoms persist, or new ones occur, consult your physician".

(2) *For products containing salicylates.* (i) "Take this product for the treatment of arthritis only under the advice and supervision of a physician".

(ii) "Stop taking this product if ringing in the ears or other symptoms occur".

(iii) *For products intended for oral administration as a solid dosage form, e.g., tablets.* (*a*) "Adults: Drink a full glass of water with each dose".

(*b*) "Children under 12 years: Drink water with each dose".

(iv) *"Caution:* Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

(v) *"Caution:* Do not take this product if you are presently taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout or arthritis except under the advice and supervision of a physician".

2. CATEGORY II CONDITIONS UNDER WHICH ANALGESIC AGENTS ARE NOT GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE OR ARE MISBRANDED

Category II Active Ingredients

The Panel has classified the following claimed analgesic active ingredients as not generally recognized as safe and effective or are misbranded:

Acetanilid	Iodopyrine
Codeine preparations:	Phenacetin
Codeine	Quinine
Codeine phosphate	
Codeine sulfate	

a. *Acetanilid.* The Panel concludes that acetanilid is an effective OTC analgesic when taken in the recommended dosage of 200 to 300 mg but is not safe for OTC use.

(1) *Effectiveness.* Acetanilid was introduced into medicine in 1886 as an antipyretic, and subsequently in the same year its analgesic properties were also recognized. Studies, prior to 1946, on the pharmacology and toxicology and on the analgesic and antipyretic effectiveness of this drug were reviewed in detail by Gross (Ref. 1). Acetanilid maintained "official" status in the *United States Pharmacopeia* through its 14th revision, but was deleted from the 15th revision in 1955.

Though acetanilid has long been generally recognized as an effective analgesic and antipyretic, no well-controlled studies of its effectiveness in the clinical situation have been reported, and it has not been quantitatively compared with aspirin in this respect in controlled tests in humans.

Because of its relative toxicity compared to other drugs used for the same therapeutic purposes there is little or no commercial interest in the drug at the present time. Two industry submissions (Refs. 2 and 3) contained only the labels of two products containing 120 mg and 150 mg of acetanilid, respectively, with caffeine and other miscellaneous ingredients. No effectiveness or safety data were submitted. One of these products has been withdrawn from the market. Current pharmacology texts consistently either ignore acetanilid completely, or mention it only as of historical interest and condemn its use as an analgesic and antipyretic.

Because of the high incidence of toxic side effects and the relatively unfavorable margin of safety, the Panel makes no recommendations for further studies of acetanilid for its analgesic effectiveness.

(2) *Safety.* The Panel concludes that acetanilid is not safe for use as an OTC analgesic.

The literature up to 1946 dealing with the toxic reactions to acetanilid in man has been reviewed in detail by Gross (Ref. 1). Though most reported poisoning cases were associated with overdosage of the drug, the Panel is impressed by the large numbers of poison cases reported with a fatal outcome and by the relatively small overdosages that were involved, even as single doses. The Panel is further impressed by the apparent wide range of individual sensitivity and the relatively narrow margin of safety between the recommended therapeutic dose and the toxic dose in sensitive individuals.

Estimates of lethal, single doses of acetanilid in laboratory animals do not indicate a high toxicity. For example, oral LD_{50}'s of 323 mg/kg for the mouse and 800 and 1,700 mg/kg for the rat have been reported. The lethal dose for rabbits was estimated to be approximately 1,500 mg/kg. Dogs and cats exhibited about the same sensitivity as the mouse. In man, on the other hand, a dose as small as 1.2 g (approximately 24 mg/kg) has been reported to cause death, and in a series of fatalities described, 4 g (80 mg/kg) was the largest dose. To illustrate the wide range in sensitivity, survival after the intake of 30 g has been observed (Ref. 1).

The predominant toxic effects of acetanilid in both acute and chronic poisoning in man include methemoglobinemia, sulfhemoglobinemia and hemolytic anemia. In chronic poisoning, these effects are accompanied by cyanosis, anorexia, various psychic and neurologic disorders, insomnia and headache. The latter symptom tends to lead to further use of the drug, which thus becomes habit-forming. Evidence of the habit-forming properties of acetanilid is reviewed by Gross (Ref. 1).

In man it has been shown that about 85 percent of an administered dose of acetanilid is converted to acetaminophen, and about 0.04 percent is metabolized to aniline (Ref. 4). The analgesic and antipyretic properties of acetanilid are attributed to its major metabolite, acetaminophen, while the toxic effects are attributed to other as yet unidentified metabolic derivatives of the minor metabolite, aniline. Phenylhydroxylamine, a potent methemoglobin former, has been postulated as a metabolite of aniline which could account for the methemoglobinemia caused by acetanilid.

In the final analysis, the metabolism of acetanilid through aniline is held responsible for the toxic effects of the drug. Furthermore, it may be assumed that the many individuals who are highly sensitive to the toxic action of acetanilid have a genetically determined capacity to metabolize greater amounts of the drug through the aniline pathway.

(3) *Evaluation.* The Panel concludes because of the high incidence of toxic effects and the relatively unfavorable margin of safety that the risks from use outweigh any benefit and therefore classifies acetanilid not safe for use as an OTC analgesic.

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b. *Codeine preparations (codeine, codeine phosphate, codeine sulfate).* The Panel concludes that codeine is an effective analgesic when taken in the recommended oral dosage of 30 to 60 mg and is safe for prescription use but because of its potential for dependence and other adverse effects is not safe for OTC use as an analgesic. The Panel notes that there were no submissions of data provided to the Panel, nor was the suggestion made through any other source, that codeine in effective analgesic doses be considered for OTC use.

(1) *Effectiveness.* In a collaborative study, cited by Eddy et al. (Ref. 1), the oral effectiveness of codeine, aspirin and other analgesics was compared in the treatment of postoperative pain at several U.S. Veterans Administration hospitals (Ref. 1). The drugs were administered when postoperative pain began to subside so that parenteral medication was no longer needed. Oral doses of 30 and 90 mg codeine were compared with 300 and 900 mg aspirin. The studies showed the estimated potency of codeine to be approximately 10 times that of aspirin. These results indicate that the effectiveness of 30 to 60 mg codeine as an analgesic would be approximately comparable to the recommended analgesic OTC dosage range of 325 to 650 mg for aspirin.

On the other hand, Lasagna (Ref. 2) concluded that codeine, orally, was a moderately effective analgesic, but not superior, on the average to aspirin when these drugs are given in the usual doses. For short term use, he considered that the evidence suggested that aspirin is a more reliable and effective agent.

Codeine is often combined with analgesic-antipyretic drugs for prescription use. Eddy et al. (Ref. 1) cite 25 studies on the analgesic effectiveness of codeine and codeine combined with aspirin or "aspirin mixtures". Most of these studies utilized usual analgesic doses (30 to 60 mg) of codeine alone or in combination, and it was concluded that combinations of codeine with other drugs were slightly more effective than either component alone possibly because of different sites of action for codeine and the analgesic-antipyretic drugs. Four unpublished studies using 5 to 15 mg of codeine were cited. The results of one study in which doses of 15 to 30 mg codeine were used suggested that 15 mg might have some analgesic effect. Three studies utilized 5 to 10 mg codeine in combination with 100 to 400 mg aspirin. The degree of pain relief was similar for all doses and combinations studied, i.e., 5 to 10 mg codeine combined with 100 to 400 mg aspirin was no better than 400 mg aspirin alone.

The Panel is aware that the Federal Controlled Substance Act classifies codeine as an ingredient having dependence liability and restricts its OTC sale under Schedule V of that act to not more than 200 mg/100 ml container or approximately 10 mg to 20 mg codeine/dose and then only when it is combined with other nonnarcotic active ingredients. The Panel agrees with this limitation on OTC sale. The Panel notes that the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products, in their report published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38312), found codeine suitable for OTC use as an antitussive in the dosage range of 10 to 20 mg. If the studies reported by Eddy et al. (Ref. 1) which showed that the potency of codeine is approximately 10 times that of aspirin are considered, this dosage range for codeine is approximately comparable to a range of 100 to 200 mg aspirin which is about ⅓ of the effective analgesic dosage range of 325 to 650 mg aspirin. At the doses permitted to be sold OTC, codeine is ineffective as an analgesic.

(2) *Safety.* The Panel concludes that codeine is not safe for use as an OTC analgesic.

Codeine is one of the opium alkaloids. It was isolated from opium in 1832 (Ref. 3). It is listed and described in virtually every major pharmaceutical text and details need not be reiterated here.

The *AMA Drug Evaluations* (Ref. 4) state, "adverse reactions to antitussive doses of narcotics occur infrequently because the doses used are less than those usually given for analgesia" and "Dependence liability of codeine is less than with morphine or meperidine, and physical dependence occurs only rarely from its use as an oral analgesic; however, the abuse of the drug, particularly in the form of cough syrup, is not uncommon."

Codeine as a single ingredient regardless of amount is classified under the Federal Controlled Substances Act as a Schedule II prescription (high potential for abuse) drug. When combined with other active medicinal ingredients in quantities of not more than 1,000 to 8,000 mg codeine/100 ml container or 90 mg codeine/dosage unit, codeine is classified as a Schedule III prescription drug. Only in quantities of 200 mg codeine/100 ml container or approximately 10 to 20 mg codeine/dose combined with other non-narcotic active medicinal agents is codeine classified as a Schedule V OTC (low potential for abuse) drug and OTC marketing is permitted.

While the Panel does not believe that codeine has a high potential for the development of dependence, serious safety considerations of abuse have caused the severe marketing restrictions now placed upon it.

(3) *Evaluation.* The Panel finds that codeine is an effective analgesic drug at the dosage restricted to prescription use and at the doses permitted to be sold OTC is ineffective as an analgesic. However, because of the known abuse and potential for dependence of this ingredient leading to severe restrictions under the Federal Controlled Substances Act, the Panel concludes codeine is not safe for OTC use as an analgesic and should only be used under proper medical supervision. For these reasons, the Panel recommends that codeine's availability for analgesic use continue to be restricted to perscription use only.

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c. *Iodopyrine.* The Panel finds that there are no data to demonstrate effectiveness and there are data showing it not safe and therefore concludes that iodopyrine is not safe and not effective for use as an OTC analgesic.

(1) *Effectiveness.* No studies were found concerning the effectiveness of iodopyrine which is also known as iodoantipyrine. Chemically, iodopyrine is the iodide salt of antipyrine. The seventh edition of the *Merck Index* recommended its use as a substitute for metal iodides and as an analgesic but also cautioned that the drug is capable of producing iodism (Ref. 1). The eighth edition of the *Merck Index* contains no reference to the drug.

The Panel received only one submission for an OTC combination product containing 30 mg iodopyrine, 870 mg antipyrine and 100 mg citrated caffeine (Ref. 2). This product has since been reformulated without iodopyrine. Since the original submission, the drug manufacturer has submitted more recent information to the Panel indicating that the product has been reformulated to contain only 975 mg antipyrine (Ref. 3). The iodopyrine and citrated caffeine have been removed from the product. The reasons for the removal of the iodopyrine and citrated caffeine were not given.

The manufacturer had noted in the original submission that the combination had been historically marketed in Germany as an antiasthmatic product. The manufacturer also acknowledged that there is no known rationale for its use in the treatment of asthma but that nevertheless millions of doses have been used for that purpose. However, the product is now currently marketed in the U.S. only as an OTC analgesic-antipyretic. The manufacturer indicated, "We have no new data to contribute to the protracted deliberation whether caffeine should or should not be included in analgesic formulations. Nor do we have data substantiating the contribution of iodopyrine to the analgesic action of the drug. Suffice it to say that halogens have long been used in analgesic combinations and the superiority, if any, of iodopyrine arises from its contribution of additional pyrazole along with the contained iodine."

Since the Panel has been unable to find any data to support the effectiveness of iodopyrine alone or in combina-

tion as an analgesic, and even the manufacturer who previously marketed the ingredient could find no data to demonstrate any effect, the Panel concludes that although it may be possible to determine by appropriate testing whether the ingredient has analgesic activity or not, the following discussion regarding its safety makes iodopyrine unsuitable for clinical study.

(2) *Safety.* The Panel concludes that iodopyrine is not safe for use as an OTC analgesic. Iodopyrine is the product of a reaction between antipyrine and iodine. Free iodide is liberated after oral ingestion by humans. The Panel can find no rationale for administering a claimed analgesic as an iodide salt because of the danger of iodism (iodine poisoning). The Panel finds that the toxic effects of the ingredient are due to the iodide. It should be noted that approximately 40 percent of iodopyrine, on a weight basis, is iodide.

Iodopyrine when fed to young rats has been shown to retard growth (Ref. 4). However, the study did not demonstrate any goitrogenic effect. Toxic effects included depressed basal metabolic rate, poor health and deaths. The drug had no effect on the size or morphology of the thyroid. Single doses of iodopyrine inhibited the incorporation of radioactive iodine into organic compounds. This effect subsided at about the same rate as that of comparable doses of iodide. It was concluded by the investigators that the data suggest that the effects of iodopyrine on the thyroid can be attributed to the release of iodide very soon after ingestion. They further noted that the effects of iodopyrine and an equivalent amount of iodide are similar, suggesting that the only effect of iodopyrine on the thyroid is due to iodide.

Wilkinson et al. (Ref. 5) have reported a case of iodide-induced hypothyroidism and dwarfism attributed to the use of a combination product containing iodopyrine (identified as 18 mg phenazone with 12 mg iodide). A 24-year-old male was hospitalized with signs of hypothyroidism that had developed gradually over 3 years. The patient had suffered from asthma and had taken the iodopyrine-containing product for 17 years, 3 times a day since the age of 7 years until admittance into the hospital. Earlier, at the age of 11 years, he was found to have a goiter. Following the clinical diagnosis in the hospital of iodide-induced hypothyroidism, the drug was discontinued and 5 months later all features of hypothyroidism had remitted.

The Medical Letter has reported that congenital goiter and hypothyroidism can result in the fetus when a pregnant woman uses iodide-containing drugs (Ref. 6). Iodides, themselves, are not known to cause malformation of the fetus. However, iodides do cross the placental barrier and after about the 12th week of gestation are taken up by the thyroid. *The Medical Letter* concluded, that because of these potential hazards, prolonged use of iodide preparations should be avoided by pregnant women. It was further concluded that normal children and adults also carry some risk of goiter.

Morgans and Trotter (Ref. 7) have reported the development of goiter in three adults who had been taking an iodopyrine-containing combination drug product. In all cases, the goiters became smaller when the patients were given the same product without iodopyrine. The authors also reported that a baby whose mother was taking the drug during pregnancy had a goiter at birth. This later disappeared spontaneously. They concluded that iodopyrine inhibits the organic binding of iodine by the human thyroid and that the effect of the drug on the thyroid is wholly due to the iodide liberated shortly after ingestion.

(3) *Evaluation.* The Panel finds that iodopyrine is not safe for OTC use because of the significantly high availability of iodide following oral administration and increased likelihood of iodism. Accordingly, the Panel concludes that the risks from use of iodopyrine outweigh any possible benefit and classifies the ingredient not safe for use as an OTC analgesic.

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d. *Phenacetin.* The Panel concludes that phenacetin is an effective OTC analgesic but not safe for OTC use because of the high potential for abuse, the high potential for harm to the kidney and the possibility of hemolytic anemia and methemoglobinemia resulting from abuse and the lack of compensating benefits of the drug. The benefit to risk ratio of phenacetin compounds compares unfavorably with other single agents and combination analgesic preparations available to target populations.

(1) *Effectiveness.* The nonsalicylate phenacetin was first synthesized in 1887 (Ref. 1). It was introduced as a therapeutic agent before controlled clinical trials were established. It was first used as an antipyretic and then as an analgesic. Its use has been widespread for over 80 years. In contrast to the salicylates, this drug has no anti-inflammatory or antirheumatic properties and therefore is mostly used for the relief of "ordinary aches and pains" (Ref. 1). However, Mandel and Davison (Ref. 1) stated:

> Psychologic effects from acetophenetidin (phenacetin) are more pronounced than from aspirin. Relaxation, drowsiness, and difficulty in mental activity are noted; concentration, attention, and retention are slightly impaired; restlessness is allayed, and anxiety is diminished. There is no euphoria. It is possible that these effects of acetophenetidin, coupled with the pain threshold-raising action, are responsible for the popularity of the agents as headache remedies, especially when tension or anxiety is dominant.

Lasagna and Pearson compared placebo, 600 mg aspirin, 600 mg phenacetin and 600 mg acetaminophen in patients with postpartum pain (Ref. 2). They found that acetaminophen and aspirin had comparable analgesia and that this effect was superior to that of placebo. Phenacetin, although it had a greater analgesic effect than placebo, rated well behind the other two in analgesic activity.

Moertel et al. found that in patients suffering from pain due to cancer, 650 mg phenacetin relieved pain in 48 percent of the patients as compared to 62 percent of the patients receiving aspirin (Ref. 3). In their rating system (drugs rated 1 to 10 by each patient) phenacetin ranked below aspirin and mefenamic acid with all three drugs being superior to placebo.

Lasagna, Davis and Pearson, compared phenacetin, acetaminophen (a metabolite of phenacetin) and placebo in a group of patients with postpartum pain (Ref. 4). The authors concluded that their data showed no overall advantage of phenacetin over acetaminophen, and they showed that both drugs were superior to placebo for the relief of pain.

Mandel and Davison state that in human volunteers given 300 mg phenacetin the "height and duration" of the pain threshold-raising effects are of the same order as those of aspirin, but they are careful to mention the "unreliability" of pain threshold measurements (Ref. 1).

(2) *Safety.* (i) *Short-term use.* Short-term use of phenacetin at recommended doses for a period of 10 days seldom results in serious toxicity in adults. Even large doses are well-tolerated by adults and fatalities following acute overdose are rare. Complete recoveries have occurred following acute overdoses of as much as 50 to 60 g (about 200 to 300 tablets) (Refs. 5 and 6). However, serious blood disorders such as methemoglobinemia and hemolytic anemia can be induced in infants with only one or two usual doses and can be life-threatening (Refs. 7 and 8). This is because hemoglobin (the oxygen carrying component of the blood) of an infant at birth is twice as sensitive to the effects of phenacetin as that of an adult (Ref. 9). This highly sensitive fetal blood component is almost completely replaced with adult type hemoglobin within the first 6 months of life (Ref. 8). Consequently, ingestion of phenacetin during pregnancy can result in effects on the blood of an unborn child.

A 28-year-old pregnant woman, who "for some months" had ingested up to 20 tablets daily of an analgesic compound containing 250 mg phenacetin, entered the hospital with sulfhemoglobinemia. Heinz bodies, and hemolytic anemia. The woman gave birth 4 hours later and the infant had methemoglobinemia, Heinz bodies and marked ery-

throblastosis. Iron deficiency anemia persisted for 7 months in the infant (Ref. 10).

(ii) *Adverse effects of long-term use.* Unlike short-term use of phenacetin, which is relatively safe, long-term use is unsafe and can result in hazardous effects to the urinary tract, blood, gastrointestinal and central nervous systems. Chronic use is usually a result of abuse probably due to the well-documented central nervous system effects of phenacetin (Ref. 11).

Of particular significance and concern to the Panel in arriving at its conclusions on the safety of phenacetin is the evidence associating excessive chronic ingestion of phenacetin-containing analgesics with life-threatening urinary tract and kidney disease (renal papillary necrosis, nonobstructive interstitial nephritis, calcification), and cancer of the kidney and bladder.

The correlation between excessive intake of analgesic mixtures and kidney damage, first observed in Switzerland in 1963 (Ref. 12), has now been extensively studied. The fact that phenacetin-containing analgesic products have been almost universally associated with cases of renal papillary necrosis, a form of kidney disease, throughout the world, has led several countries including Denmark, Sweden, England and Canada, to limit the availability of analgesic preparations containing phenacetin on the self-therapy market.

A thorough review of the literature on the relationship between phenacetin and severe renal disease has been made by the Panel and submitted to outside statistical evaluation. Numerous experts have appeared before the Panel to discuss these and other unpublished studies. In addition, the Panel has collected new information from a variety of sources including kidney dialysis centers and regulatory agencies of other countries (Refs. 13 and 14).

In the opinion of the Panel, the evidence relating phenacetin to severe renal disease now derives from a world body of published reports so numerous and varied in design that the possibility of coincidental association is negligible and requires that phenacetin be removed from the OTC drug market.

There is a view set forth in material submitted to the Panel that phenacetin should not be singled out as the causative agent in analgesic combination products because other agents in analgesic combinations, such as aspirin or acetaminophen, have been shown to produce kidney damage when used alone in man and animals, whereas phenacetin alone has rarely been shown to produce kidney damage in man (Ref. 15). The Panel does not agree with this argument because there are now thousands of reported cases of kidney disease associated with the use of phenacetin-containing mixtures, while there are probably no more than ten well-documented cases of analgesic-induced kidney disease in the world literature that can be definitively associated with abuse of all other single agent products or combination analgesic products not involving phenacetin, even though these products are extensively used throughout the world. The Panel has discussed the adverse effects of aspirin on the kidney elsewhere in this document. (See part III. paragraph B.1.a (2)(vi) above—Adverse effects on the kidney.)

From the point of view of safety of phenacetin, whether it causes kidney disease itself, augments effects of other active ingredients or increases the use of other nephrotoxic agents, it is the Panel's opinion that prolonged excessive ingestion of any common analgesic product containing phenacetin will significantly increase the probability of serious kidney disease and premature death. These levels and duration of ingestion, far exceeding label directions for use of such analgesic mixtures, are indicative of a serious potential for abuse problem that the Panel believes is associated with CNS effects of phenacetin and other components of such mixtures. This is especially true for powder formulations.

Phenacetin is virtually never used as a single agent in the U.S. or any other country. It is almost always commercially available and used only in combinations containing other analgesic compounds. Obviously, since the actual use of phenacetin as a single entity is rare, it could not be expected that renal disease resulting from its use alone would occur or be reported. It should be noted though that at least one case allegedly involving only phenacetin has been reported (Ref. 15). Although epidemiological or experimental studies on the effects of phenacetin alone in producing renal disease in man are not available or feasible, several other types of evidence indicate the major involvement of phenacetin in analgesic-induced renal disease.

In several major industrialized countries, where kidney disease induced by analgesic abuse has been a problem, many analgesic mixtures have been involved. Phenacetin has been the common denominator of analgesic products responsible for the problem. In the U.S., available data also indicate that phenacetin-containing products are involved in almost all reported cases of analgesic-induced kidney disease (Ref. 13).

In addition to phenacetin being involved qualitatively as the common denominator, data from several countries show similar quantitative relationships between the dose of phenacetin required to produce a given degree of kidney injury or incidence of kidney disease, irrespective of the dose of other agents involved (Ref. 16).

Retrospective case control studies indicate that total doses of 2 to 4 kg phenacetin over a period of about 10 years would result in approximately a 70 percent probability of renal papillary necrosis. The probability of death due to kidney failure in patients with degeneration of the part of the kidney affected by phenacetin is about 30 to 40 percent. This incidence appears to be similar for all mixtures of phenacetin regardless of whether they contain aspirin, antipyrine, or caffeine.

Several different types of studies consistently suggest temporal and dose relationships between phenacetin ingestion and renal dysfunction. In the opinion of the Panel, and consulting reviewers, studies following changes in renal function in the same individual or groups of individuals when phenacetin is removed, replaced, or readministered provide strong evidence for a direct causal effect. Followup studies in countries after complete removal of phenacetin from nonprescription use have shown a decrease in the incidence of kidney damage associated with analgesic abuse as will be discussed later in this document. (See part III. paragraph B.2.d.(2)(ii)(*b*) below—Evidence for a relationship between phenacetin abuse and kidney disease.) This not only supports the assumption of causality but also the conclusion that removal from OTC drug status would be beneficial. Data collected from kidney dialysis units in the U.S. and previous autopsy studies suggest the incidence of analgesic-induced kidney disease to be significantly high to warrant the Panel's action to recommend restriction of this drug from the OTC drug market (Ref. 13).

The Panel further believes that these data provide the same early warning indications seen in other countries just before analgesic-induced kidney disease was diagnosed as a major public health problem. The "lag time" between several initial diagnoses of analgesic-induced kidney disease and the realization that in fact the problem was widespread is what most concerns the Panel. While there are not large numbers of cases of analgesic-induced kidney disease being presently reported in the U.S., the Panel believes that if the medical community were aware of this problem and looked for this type of kidney disease, the incidence of analgesic-induced kidney disease would in fact be found to be a major public health problem in the U.S.

The following sections provide more detailed examination and documentation of the available data supporting these conclusions.

(*a*) *Central nervous system effects.* The central nervous system effects of phenacetin appear to be a major factor in the chronic abuse of combinations containing this drug. The habituation potential has been noted by several authors (Refs. 17 through 20).

Most chronic phenacetin takers have used the drug for nonanalgesic purposes. This is probably due to its euphoric and stimulant effects. For example, analgesic kidney disease has occurred most often in middle-aged women with an anxiety syndrome (Refs. 5, 6, 11, 15, and 17 through 20) or in male factory workers who have taken the drug as a stimulant to increase work output. The latter group includes Swiss watch workers (Ref. 11), Huskvarna factory workers (Ref. 12) and workers in the southern part of the U.S. (Ref. 11).

Krumholz, Sheppard and Merlis found fearfulness and depression were more effectively reduced by a phenacetin-containing product than by aspirin, placebo or a mild tranquilizer (Ref. 21).

Eade and Lasagna (Ref. 22) compared the subjective effects of phenacetin and acetaminophen in 20 normal male volunteers. Phenacetin depressed mood, energy and mental activity. It was assessed as a drug with a striking effect while acetaminophen and aspirin did not differ from a placebo. It is of interest that this is the only study found in which a depressant effect was noted rather than euphoria or stimulant effects which have been noted by Zeman (Ref. 19), Moeschlin (Ref. 5), and Gsell, Kielholz and Hegg (Ref. 23).

The acute central nervous system (CNS) effects appear to be due to a direct effect of phenacetin rather than the effect of its metabolite, acetaminophen. This was demonstrated by Prescott et al. (Ref. 24) who studied phenacetin and acetaminophen blood levels and CNS effects resulting from administration of different formulations containing phenacetin. In this study the peak blood levels of phenacetin correlated very well with the appearance of CNS effects while maximum blood levels of acetaminophen were usually achieved at a stage when the CNS effects were diminishing.

There appears to be a dual liability involved in the central nervous system effects of phenacetin. Initially the drug may be taken for pain or for the CNS effect of phenacetin as a "pick-me-up" or stimulant. After prolonged use, however, chronic headache, fatigue and apathy begin to appear (Refs. 5, 19, and 25). Individuals with these symptoms experience temporary relief shortly after taking phenacetin but these symptoms then reappear. Abnormal (epileptiform activity) brain EEG patterns (Ref. 25), and psychic symptoms including instability, disordered volition and acute disturbances may occur (Ref. 23). However, all these effects generally decrease or disappear when phenacetin is discontinued.

Schweingruber found neuropsychiatric symptoms in 28 percent of all phenacetin abusers (Ref. 26).

Murray and coworkers (Ref. 27) found a high incidence of abuse of phenacetin-containing preparations in psychiatric patients. Sixteen of 181 patients (9 percent) took an average of 5.2 kg aspirin (1.3 to 16 kg range) and 3.3 kg phenacetin (1.5 to 11 kg range). An additional 26 patients (14.40 percent) had taken analygesic products daily for 6 months. In virtually all cases the products were taken for psychological rather than analgesic effects.

(b) *Evidence for a relationship between phenacetin abuse and kidney disease.* (1) *Epidemiological studies.* Evidence that ingestion of phenacetin-containing analgesics can result in renal disease can be obtained from either epidemiological studies or direct experimental studies. For ethical reasons direct experimentation is generally possible only in animals which without collaborative studies in humans are usually inconclusive. Therefore, the primary evidence regarding the role of phenacetin in kidney disease must be derived from a variety of epidemiological studies. These are generally restrospective case-control studies in which patients with renal disease (cases) are compared with patients who do not have renal disease (controls) relative to the frequency or degree of drug intake.

Several types of epidemiological studies (Refs. 12, 16, 22, and 28 through 46) of possible relationships between phenacetin-containing compounds and kidney disease were initially selected by the Panel for detailed study for one or more of the following reasons: The studies were carried out over a period of 10 years, 1962 to 1972, in several different countries; the conclusions of many of these studies were instrumental in the decision of various countries to remove phenacetin from nonprescription use; in most of the studies, large numbers of patients and controls were studied and statistical evaluation of the data was possible; and several types of experimental design models were used to assess drug intake and renal disease variables. Therefore, extraneous variables, sources of possible bias, and deficiencies in experimental design would be expected to be different in the various studies.

The association between renal disease variables and drug intake variables have been established by showing that the incidence of kidney disease is higher in people who abuse analgesics (abuse is usually defined as a total intake of 1 kg or greater). This has been shown by many investigators including Nordenfelt and Ringertz (Ref. 47), Larson and Mullen (Ref. 48), Gault, Rudwal and Redmond (Ref. 49), Burry (Ref. 16), and Murray, Lawson and Linton (Ref. 38). In addition, the incidence of analgesic abuse is higher in people who have renal disease. This relationship has been shown by Olafsson, Gudmundsson and Brekkan (Ref. 50), Wilson (Ref. 41), and Murray and Goldberg (Ref. 15).

Even though a statistically valid association between two variables may be shown, this does not necessarily prove that a causal relationship exists in which one variable is the direct consequence of the other.

To prove that a cause and effect relationship exists between two variables in an epidemiological case-control study, it is necessary to show that all other interacting variables are constant and are the same in the patient and control populations. This is usually not possible in the clinical setting.

There are other types of analysis which take into consideration well-established pharmacological principles relating to dose-response relationships as a function of time, that can be used to examine causal relationships between drug intake and drug effect. If a true causal relationship exists between some function of drug intake (independent variable) and some measure of renal disease (dependent variable), then the following relationships between the drug intake and renal disease variables would be expected: If the variables are continuous functions, i.e., not all-or-none phenomena, then a correlation should exist between the degree of drug use (rate or total amount of drug intake) and the degree or incidence of renal dysfunction. Evidence for a continuous dose response curve has been given by Grimlund (Ref. 12), Burry and coworkers (Ref. 16), and Olafsson, Gudmundssen and Brekkan (Ref. 50); if both events are reversible then a change in the independent variable (drug intake) should be followed by a corresponding change in the dependent variable (degree incidence of renal disease). This has been shown in individuals (Refs. 31, 33, 35, 37, 38, and 41) and large populations (Refs. 12 and 39) when phenacetin is withdrawn; a history of drug intake (the independent variable) should precede the onset of renal symptoms (dependent variable), and a similar lag time should be observed between changes in intake and changes in the degree of renal function in an individual or changes in the incidence of renal disease in a population. Several examples of this type of data were found (Refs. 12, 39, and 43).

Studies that provide data which meet these criteria and provide convincing evidence of a causal relationship between phenacetin ingestion and kidney disease are discussed below.

The detailed, continuing studies of employees of a large company and other residents of Huskvarna, Sweden, provide some of the most significant epidemiological information regarding phenacetin abuse and its consequences (Ref. 12). This community provides data to assess the correlations between the degree of analgesic intake, incidence of renal dysfunction, and the disease prognosis, the time involved in development of nephropathy (kidney disease), and the effect of removal of phenacetin from the OTC drug market on the degree of analgesic abuse and the incidence of kidney disease. These data present very strong evidence for the association between phenacetin-containing analgesic products and kidney damage.

The town of Huskvarna had a population of 13,000 in 1963. Three thousand of these worked at the Huskvarna Factory which manufactures appliances, guns, small machinery, etc. Following an influenza epidemic in 1918 to 1919, Dr. Hiorton, a leading town physician, introduced a product containing 500 mg phenazone (antipyrine), 500 mg phenacetin and 150 mg caffeine which immediately gained widespread acceptance and began to be widely misused.

The use of the product apparently was primarily to increase working ability at the Huskvarna Factory where its virtues were extolled by senior workers to new apprentices. Fifty years later, a serious attempt was made through advertising and lectures to decrease use of the product. The consumption continued unabated. When phenacetin was removed from this product in 1961, most habitual users kept taking the product and estimates of sales figures at pharmacies indicated the high consumption of the product had not been significantly changed even though users knew it had been altered and stated it did not have as satisfactory an "effect" as the previous preparation.

Phenacetin was removed from this product as a result of the action of the

Swedish government in 1961, which removed phenacetin from all OTC products. Consequently, the consumption of phenacetin-containing tablets and powders fell from 31.4 million units in 1959 to 1.8 million in 1962. Nordenfelt (Ref. 39) evaluated the effect of removal of phenacetin from the OTC drug market by following all deaths from uremia (blood poisoning due to kidney failure) from 1960 to 1970 in Jenkoping County Hospital (the hospital which normally received Huskvarna residents). Definitive diagnosis of uremia was made on autopsy of 180 patients, 86 (47 percent) of whom were abusers of analgesic drugs. The ratio of men to women was consistent with earlier years (64 men, 22 women) and 45 of the men were Huskvarna workers.

The number of deaths of abusers did not diminish until 1968 which is consistent with the lag time of 6 to 8 years observed by others. In 1970 only 3 deaths due to uremia were noted.

This study showed that while removal of phenacetin from the OTC analgesic market did not affect the degree of analgesic abuse, the incidence of kidney damage dropped significantly.

Studies in Huskvarna also provide data which strongly suggest that the high female to male ratio of analgesic kidney injury in other countries is due most likely to a difference in the incidence of abuse rather than susceptibility since in this town it was the male workers who used phenacetin compounds in large quantities.

The study of Grimlund, the Huskvarna factory physician, provides a clear correlation between the degree of drug intake and the incidence of kidney impairment measured by two renal function variables, the inability to concentrate urine and increased serum creatinine (greater than 1.5 percent is a measure of uremic blood poisoning). Grimlund (Ref. 12) also carried out a prospective follow-up study on 64 patients with serum creatinine levels above 1.5 percent (uremic blood poisoning) over a period of time from 18 months to 4 years. There was a correlation between the degree of elevated serum creatinine and prognosis in patients. Three types of relationships were established by the Grimlund study and are summarized as follows:

(*i*) In 936 representative Huskvarna employees in apparent good health, it was found that renal function was reduced in 34 percent of phenacetin takers but only in 2.4 percent of nonphenacetin takers.

(*ii*) The incidence of renal dysfunction, as measured by serum creatinine and decreased concentrating ability, increased proportionately to the amount of phenacetin ingested, and is indicative of a dose-response relationship (Ref. 12). The following table summarizes these findings:

Incidence of renal dysfunction with ingestion of phenacetin

[In percent]

	Phenacetin—amount ingested—			
	0	1 to 4 kg	5 to 9 kg	10 to 29 kg
Incidence in total population	79.0	12.7	4.8	2.7
Incidence of increased serum creatinine (milligram percent) in group	2.4	19.0	50.0	76.0
Incidence of reduced concentrating ability in group	2.4	15.0	52.0	72.0

(*iii*) The degree of elevated serum creatinine correlated with the prognosis of recovery or death in the patients is summarized in the following table:

Correlation of serum creatinine to patient prognosis

[In percent]

Serum creatinine (milligram percent)	Total	Recovery	Unchanged	Deterioration	Death
1.5 to 2.5	64	35.0	35.0	30.0	2.4
2.6 to 3.5	21	21.4	28.6	42.9	7.0
3.5	14	0	0	22.2	78.0
Total	100	46.9	15.6	64.0	14.0

In addition to an evaluation by the Panel, several of these studies were also submitted to two consultant review groups (Refs. 51 through 53) for an independent evaluation of the validity of statistical procedures and factors in the experimental design which would support or invalidate the conclusions of the studies. Evaluations of the studies by the two groups were carried out independently.

Based on the studies reviewed, one group concluded that there is an association between the use of phenacetin-containing analgesic compounds and kidney disease and that statistically there is an increased incidence of kidney disease in abusers of phenacetin compounds compared to nonabusers and decreased renal function in abusers compared to abusers who cease abuse. This group felt that Grimlund's study of the Huskavarna workers (Ref. 12) provided the strongest evidence for association between phenacetin compounds and nephropathy (Ref. 52).

The second consultant review group concluded that the paper by Waters (Ref. 45) represents the only paper out of the 14 reviewed which does not support a relationship between analgesic consumption and renal damage. The remaining papers all tend to support a relationship between phenacetin-containing compounds and renal damage (Ref. 53).

Based on experimental design, the strongest evidence, in their opinion, were the studies by Bell and coworkers, (Ref. 34), Pearson (Ref. 32), and Wilson (Ref. 41) which rely on the patient as his own control and where improvement in the patient's renal condition occurred once the analgesic abuse was stopped.

A common variable which might bias correlations between the amount of drug used and nephropathy incidence would be the age of the patient. As age increases, a person is more likely to have renal disease and is more likely to have consumed more analgesics which could give a false correlation unless a control group was used which was matched relative to age. This criticism is given by one of the consultant review groups as a major factor in evaluating the dose-response data in Grimlund's study (Ref. 12). While the age factor conceivably could have biased the relationships shown by Grimlund, it is highly unlikely that the correlations were spurious due to the age effect because the magnitude of the changes in drug intake or renal function is much greater than would be expected due to increased age alone and also because in other detailed studies there has been no correlation between the age of patients, duration of use, or incidence of use.

An analysis of the data of Bell and coworkers (Ref. 34) shows no correlation between age (average 57 years, range 33 to 70), duration of use (average 12 years, range 6 to 23 years) and phenacetin total dose (average 5.6 kg, range 2.2 to 12.0 kg). The average age of patients in Grimlund's study was 63 years.

Several other researchers have found a correlation between the degree of phenacetin intake and probability of serious kidney damage (Refs. 16, 34 and 38).

The prospective autopsy study of Burry, de Jersey and Weedon (Ref. 16) provides significant evidence for phenacetin involvement in renal papillary necrosis. Pathological diagnosis and degree of analgesic consumption, as determined by questioning the next of kin, were determined independently. In 507 autopsies when other possible reasons for renal papillary necrosis (obstruction, diabetes, and papillary amyloidosis) were excluded, severe papillary necrosis (42

cases) correlated with heavy phenacetin abuse (2 to 4 kg total).

This retrospective case-control study indicated that total doses of 4.0 kg would result in a 73 percent probability of renal papillary necrosis (kidney damage). The probability of death in patients with papillary necrosis was 37 percent. This is similar to the findings of Bell, Kerr, Swinney and Yeates, who reported that 29 percent of patients with renal papillary necrosis associated with phenacetin abuse died of renal (kidney) failure (Ref. 34). Murray, Lawson and Lenton (Ref. 38) found that total analgesic intake greater than 1 kg resulted in the finding of renal papillary necrosis (kidney damage) in 85 percent of autopsies; 26 percent of these patients died of uremia (uremic blood poisoning) due to kidney failure. Olafsson, Gudmundsson and Brekkan (Ref. 50) have also shown a correlation between increased intake of phenacetin compounds and decreased renal function.

A change in renal function in individuals following a change in drug intake has been shown in several studies. The effect of substituting aspirin for phenacetin in products used by analgesic abusers was studied by Murray, Lawson and Lenton (Ref. 38). The study took advantage of a change in formulation of two powders which were among the most commonly abused compounds in Scotland and in which phenacetin was removed and aspirin substituted. Other preparations which retained phenacetin provided a basis for comparing aspirin-phenacetin compounds with preparations containing aspirin only. As seen in other studies, the lag time after removal of phenacetin until changes in the incidence of renal disease (nephropathy) were observed was found to be from 4 to 8 years. Renal function of those who continued to abuse analgesics containing aspirin only or aspirin with phenacetin as measured by creatinine clearance continued to deteriorate. The study showed that renal function continued to deteriorate when aspirin-containing products were abused but the rate of progression was significantly less rapid (4.9 ml/minute/year compared to 12.9 ml/minute/year) for phenacetin compounds.

Furthermore, the incidence of deaths due to uremia was less (3 out of 12 patients) in patients taking nonphenacetin-containing products than the number of deaths in patients taking products containing phenacetin (9 out of 14 patients), and the total number of new cases was reduced.

Bell and coworkers substituted acetaminophen for phenacetin in 5 patients with renal disease (0.5 to 6 g acetaminophen daily) and aspirin for phenacetin in 2 patients (0.1 to 1.8 g aspirin daily) with no apparent difference in renal function from that seen in patients with total withdrawal of analgesics (Ref. 34).

Evidence of the beneficial effects of removal of phenacetin from the OTC drug market can also be seen in countries which have removed phenacetin from nonprescription use. The total withdrawal of phenacetin compounds from the OTC drug market has resulted in significant decreases of renal disease in Sweden and Denmark.

As a basis of comparison, in Australia and Switzerland, countries which have attempted public education on the hazards of analgesic abuse but have not restricted nonprescription use of phenacetin compounds, the incidence of analgesic-induced renal disease has not changed appreciably in spite of the widespread awareness of the problem (Ref. 14).

In Sweden, Bengtsson (Ref. 28) reported that following restriction of OTC drug sales in 1961, consumption decreased 10 fold and the incidence of renal disease decreased from 58 percent in 1961 to 25 percent in 1965 and according to Nordenfelt continued in a favorable direction after 1965 (Ref. 39).

In Denmark, it has been reported that the incidence of renal papillary necrosis in all deaths due to renal disease decreased when phenacetin compounds were removed from nonprescription use (Ref. 43).

In Switzerland, where nonprescription phenacetin compounds are still available, the deaths due to uremia have not changed during the period from 1966 to 1971. The total number of uremic deaths each year during this period were 73, 71, 69, 70, and 68, respectively (Ref. 14).

Australia has been cited as an example of a country where the removal of phenacetin compounds from the OTC drug market has not modified the incidence of analgesic nephropathy. The Panel finds that statements of this nature are a misrepresentation of the actual facts since phenacetin compounds have never been actually withdrawn from the OTC drug market in Australia. In 1966, phenacetin compounds were withdrawn from the public health list which simply prevents payments for these products from National Welfare funds. Phenacetin-containing products are at least as readily available for unlimited self-treatment as they are in the U.S. (Ref. 34). The Panel was unable to find any evidence that the act of excluding phenacetin compounds from free payment on the National Health list or the public education campaign resulted in any change in the ingestion habits of the analgesic abusers or the increasing incidence of analgesic renal disease in Australia.

As briefly mentioned above, the lag time between ingestion of drug and the appearance of kidney effects is relatively long and provides further evidence of a causal relationship between chronic phenacetin intake and analgesic-induced kidney disease. Burry and others noted that in 52 cases of analgesic nephropathy involving patients consuming greater than 2 kg phenacetin total, only 1 of 19 deaths occurred in less than 10 years. Severe renal damage was rarely seen in less than 5 years (Ref. 16).

Wilson (Ref. 41) observed that analgesic kidney disease required a development period of 5 or more years in 84 percent of patients and more than 10 years in 62 percent of patients. Thus after 10 years of use, one would see only 38 percent of the total number of individuals who ultimately will develop symptoms. This provides an explanation for the continued appearance of analgesic nephropathies for several years after drug-intake is stopped.

In 35 patients from Huskvarna who died of uremia the time between initial use and onset of symptoms was several years. The time between onset of symptoms and death, however, was quite rapid, usually 1 year or less in 75 percent of patients. Only 2 of 35 patients survived for 4 to 5 years. Abuse of the product containing phenacetin was probably continued in most of these cases.

A few authors have suggested the possibility that high analgesic use is a result of renal disease rather than the cause. It has been suggested that renal pain may be subthreshold and not be recognized except for a better feeling after analgesic use. Because of the long lag time (3 to 10 years) between initial analgesic use and the first indication of renal dysfunction, which has been observed in many different studies, there is very little possibility that this is a reasonable explanation in most reported cases. Other authors have provided other valid reasons or data to clearly refute any serious considerations of analgesic abuse being a result of renal dysfunction.

Burry and others (Ref. 16) refuted the idea that patients take analgesics to allay the pain of kidney infection (pyelonephritis). In his study there was no association between analgesic consumption and pyelonephritis in the absence of papillary necrosis. Furthermore, many cases of papillary necrosis were associated with analgesic abuse in the absence of pyelonephritis.

(2) *Mechanism of action producing nephropathy.* The difficulty of showing the mechanism by which phenacetin causes nephropathy in animals, even when large amounts of phenacetin are administered over long periods of time, has been a primary factor in the belief of some authorities that it is not the primary agent responsible for analgesic-induced nephropathy. However, this difficulty in showing kidney disease in animals has also been shown to be a factor of experimental variables such as difference in metabolism between different species, type of diet, water intake, and others.

Clausen (Ref. 46) found rabbits given either 325 mg aspirin or phenacetin orally developed interstitial nephritis (kidney inflammation) with both drugs and an increased susceptibility to kidney infection. Abrahams et al. (Ref. 54) found papillary necrosis (kidney disease) in two rats who received an aspirin-phenacetin-caffeine combination. Renal papillary hemorrhage (kidney bleeding) was noted in rats orally given both phenacetin alone and in the aspirin-phenacetin-caffeine-containing product.

Fordham et al. (Ref. 55) administered phenacetin to Sprague-Dawley rats (300 mg for 10 days, or 450 mg for 10 days, or 600 mg for 20 days) resulting in physiologic and histologic evidence of renal

dysfunction including papillary necrosis in 3 of 39 rats. Boyd et al. (Refs. 56 and 57) found that hepatorenal necrosis (liver and kidney disease) that occurred in acute toxicity to phenacetin was influenced by diet and mode of administration (dietary against intragastric). Eisalo and Talanti (Ref. 58) showed interstitial nephritis (kidney inflammation) in 7 of 18 rats given 100 mg/day of phenacetin in food and in 5 of 18 rats given 100 mg acetaminophen in water. However, no papillary necrosis (permanent kidney injury) was observed.

Animal studies are useful to study mechanisms of toxicity. However, care must be taken in extrapolating data from animal to man. Furthermore, it must be realized that strain difference is important. Recently Mazze, Cousins and Kosek showed that dose-related methoxyflurane nephrotoxicity in rats varied markedly with strain (Ref. 59). Thus, when studying a toxic effect in animals extreme care must be taken in interpreting whether results are positive or negative.

The primary sites of kidney injury are the papillae and medulla. Papillary necrosis is thought to be vascular in origin, resulting from ischemia. In lay language, this means that the type of kidney disease which occurs is thought to be due to constriction or obstruction of blood vessels in the kidneys.

Kincaid-Smith has shown early lesions in the efferent vasa recta of rats treated with phenacetin and aspirin/phenacetin/caffeine (Ref. 60).

Abrahams and Levin have observed platelet deposition in the vasa recta in treated animals (Ref. 61).

Secondary chronic atrophic lesions in the overlying renal cortex result in changes which have been referred to as "chronic interstitial nephritis" (Ref. 62).

The medullary blood flow is particularly susceptible to a number of drugs and the medulla is quite sensitive to ischemia.

It is possible that the anemia which accompanies or perhaps precedes renal effects may contribute to the ischemia.

The hemolytic effect (red blood cell destruction) of phenacetin may play a role in the mechanism of renal damage. The pathological picture of centrally located papillary necrosis is the same as that seen in sickle cell anemia in which the deformed erythrocytes occlude the vasa recta (Ref. 63).

The possible sequential effects of erythrocyte damage caused by phenacetin resulting in urinary excretion of abnormal hemoglobin which produces a "sludging" effect and interstitial nephritis has been discussed by Grobin (Ref. 64).

(3) The incidence of analgesic-induced kidney disease. The true incidence of analgesic-induced kidney disease is difficult to assess and is undoubtedly underestimated for several reasons. First, it is clear that unless physicans are alerted to the possibility of analgestic-induced kidney injury and specifically consider it during diagnosis, it is likely to be missed (Refs. 34, 63, and 65). Secondly, accurate drug histories are frequently not obtained because of the reluctance of the patient or oversight by the interviewer, and thirdly, the distinguishing characteristics of this type of kidney injury have not until recently been generally accepted or recognized.

The experiences reported by many investigators indicate that correlations between drug intake and disease variables may be biased due to underestimates of the values given for incidence of and amount of drug used.

Several authors have stated that there is a definite tendency of patients to withhold information on the frequency and degree of analgesic intake, particularly if a stigma of abuse has been associated with intake of these drugs. In some cases only persistent questioning of the patient or relatives eventually established the incidence of drug intake (Refs. 28, 37, and 39).

Bell et al. (Ref. 34) commented that the difficulty of establishing drug intake may often be the failure of the physicians to include direct questioning of analgesic intake in routine interviews rather than a reluctance of the patient, noting that each of the 13 patients with analgesic-induced kidney disease that he reported were seen previously by one or another of the authors who did not suspect an excessive analgesic intake. A history of excessive drug ingestion was readily obtained when the patients were specifically asked regarding the frequency of drug use.

Although early workers did not believe the renal lesion to be specifically related to analgesic abuse, and, in fact, originally described the pathology as chronic pyelonephritis or interstitial nephritis, there is general agreement among authorities that a specific type of kidney injury, renal papillary necrosis, is the primary lesion observed most often with analgesic abuse (Ref. 63). Koch states that renal papillary necrosis associated with analgesic abuse can be distinguished morphologically from renal papillary necrosis associated with diabetes and other nondrug-related causes.

The histologic and electron microscopic studies of Gault et al. (Ref. 37) provide a clearer picture of the relationship between disease development and functional changes in analgesic-induced kidney disease. The first events are morphologic changes in interstitial collagen and medullary sclerosis accompanied by slight changes in concentrating ability. A reduction in creatinine clearance, one of the usual diagnostic methods to detect renal disease, is not apparent until significant medullary sclerosis and papillary necrosis occur.

Differentiation of analgesic kidney disease from bacterial interstitial nephritis or pyelonephritis is often complicated by the difficulty of finding analgesic kidney disease in the presence of renal infection. Thus, a histological picture of chronic pyelonephritis is often superimposed on the analgesic-induced papillary necrosis. Rubenstein et al. (Ref. 66) state that 50 patients with analgesic kidney disease were previously diagnosed as having chronic pyelonephritis. It is possible that misdiagnosis may have been and in some cases still is a factor in low incidence of detection. Rubenstein et al. (Ref. 66) state that in those cases where sterile urine is found, analgesic nephropathy can be distinguished from chronic pyelonephritis by microscopic findings of papillary necrosis.

In the series of 13 patients with analgesic nephropathy discussed by Bell (Ref. 34), 12 patients underwent intravenous pyelography. Nevertheless, in eight cases, the initial diagnosis was chronic pyelonephritis even though the cardinal signs (Ref. 63) of renal papillary necrosis were present including small kidney (seven cases), clubbed calices (five cases) and lobulated outline (three cases). Bell concluded that the detection of renal papillary necrosis is likely to be missed unless a conscious effort is made, and the true incidence is likely to be much higher than reported.

An additional factor in poor detection of analgesic nephropathy may be related to the erroneous conclusion frequently reached in the literature that because analgesic-induced kidney injury has not been reported in a given area or country it does not exist.

Such statements often attempt to relate differences between countries in the number of cases reported to possible genetic or environmental differences between countries rather than a difference in accurate diagnosis and thus may compound the basic problem of lack of awareness in the medical community.

The slow rate at which the medical and scientific community throughout the world has become aware of and reported new cases of analgesic-induced kidney disease clearly shows the difficulties of using reported cases at a given point in time as an estimate of the true incidence in a given country.

In 1967 Shelley (Ref. 67) reviewed over a thousand cases of analgesic-induced kidney disease throughout the world from the time it was first described by Spuhler and Zollinger in 1953. These reports were largely from Scandanavian countries and Australia. Prior to 1966, there were only 11 cases reported in Great Britain. That year Prescott reported 36 cases in northeast Scotland alone (Ref. 68). Four years later in 1970, only 117 total cases had been reported, 89 of which were from Scotland, 28 from England and Wales. There was only one from the London area (Ref. 69). This led to the false conclusion that the problem was confined primarily to Scotland.

Between June 1964 and January 1970 Koutsaimanis and de Wardener (Ref. 65) detected 16 cases at a small 200 bed hospital in London. Seven of these patients had first been seen in other departments of the hospital before the diagnosis was made. Based on these cases they estimated that the overall incidence of analgesic-induced kidney disease in England and Wales was 500 cases per year. The actual rate of detection, however, was only 5 percent of this number.

The same lag time in recognition of the problem has occurred in Canada. In 1967,

14 years after the first Swiss report, there were only seven cases reported in Canada. In 1968, Koch reported 26 cases of kidney injury in 195,004 cases (0.013 percent) admitted to the Ottawa civic hospital between 1961 to 1966. Fifteen of these cases (58 percent) were analgesic abusers who had taken more than 1 kg phenacetin-containing products (Ref. 63). In the same year Gault and coworkers (Ref. 49) reported 22 patients with analgesic-induced kidney disease seen in two hospitals in Montreal over a 4-year period. In 1972, 100 cases in two Ontario cities, London and Glasgow, were reported by Linton (Ref. 40). In Canada analgesic kidney disease now accounts for 5.5 percent of all renal dialysis in Ontario.

A similar time lag is now occurring in recognition of the association of kidney tumors with phenacetin abuse which was first noted in 1965 in Sweden, 12 years after the association between analgesic compounds and kidney disease was noted. Four years later an editorial in *Lancet* pointed out that reports had not come from any other country suggesting that perhaps factors other than phenacetin may be involved (Ref. 70). Finally, in 1971, after an additional 6 years, reports are now beginning to appear from several other countries, showing again that a low incidence of reported disease in a particular region does not necessarily assure that the true incidence is low.

(4) *Incidence of analgesic-induced kidney disease in U.S.* It has been stated that analgesic kidney disease is less frequent in the U.S. than in other countries with similar per capita ingestion of phenacetin-containing analgesics. Recent evidence suggests that the lower incidence of reported cases may simply represent differences in detection rather than real differences as has been seen in other countries. In the past 10 years about 100 cases of analgesic kidney disease have been reported in the literature in the U.S. (Refs. 71 and 72). Murray and Goldberg have reported that 20 percent of patients with newly clinically diagnosed chronic interstitial nephritis at the University of Pennsylvania Hospital, during the period 1969 to 1972, had abused analgesics which was considered the likely cause of renal disease (Ref. 15). This is similar to the incidence of 3 to 17 percent of analgesic abusers in patients with otherwise unexplained end-stage renal disease in Canada (Ref. 41) and Europe (Refs. 73 and 74). The signs and symptoms of this group (headache, anemia, hypertension, urinary tract infection and papillary necrosis) also were comparable in incidence to previous reports. The authors state that this high rate of detection was not due to a selective population but was simply due to the fact that they were aware of and specifically looked for analgesic kidney disease in these patients. It is significant that the referring physicians did not make the correct diagnosis in any of the 20 cases nor did the primary intern in 13 of the cases. Furthermore, as in many other studies, 7 of the patients denied analgesic intake, and accurate drug histories could be obtained only from relatives. Two of the cases had other family members with analgesic kidney disease. The authors conclude that their experience is typical of what would be expected elsewhere and suggest that the prevalence of analgesic kidney disease in the U.S. may be about 7 percent of all end-stage renal patients.

The incidence of renal papillary necrosis in the U.S. and other countries has been estimated by Heptenstall (Ref. 75). These figures summarized in the table below probably represent the minimum incidence and are compared to estimates of the per capita consumption of phenacetin in different countries (Refs. 49 and 50):

Incidence of renal papillary necrosis compared to phenacetin consumption

Countries surveyed	Minimum incidence of renal papillary necrosis at autopsy	Per capita consumption of phenacetin (grams per year)
Australia	3.7 to 5	40
Canada	0.15 to 0.5	6 to 7
Copenhagen	1.05	25
Northern England	0.16	Not available
Scotland	0.54 to 0.59	12
Switzerland	1.32	22
United States (3 series)	0.16 to 0.26	10

This Panel has requested information on the cases of analgestic kidney disease that had been detected in several renal dialysis centers. A total of 103 cases of suspected analgesic nephropathy were reported which represented about 1.1 percent of all renal dialysis patients. Only two of these cases were stated to have involved aspirin preparations not containing phenacetin. Five cases were not specified. The remaining 95 cases were stated to have involved phenacetin-containing compounds (Ref. 13).

In a recent report (Ref. 15), analgesic abuse was identified as the primary cause of renal disease in 30 (1.25 percent) of 2,395 chronic hemodialysis patients treated in 91 dialysis centers in California between January 1, 1974 and September 1, 1974. Of 332 deaths in 1974, seven (2.71 percent) were attributed to abuse of analgesic compounds.

A detailed analysis of cases of suspected analgesic kidney disease was supplied by the Minneapolis Regional Kidney Disease Program (Ref. 13). The amounts used (1 to 3 g/day), duration of use (6 to 12 years) and reasons for use (headache, nervous tension) are essentially the same as reports in the literature.

The Panel can only conclude that the same lag time in detecting and reporting analgesic-induced kidney disease is now occurring in the U.S. as has previously occurred in the United Kingdom and Canada.

(c) *Cancer of the urinary tract.* During the past few years, several reports have implicated long term use of phenacetin-containing products with cancer of the renal pelvis (kidney) and urinary bladder. The first report, in 1965, was a retrospective study by Hultengren et al. of fifteen patients with cancer of the renal pelvis in the Huskvarna Hospital (Ref. 76). All but two had renal papillary necrosis associated with long term analgesic use.

Bengtsson and colleagues (Ref. 77) reported a study of 192 patients with documented nephropathy in which patients were followed for a period of 1 to 11 years (average 5.3 years). During this time, nine patients developed renal pelvis carcinoma (cancer of the kidney) and another two patients developed cancer of the urinary bladder. No tumors were found in 88 individuals with chronic pyelonephritis (kidney inflammation) who served as a control population of nonanalgesic abusers observed during the same period of time. In a followup study by Angervall et al. (Ref. 78), it was shown that renal pelvic carcinoma (cancer of the kidney) is an infrequent disease in Sweden, the average yearly incidence being only 11 cases per 156,000 inhabitants which is about 1,000 times less than the incidence reported for analgesic abusers. A more recent study by Johansson and coworkers (Ref. 79) was based upon known abusers of phenacetin compounds (29 men and 33 women) who had uroepithelial tumors of the renal pelvis (carcinomas) treated at the hospitals throughout Sweden. All tumors were diagnosed during the years 1960 through 1972. All patients had been abusers of drug products containing phenacetin. The preparation used by 80 percent of the patients contained 0.5 g phenacetin, 0.5 g antipyrine and 0.1 g caffeine. The other patients (20 percent) took compounds of the same composition but containing varying amounts of the same ingredients. In 38 patients, detailed data of drug intake were available. The average total ingestion of phenacetin was estimated to be 9.1 kg, with a mean exposure time of 17 years. Chronic kidney disease had been established in 23 patients for a period of 3 to 15 years before a diagnosis of kidney cancer was made. Forty patients had a history of urinary tract infection. A diagnosis of analgesic-induced papillary necrosis (permanent kidney injury) was made in all but five of the patients. In two patients, examination was not possible. In the remaining three patients, there were no signs of papillary necrosis even though these patients were known analgesic abusers. The authors concluded that renal papillary necrosis was a prominent feature, but not essential, for the development of renal pelvic tumors in abusers of phenacetin-containing drugs. The sudden appearance of this relatively rare condition in patients, almost universally associated with analgesic abuse, leaves little doubt that a strong association exists. There are now many case reports available from Sweden, Denmark, Germany, Canada and the U.S. which associate phenacetin abuse with cancer of the kidney (Refs. 80 through 88).

A large number of cases of tumors of the renal epithelium (cancer of the kidney) associated with analgesic abuse have been reported in Germany by Rathart and workers (Ref. 83) and Schabert, Nagel and Leistenschneider

(Ref. 84). Hoyby and Neilson (Ref. 80) have summarized a number of cases of transitional cell tumors of the renal pelvis (kidney cancer) in Denmark over a 5-year period.

Their retrospective review of patients with chronic pyelonephritis (kidney inflammation) and abuse of phenacetin, revealed two cases of transitional tumors among 101 patients who abused phenacetin. They conclude that cancer of the kidney should be suspected in patients with renal papillary necrosis (kidney injury) associated with abuse of phenacetin, particularly when hematuria occurs without accompanying pain. Liu, Smith and Rankin have reported one case in Canada (Ref. 81). There is a report of bladder tumor associated with phenacetin abuse in one patient in the U.S. Mannion and Susmano (Ref. 87) describe a 48-year-old man suffering from chronic headaches first admitted to the hospital with urinary tract symptoms in 1965, during which time a small cancerous tumor was removed from his bladder. This individual continued analgesic ingestion in fairly large amounts of 15 to 20 tablets daily intermittently until 1969 when he was readmitted and another cancerous tumor was removed from the same location. At this time the patient had been ingesting aspirin-phenacetin-caffeine-containing tablets intermittently for the past 20 years. The patient had never smoked. He worked and lived in an environment where obvious carcinogenic contamination was not apparent. It is interesting that this individual did not have papillary necrosis and was therefore similar to some of the cases reported by Bengtsson, Hultengren and associates (Ref. 76) also found that in six cases where papillary necrosis (kidney disease) and renal pelvic carcinoma (cancer of the kidney) occurred together in patients who abused phenacetin, the papillary necrosis antedated the cancer in only four cases. This may indicate that the two events are unrelated. Perhaps different metabolites are involved.

(d) *Adverse effects on blood.* Phenacetin has been implicated as a cause of hemolytic anemia, decreased red blood cell survival time, enlarged spleen, methemoglobinemia and sulfhemoglobinemia (serious blood disorders) (Refs. 89 through 91). Hutchinson, Jackson and Cassidy discussed three cases of hemolytic anemia following large doses of phenacetin compounds (Ref. 92). The studies of Lorenzen and Schwartz, and of MacGibbon and workers, indicate that phenacetin or its metabolites may activate an allergic type sensitization mechanism which leads to acute hemolytic anemia and acute kidney failure (Refs. 93 and 94).

Bird et al. (Ref. 95) have reported a case of a patient with an immune hemolytic anemia which was associated with both tolbutamide and phenacetin.

The studies of Lorenzen and Schwartz showed that hemolysis took place in the spleen of women ingesting large amounts of phenacetin compounds (Ref. 93). An enlarged spleen is a common symptom of phenacetin abusers. Duggan (Ref. 96) also reported 10 women with significant enlargement of the spleen which were apparently related to chronic ingestion of phenacetin. He found parallel phenomena in his experimental studies in rats.

(e) *Additional considerations of benefit to risk consequences of removal of phenacetin from OTC analgesic preparations* The Panel has discussed the evidence showing that OTC analgesic preparations containing phenacetin were subject to abuse and that the chronic misuse of such preparations resulted in a high incidence of life-threatening kidney disease. In addition to its toxic effect on the kidney, phenacetin has also been reported to cause serious blood dyscrasias. It is thought that the central nervous system effects, such as euphoria and stimulation, are the major factors contributing to the chronic abuse (habituation potential) of OTC combinations containing phenacetin. The Panel, therefore, concludes that because the risks from use far outweigh any possible benefits, phenacetin in combinations is not safe for OTC use as an analgesic and should be removed from analgesic preparations (Category II).

Several presentations have been made in response to the Panel's conclusion. These presentations are in favor of the retention of phenacetin in OTC analgesic preparations. In making its final recommendation, the Panel considered the questions submitted by these groups. The questions and the Panel's replies are summarized below.

(1) If phenacetin were removed from the OTC market would the general public be deprived of a useful agent for which alternative drugs are not available?

Unlike other analgesics, such as aspirin and acetaminophen, phenacetin is mainly available in OTC combinations, whereas aspirin and acetaminophen are available in single ingredient products as well as in combinations. These phenacetin combinations are no more effective analgesics than combinations that do not contain phenacetin, but phenacetin combinations are less safe than preparations that do not contain phenacetin. Because phenacetin is less safe than other analgesics, the general public would not be deprived of a useful agent for which alternative drugs are available if phenacetin were removed from the OTC market. The risks from the use of phenacetin combinations are much greater then the risks from the use of analgesic combinations that do not contain phenacetin.

In addition, phenacetin preparations offer no advantages to individuals unable to take other analgesic preparations, i.e., individuals sensitive to aspirin. Phenacetin is virtually never marketed as a single entity in this country and the APC combination products (aspirin-phenacetin-caffeine) are not useful as substitutes for individuals with aspirin sensitivity.

In contrast, acetaminophen has been available alone. Although it is the major metabolite of phenacetin it is safer than the parent compound in many respects. Acetaminophen lacks the intrinsic CNS effects of phenacetin and therefore has less abuse potential. Other minor metabolites of phenacetin associated with methemoglobinemia, hemolytic anemia, splenomegaly and thrombocytopenia, occur to a lesser extent when acetaminophen is given as such.

(2) Is the combination of aspirin and phenacetin as safe as those drugs alone? Experimental evidence available strongly suggests that the potential toxicity may actually be increased for combinations of phenacetin and aspirin.

(i) Phenacetin appears to be a major factor in the excessive use of analgesic preparations. Its presence may increase use and thus the incidence of serious toxic effects of aspirin or other agents ingested in large amounts in combination products.

(ii) The evidence implicating both aspirin and phenacetin with experimentally-induced papillary necrosis in animals suggests that combinations of these drugs may be more nephrotoxic than phenacetin alone. The studies of Kincaid-Smith and others show greater effects of aspirin-phenacetin-caffeine combinations than phenacetin or aspirin alone.

The direct effects of phenacetin, including production of methemoglobinemia and hemolytic anemia may interact with direct hematologic effects of aspirin which include effects on platelet function, thrombocytopenia and anemias associated with occult gastric bleeding. These combined effects may be related to gastric and renal hemorrhage, ischemia and focal necrosis.

(3) Would the risk potential associated with abuse be greater or less with alternate preparations?

In cases where phenacetin compounds have been substituted by nonphenacetin containing compounds, the renal consequences of abuse are less severe. Substitution has resulted in decreased progression of existing nephropathy or decreased incidence of new cases.

Some authors have opposed the removal of phenacetin because acetaminophen may be substituted and the combinations with this agent may be equally nephrotoxic. While there is some evidence that acetaminophen may be nephrotoxic, it is likely to be less so for several reasons:

(i) The decreased CNS effect of acetaminophen reduces abuse potential.

(ii) Decreased amounts of potentially nephrotoxic metabolites are formed after acetaminophen ingestion compared to phenacetin ingestion.

This is supported by several substitution studies in patients with existing renal papillary necrosis in whom the substitution of acetaminophen for phenacetin produced less renal dysfunction.

(4) *Considerations of gastrointestinal effects.* Will the removal of phenacetin from OTC products simply result in additional amounts of aspirin being added to combination products, increasing the risk of gastrointestinal ulceration asso-

ciated with aspirin? There is no evidence that the substitution of phenacetin for aspirin in APC preparations decreases the ulcerogenic potential of the product. A review of the medical histories of patients described in the literature shows a clear pattern of gastric bleeding and ulceration in patients taking large amounts of phenacetin-containing analgesic preparations.

The incidence of adverse effects of aspirin on the gastrointestinal system may be increased when aspirin is used as a component of mixtures taken primarily for the central nervous system effects of phenacetin since increased amounts of aspirin are ingested.

Plass (Ref. 97) reported a case of a 35-year-old man who had intractable ulcer symptoms and renal papillary necrosis. Cessation of intake of an APC compound, which had been taken for 20 years, resulted in relief of ulcer symptoms as well as a return to normal BUN (blood urea nitrogen) values.

Ramsay and White (Ref. 98) reported clinical data on four patients with analgesic nephropathy who had taken large amounts of an APC compound over 20 to 30 years. Each of these patients also had symptoms of gastric damage including gastrointestinal hemorrhage, a history of gastrectomy and peptic ulcer.

Tan, Rabbino and Hopper (Ref. 99) reported that 4 of 23 patients with analgesic nephropathy had gastric or duodenal ulcers. Rapaport, White and Rankin (Ref. 100) reported that two patients with suspected phenacetin/analgesic nephropathy also exhibited a history of peptic ulcer.

An increase of gastric ulcers in eastern Australia has been attributed to the effects of aspirin. However, the preparations involved in 80 percent of these cases contained aspirin, phenacetin or acetaminophen, and caffeine (Ref. 17).

There are now several reports of a combination of renal, hematologic, gastrointestinal and psychological symptoms which occur so frequently with analgesic abuse that Gault and coworkers state that they warrant a syndrome status. The combination of symptoms include anemia, renal disease, gastric ulcer, frequently with a history of gastrectomy for intractable ulcer, hypertension, and psychiatric disturbances (Refs. 37, 49, 71, and 101). It has been speculated by other authors that additional effects are possibly associated with the abuse of phenacetin-containing compounds.

Other complications which have been stated to be a result of analgesic abuse of phenacetin-containing analgesics include greater risk of mortality following surgical procedures. Koutsaimanis and de Wardener (Ref. 65) reported a study of phenacetin abusers who underwent surgery; in 3 out of 7, the operation was followed by a severe deterioration of renal function and they all died shortly after surgery.

Dawborn et al. (Ref. 101) in a study on the association of peptic ulcer, chronic renal disease and analgesic abuse (of phenacetin-containing analgesics) found 17 of 30 patients had such severe gastric symptoms that they required gastrectomy. Nine of these 17 patients died during the period of followup (4-year period). Uremia was invariably present at the time of death; however, it did not constitute the major cause of death.

(3) *Evaluation.* The Panel concludes because of the high potential for abuse, the high potential for harm to the kidney and the possibility of hemolytic anemia and methemoglobinemia resulting from abuse, that the risks from use outweigh any benefit and therefore classifies phenacetin not safe for OTC use as an analgesic.

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e. *Quinine.* The Panel concludes that quinine is an effective analgesic but that it is not safe for OTC use.

(1) *Effectiveness.* The analgesic and antipyretic properties of quinine have been known since the introduction of cinchona bark into medicine in the 17th Century. Because it lowered the fever of malarial patients it was tried in many febrile illnesses, but was relatively ineffective in fevers due to diseases other than malaria. However, when used as an antipyretic in febrile illnesses it was noted that pain and discomfort were relieved and thus the analgesic action was discovered. Modern use of quinine for analgesia and antipyresis is based on long experience instead of controlled studies. In the first edition of the Pharmacological Basis of Therapeutics, published in 1941 (Ref. 1), Goodman and Gilman stated:

> Quinine in oral doses of 0.3 to 0.6 gram is employed for the relief of headache, myalgia, arthralgia, neuralgia, etc., and for reducing fever. It has, therefore, the same general field of usefulness as the salicylates but is somewhat less effective. Repeated medication may cause unpleasant symptoms of cinchonism.

An almost identical statement is made in the fourth edition of Goodman and Gilman's text published in 1970, indicating no change in the status of quinine for treatment of pain and fever during the last 30 years.

Apparently, there has never been complete agreement as to the dose. For instance in the eighth and last edition of his text, Sollmann states that the clinical antipyretic dose of quinine is 0.05 to 0.2 g, 1.0 to 3.0 gr may be used for pain in colds, headaches and neuralgias (Ref. 2). Further evidence that the antipyretic-analgesic action of quinine is still recognized but considered inferior to other drugs is found in the following quotation from the *AMA Drug Evaluations* (Ref. 3): "Quinine has been used * * * as an antipyretic analgesic * * * however * * * more effective drugs are currently available for these purposes." No controlled or uncontrolled effectiveness studies on either antipyretic or analgesic activity of quinine were found in an industry submission which included quinine in combination with other ingredients as a cold preparation. It may be noted that the doses recommended by Sollmann for pain are lower than those recommended by Goodman and Gilman and therefore, modern controlled clinical trials would be necessary to establish the effective analgesic and antipyretic doses for quinine.

The use of quinine for relief of nocturnal leg cramps was introduced in the 1940's when Moss and Herman (Ref. 4) and Gootnick (Ref. 5) reported on the basis of uncontrolled trials that quinine in the doses of 3 to 5 gr (200 to 325 mg) abolished the spasms. Nicholson and Falk (Ref. 6) reported relief following quinine treatment in about ¾ of 35 young men with disturbing nocturnal cramps. Rawls (Ref. 7) found a combination of quinine and aminophylline superior to quinine alone. *The Medical Letter* (Ref. 8), while stating that controlled clinical trials evaluating quinine's effectiveness for nocturnal or recumbancy cramps were needed, did recommend trying quinine for nocturnal cramps pending the outcome of trials to establish efficacy and dosage. These uncontrolled studies suggest that quinine may be useful for leg cramps but the lack of controlled studies and comments by authors that patients may remain free of cramps for indefinite periods following quinine therapy suggest that trials of quinine against placebo are in order. In addition, the recommended dosage varies widely, from 200 mg at bedtime to 5 gr (325 mg) 4 times daily as recommended by Perchuk (Ref. 9) who also suggests that the drug should be used only when everything else has failed. Until controlled studies show that a dose of not more than 325 mg daily is safe and useful for relief of nocturnal leg cramps the drug should not be available for OTC use for treatment of nocturnal leg cramps.

(2) *Safety.* The Panel concludes that quinine is not a safe analgesic for OTC use when taken in the recommended dosage.

Although quinine has demonstrated analgesic, antipyretic and muscle relaxant actions, its numerous toxic effects give it an unfavorable benefit to risk ratio for these purposes. The high dosage recommended by some for relief of nocturnal leg cramps should be dispensed only by prescription. The toxicity of quinine has been the subject of innumerable reports and is well summarized in many modern text books of pharmacology and toxicology. The toxicology of quinidine and its stereoisomer quinine is well summarized by Gleason et al. (Ref. 10), and in the fourth edition of Goodman and Gilman, Rollo (Ref. 11) states that the fatal oral dose of quinine for adults is approximately 8.0 g. When quinine is repeatedly given at full doses, e.g. 0.3 to 0.6 g with a total daily dose of not more than 2.0 g, a group of symptoms known as cinchonism appear. These include tinnitus, headache, nausea and visual disturbances. The body systems which may be involved include the gastrointestinal, nervous and cardiovascular systems, and the skin. Actions on the gastrointestinal tract are evidenced by nausea, vomiting, abdominal pain and diarrhea. Damage to the nervous system is usually manifested by the disturbances in hearing and vision due to actions on the optic and auditory nerves. Other actions on the central nervous system may be expressed by headache, fever, apprehension, confusion, excitement, delirium and syncope. Respiration is stimulated and then depressed. Cardiovascular toxicity may be manifested by hypotension, weakness, shock, coma and death. Renal damage has been reported, as has acute hemolytic anemia and hypoprothrombinemia. Thrombocytopenic purpura (Refs. 12 and 13) has been reported in young people taking quinine for nocturnal leg cramps. Some cases of agranulocytosis have been reported following quinine ingestion. Idiosyncrasy to quinine is a frequent subject of medical reports.

(3) *Evaluation.* The Panel concludes that because the toxic effects described above may occur following repeated administration that the risks from use outweigh any benefit and therefore classifies quinine not safe for use as an OTC analgesic.

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CATEGORY II LABELING

The Panel has examined the submitted labeling claims for analgesics alone and for combination products with nonanalgesic ingredients and has placed certain claims into Category II. These Category II claims have been further divided by the Panel into those labeling claims that are unsupported by scientific data or by sound theoretical reasoning, claims containing modifying adjectives associating pain with illnesses, and unacceptable claims related to product performance as follows:

a. *Certain labeling claims that are unsupported by scientific data and in some instances by sound theoretical reasoning.* (1) *Claims not clearly defined nor clinically recognized.* These claims are not clearly defined nor clinically recognized and would confuse the consumer because the use of these words have different significance to different people and no meaning for others. Examples of such

claims are "jumpy nerves", "fretfulness", "under the weather", etc.

(2) *Claims requiring diagnosis and care of a physician.* These claims are not amenable to self-diagnosis and self-treatment and require medical diagnosis and supervision for safe use. Examples of such claims are "bursitis", "arthritis", "rheumatism", "gout", "swollen tissues", "functional mentrual pain", etc. In addition, there are claims for conditions which are appropriately treated by mild analgesics but presuppose that the patient is under the care of a physician or dentist. Examples of such claims are: "pain following dental work", "inoculation" or "vaccination". "Pain of teething" is also included here because the use of OTC drugs in children under 2 years of age requires the advice and supervision of a physician.

b. *Modifying adjectives associating pain with illnesses.* In its discussion of the indications and directions for use information on the labeling of OTC drug products, the Panel concluded that the indications for use should be simply and clearly stated, should include the statement that the preparation is for the temporary relief of symptoms applicable to the ingredient(s) in the product, and the implication that these drugs are to be used for the treatment of diseases should be discouraged. (See part II. paragraph C. above—Labeling of Analgesic, Antipyretic and Antirheumatic Drug Products.) Although analgesic ingredients may effectively ameliorate the pain due to various physical conditions, disease entities or specific physical sites, the listing of a plethora of conditions and sites in order to be factual and all inclusive would not only result in a lengthy list that would tend to be confusing but would also mislead the consumer by the implied assumption that the product treats the physical conditions and/or disease rather than just temporarily relieves the pain associated with the physical condition and/or disease.

In addition, the Panel feels that the use of only a partial list of some claims such as "low back pains, pains due to overexertion" in the labeling of one manufacturer's product and the omission of these claims from the labeling of the same drug by another manufacturer would mislead the user into believing the preparations are different. The misdirection would be even greater if the products were of different ingredients as for example one manufacturer's aspirin tablets versus another manufacturer's acetaminophen tablets.

c. *Unacceptable claims submitted for specific analgesics.* Examples of unacceptable claims that have been submitted for specific analgesics that are unsupported by scientific data and/or sound theoretical reasoning, and that contain modifying adjectives associating pain with various physical conditions, disease entities or specific physical sites are listed below:

(1) *Acetaminophen:* "nervous tension headache", "cold symptoms", "simple exertion", "simple pain of teething", "simple pain of immunization", "simple pain of tonsillectomy", "toothache", "fretfulness", "pain of neuralgia", "pain of neuritis", "pain of flu", "pain following dental procedures", "sinusitis", "overexertion", "similar discomforts", "bursitis", "sprains".

(2) *Aspirin:* "comforting relief of aches", "pains caused by: colds and flu, inoculations, minor ailments, tonsillectomy", "pains caused by teething", "under the weather", "pains of neuralgia", "pains of neuritis", "gargle for sore throat", "sinusitis", "pains of mild migraine", "tooth extraction", "pains of minor injuries", "pains of dysmenorrhea", "discomfort of ordinary colds", "pains of sciatica", "swollen tissues", "jumpy nerves", "minor sore throat irritation", "sleeplessness caused by minor painful distress", "normal menstrual distress", "pre-menstrual tension", "functional menstrual pains and cramps", "the blues", "nervous tension headache", "feeling of depression", "minor pain of arthritis", "minor pain of rheumatism", "sore, stiff aching muscles", "muscular fatigue", "muscle tension", "low back pain", "bursitis", "lumbago", "low body ache due to fatigue", "body aches".

(3) *Calcium carbaspirin:* "pains due to sinusitis", "minor aches and pains of arthritis", "minor aches and pains of rheumatism".

(4) *Choline salicylate:* "menstruation", "menstrual cramps", "neuralgia", "pains of arthritis", "pains of rheumatism".

(5) *Magnesium salicylate:* "pain of menstrual period", "pains of sciatica", "dental pains", "overexertion", "fatigue", "minor aches and pains of rheumatism", "minor aches and pains of arthritis", "minor muscle aches", "aches and pains due to fatigue".

(6) *Sodium salicylate:* "minor muscle pains and aches", "arthritis", "rheumatism".

(7) *Salsalate (salicylsalicylic acid):* "minor pains, swelling, stiffness of arthritis", "minor pains, swelling, stiffness of fibrositis", "minor pains, swelling, stiffness of osteoarthritis", "aspirin—for relief of arthritis".

(d) *Unacceptable claims related to product performance.* Terms such as "fast pain relief", "special pain relieving formula", "so strong and so gentle", "so gentle can be taken on an empty stomach", "acts 5 times faster than aspirin", "reaches peak action 12 times faster than aspirin", "long-lasting pain reliever", "enhanced relief of pain", etc., are in the opinion of the Panel confusing and misleading to the consumer unless they can be substantiated and clearly supported by scientific data.

Terms were submitted for buffered and highly buffered aspirin products that allude to the beneficial performance of these products as a result of the antacids or buffering agents they contain. The Panel has examined these terms which in essence assert that these products are more rapidly absorbed into the blood and that they consequently prevent the adverse reactions to the stomach that may be caused by plain (unbuffered) aspirin products.

The Panel concludes that until adequate data are available, labeling terms pertaining to product performance for buffered and highly buffered aspirin should be restricted to the following: "Faster to the bloodstream than plain aspirin" and "Provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label". The Panel has discussed this labeling elsewhere in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.) The Panel further concludes that any other statement(s) are classified as Category II.

3. CATEGORY III CONDITIONS FOR WHICH THE AVAILABLE DATA ARE INSUFFICIENT TO PERMIT FINAL CLASSIFICATION AT THIS TIME.

CATEGORY III ACTIVE INGREDIENTS

The Panel has concluded that the available data are insufficient to permit final classification of the following claimed analgesic active ingredients listed below. The Panel believes it reasonable to provide 3 years for the development and review of such data. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 3 years, however, the ingredients listed in this Category should no longer be marketed in OTC products:

Aluminum aspirin	Salsalate (salicylsalicylic acid)
Antipyrine	
Salicylamide	

a. *Aluminum aspirin.* The Panel concludes that aluminum aspirin is safe but that there are insufficient data to determine effectiveness as an OTC analgesic in the recommended dosage of 365 to 730 mg every 4 hours while symptoms persist not to exceed 4,380 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* Aluminum aspirin (aluminum acetylsalicylate) is chemically very similar to aspirin. The aluminum salt has been used because of greater palatability with less astringence to the taste. Its greater stability gives it no acetic odor. It has been reported that because of its greater stability, it is compatible with more drugs than is aspirin (Ref. 1). However the presence of the aluminum makes the salt practically insoluble in water and probably accounts for the greatly decreased dissolution, and subsequent slower absorption when compared to aspirin, possibly rendering this ingredient ineffective. Several studies relating to absorption, point out that aluminum aspirin is poorly absorbed from the gastrointestinal tract (Refs. 1, 2, and 3). Yet, it is claimed that although this drug is absorbed somehow more slowly than aspirin it apparently produces a satisfactory degree of analgesia similar to that produced by aspirin (Ref. 4).

Levy and Sahli (Ref. 2) compared the absorption of aluminum aspirin and aspirin in man. They concluded that "acetylsalicylic acid (aspirin) absorp-

tion from orally administered aluminum acetylsalicylate (aluminum aspirin) was found to be less rapid than from aspirin, probably due to the very slow dissolution of the aluminum salt in gastrointestinal fluids." This may be due to its water insolubility. They suggested that this drug be carefully evaluated with respect to absorption rate and biological availability.

Nogami and Hanano (Ref. 3) compared the release rate in vivo of several antipyretic and analgesic drugs in humans. They compared six sugar coated analgesic tablets. The ingredients were: sulpyrine, aminopyrine, phenacetin, bucetin, N-acetyl-p-aminophenol, salicylamide and aluminum aspirin. They concluded that aluminum aspirin release rate was slower than that of any of the others and this difference was statistically significant.

However, one submission cites two bioavailability studies which are pertinent; the first, an oral study in rabbits and the second, a study of absorption by man of aluminum aspirin from suppositories (Ref. 1). The data are presented in raw form and no conclusions are drawn. Nevertheless, both studies found that the levels of salicylate in plasma remained constant between ½ and 8 hours after either route of administration of aluminum aspirin. This gives rise to the speculation that although aluminum aspirin is absorbed more slowly into the bloodstream than aspirin, it may maintain its analgesic effect longer. However, since the Panel has not been able to correlate blood levels with analgesia, the longer duration of action remains to be proven by controlled clinical trials.

As to this ingredient's analgesic potency, Watrous (Ref. 5) in an unpublished double-blind study, compared aspirin and aluminum aspirin preparations in 49 patients (employees) with pain of various causes. He concluded that there was no significant difference between the two preparations in terms of pain relief. No conclusion can be drawn by the Panel from this study since there was no placebo control nor did the author demonstrate a dose-effect curve with one of the medications. Besides, no statistical analysis of the data was performed.

In a study in experimentally induced pain it was reported that in 10 volunteers who had pain induced in their tooth pulp "there was no statistically significant difference in the analgesic response produced by aspirin compared with that of aluminum aspirin" (Ref. 6). The individuals recived 5 gr of each preparation. This information is contained in a letter and no description of the statistical analysis of the data is given. No data are provided in tabulated form. The conclusions seem to be based on "impression of efficacy." In addition, studies utilizing experimentally induced pain are only supportive and not definitive in showing analgesic effectiveness because they do not measure pain under normal conditions where pain is caused by a variety of causes.

The Panel finds that aluminum aspirin may be an effective analgesic, but because of its poor absorption, its efficacy compared to aspirin cannot be stated at this time.

(2) *Safety.* Data reviewed by the Panel indicate that aluminum aspirin is as safe as aspirin in equivalent doses. Although the evidence is not complete, it seems to indicate that the severity and incidence of adverse reactions, either prior to or after absorption, would be comparable to that of aspirin as discussed previously in this document. (See part III. paragraph B.1.a.(2) above—Safety.) Consequently, all cautions required for aspirin should be required for aluminum aspirin.

(3) *Proposed dosage.* Adult oral dosage is 365 to 730 mg every 4 hours while symptoms persist not to exceed 4,380 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 365 mg every 4 hours while symptoms persist not to exceed 1,825 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 305 mg every 4 hours while symptoms persist not to exceed 1,525 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 215 mg every 4 hours while symptoms persist not to exceed 1,075 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 180 mg every 4 hours while symptoms persist not to exceed 900 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 120 mg every 4 hours while symptoms persist not to exceed 600 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgestic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (*a*) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

(*b*) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(*c*) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(ii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of aluminum aspirin per tablet, teaspoon or other dosage units as well as the quantity by which a particular product containing aluminum aspirin differs per dosage unit from the established standard of 325 mg (5 gr) aspirin. (See part II. paragraph E. above—Standard Dosage Unit ad Analgesic Equivalence Value.)

The Panel recommends that products containing aluminum aspirin be clearly labeled on the principal display panel: "Equivalent to X mg (X gr) per dosage unit of the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 365 mg aluminum aspirin per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg (5 gr) per tablet of the established standard of 325 mg (5 gr) aspirin per tablet".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for analgesic drugs. Bioavailability studies of aluminum aspirin in man must show comparable blood levels of salicylates to those following administration of a standard aspirin as detailed below and/or clinical evaluation of efficacy. (See Part III. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) Wheeler, W. C., "Comparative Aluminum Aspirin Blood Level Test," draft of unpublished paper is included in OTC Volume 030037.

(2) Levy, G. and B. A. Sahli, "Comparison of the Gastrointestinal Absorption of Aluminum Acetylsalicylate and Acetylsalicylic Acid in Man," *Journal of Pharmaceutical Sciences*, 51:58–62, 1962.

(3) Nogami, H. and M. Hanano, "Studies on Absorption and Excretion of Drugs. VIII. The Release Rate In Vivo of Antipyretic and Analgesic Drugs from Commercial Sugar Coated Tablets," *Chemical and Pharmaceutical Bulletin*, 15:1002–1009, 1967.

(4) OTC Volume 030037.

(5) Watrous, R. M., "Clinical Trial of 2½ Grain Aluminum Aspirin Dulcet Tablets," draft of unpublished paper is included in OTC Volume 030037.

(6) Harris, S., draft of unpublished paper is included in OTC Volume 030037.

b. *Antipyrine.* The Panel concludes that there are insufficient data to determine the safety and effectiveness of antipyrine as an OTC analgesic when, as recommended, the dosage is limited to a single 975 mg dose in 24 hours while symptoms persist for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(1) *Effectiveness.* Antipyrine was synthetized in 1883 by Knorr (Ref. 1) after a 40-year search to find a safer and more effective antipyretic than quinine. When its use as an antipyretic was declining, antipyrine continued to be used for its analgesic effects which were first discovered in 1886. In the last 50 years, however, for reasons not entirely clear, antipyrine has declined in use as an analgesic. This is thought to be due to the increased popularity of the salicylates and not because of a demonstrated lesser effectiveness or safety of antipyrine (Ref. 1). In Europe, where it is much more commonly used by large segments of the population, it is found mainly in combination with other products. Therefore, there are insufficient data on the safety and effectiveness of

antipyrine as a single ingredient. The world consumption is estimated at 900 tons annually (Ref. 2).

Though antipyrine has been generally recognized since 1888 as an effective analgesic, no well-controlled studies of its analgesic effectiveness in the clinical situation have been reported. As reviewed by Greenberg (Ref. 1), numerous reports of experimental tests of the pain threshold in man, using mechanical, thermal, or electrical stimulation, describe only moderate or, in most cases, inconsistent and generally inconclusive effects of antipyrine in elevating the pain thresholds. Similar tests designed for use in animals yielded significantly positive results only when excessive doses of antipyrine were used. These questionable results are undoubtedly attributable to the inadequacy of such methods in measuring parameters related to the true clinical effectiveness of analgesic drugs.

The manufacturer of the only product submitted containing antipyrine cites in his labeling and in his submission a study by Brodie and Axelrod (Ref. 3) who state that "the transformation of antipyrine is slow, so that plasma levels after a single therapeutic dose decline only 1 to 12 percent per hour, resulting in plasma levels of 15 hours or more. This is considerably longer than with acetanilide, phenacetin or *N*-acetyl-*p*-aminophenol." Thus, from this study it is apparent that the metabolism of antipyrine is slow and that one would expect it to provide longer antipyretic and analgesic action.

The Panel finds that antipyrine may be an effective analgesic, but because of a lack of clinical studies, its effectiveness compared to aspirin cannot be established at this time.

The Panel believes that in view of these uncertainties, appropriate comparative clinical studies should be completed before antipyrine can be considered generally recognized as effective. (See part III, paragraph C. below—Data Required for Evaluation.)

(2) *Safety.* The Panel concludes that there are insufficient data to determine the safety of antipyrine when taken in the recommended dose and dosage schedule for the relief of occasional minor aches and pains, and headache. Because of safety considerations discussed below, the Panel has made no recommendations for the use of antipyrine in children under 12 years of age.

Antipyrine has been said to have fewer side effects than aspirin. It is said to not interfere with the blood clotting mechanism as does aspirin. There is no evidence that antipyrine is hepatotoxic as is acetaminophen in large doses. However, it should be pointed out that the side effect liability of this compound is not as well understood as that of aspirin because of its limited use in the U.S.

Unlike aminopyrine, antipyrine has not been established as a significant cause of agranulocytosis. According to Greenberg's extensively documented review (Ref. 1), only two cases of agranulocytosis had been reported to be due to antipyrine prior to 1950, and there was doubt that antipyrine was the specific etiologic agent even in these two cases. Since that time no further cases have come to light. Though antipyrine is closely related chemically to aminopyrine it is metabolized differently (Refs. 3 and 4), which undoubtedly accounts for the different propensities of the two drugs to produce agranulocytosis.

Of 394 cases of antipyrine poisoning, reported prior to 1950 and reviewed by Greenberg (Ref. 1), 77 percent were of an allergic nature and 18 percent nonallergic (5 percent undetermined). Of these 394 cases, 23 were reported as terminating in death, all of which were in the groups showing reactions of the nonallergic or undetermined nature. In none of the fatal cases could the contributory role of antipyrine be fully assessed because the patients were suffering from serious diseases, such as typhoid, typhus, pneumonia, puerperal fever and brain tumor, and therefore were taking or had taken other drugs, or had taken obvious overdoses of antipyrine. It is noteworthy that all of the "fatal cases" described (Ref. 1) were reported between 1885 and 1913. There is serious doubt of a definite causal relationship between these fatalities and antipyrine, except in one case of a murder by the use of 4 drachms (16 g) of the drug (Ref. 1). Subsequent to Greenberg's 1950 review (Ref. 1), no fatalities definitely attributable to antipyrine have been reported.

The Panel reviewed numerous case reports of adverse reactions in which antipyrine was suspected of playing a causative role. These case reports are summarized in the following table:

ANTIPYRINE CASE REPORTS

Case Report I (Ref. 5):
Author: Brocq (1894).
Medication: Antipyrine.
Patient description: Three white females.
Signs and symptoms: Fixed pigmented erythema.[1]
Antipyrine test dose: [2]
Other drug test dose: [2]
Outcome: [2]

Case Report II (Ref. 6):
Author: Apolant (1898).
Medication: Antipyrine (ointment).
Patient description: [2]
Signs and symptoms: Erythema reappeared after local application of an antipyrine-containing ointment.
Antipyrine test dose: +, + [3]
Other drug test dose: [2]
Outcome: [2]

Case Report III (Ref. 7):
Authors: Ritchie & Spiller (1949).
Medication: Antipyrine-containing cold medicine (2 tablets).
Patient description: One white male.
Signs and symptoms: Large, dusky erythematous and scaly machles scattered over shoulders, arms and thighs.
Antipyrine test dose: +, + [3]
Other drug test dose: +, + [3]
Outcome: Hospitalization.

Case Report IV (Ref. 8):
Authors: McDulloch & Zeligman (1951).
Medication: Antipyrine-containing cold preparation.
Patient description: One black male.
Signs and symptoms: Numerous erythematous and hyperpigmented well-demarcated plaques, some of which contained central bullae. They were located in the face, neck, chest, back, buttocks, abdomen, upper and lower extremities, scrotum and glans penis.
Antipyrine test dose: +, + [3]
Other drug test dose: [2]
Outcome: Hospitalization for more than 7 days.

Case Report V (Ref. 9):
Authors: Goldman & Rockwell (1951).
Medication: Antipyrine-containing cold preparation.
Patient description: One black male.
Signs and symptoms: 7 days history of sore lips and penis, fever and chills, loss of appetite and headache. The lips and the interior portion of the penis were edematous and denuded with crusting and bleeding.
Antipyrine test dose: +, + [3]
Other drug test dose: —
Outcome: Hospitalization for more than 19 days.

Case Report VI (Ref. 10):
Authors: Kennedy et al. 1957.
Medication: Antipyrine-containing cold preparation.
Patient description: 21 black males and 7 black females.
Signs and symptoms: Pruritus, burning of the mouth and throat, sometimes choking sensation and sometimes pain referred to the genito-urinary system. The mucosa of the eyes, mouth and genitalia was involved and large, pigmented bullous lesions, of the type seen in erythema multiforme, appeared over the body, particularly on the neck, thighs and genitals. Patients were acutely ill and had fever over 102° F.
Antipyrine test dose: —
Other drug test dose: —
Outcome: Hospitalization of various duration; one death.

Case Report VII (Ref. 11):
Authors: Nelson and Berry (1967).
Medication: Antipyrine-containing cold preparation (plus large quantities of whiskey).
Patient description: Three black males.
Signs and symptoms: "Typical skin rash" (due to antipyrine), neurological symptoms, grand mal seizures, decerebrate posturing, tremors, nystagmus and deviation of the tongue.
Antipyrine test dose: —
Other drug test dose: —
Outcome: Hospitalization; one death.

Case Report VIII (Ref. 12):
Author: Verbou (1972).
Medication taken: Dichloralphenazone (an antipyrine derivative with hypnotic properties).
Patient description: One white female.
Signs and symptoms: Severe irritation of the upper thighs and erythematous circular patches.
Antipyrine test dose: +, + [3]
Other drug test dose: —
Outcome: [2]

It is interesting to note from the above description and tabulation that the most striking feature of antipyrine hypersensitivity is the "fixed pigmented erythema" originally described by Brocq (Ref. 5). In 1894, 11 years after antipyrine had been introduced, Brocq discovered (Ref. 5), to his "intense embarrass-

[1] The term "fixed" was used because once the reaction had occurred it tended to reappear in the same areas of the body where it had occurred previously.

[2] Not specified.

[3] The first sign (+ or —) indicates whether test doses were employed to see if signs and symptoms reappeared. The second sign (+ or —) indicates whether the reaction was positive or negative.

ment" because he missed the diagnosis at first, that antipyrine could cause a dermatological reaction. He described that once the reaction occurred it tended to reappear when the drug was taken again, in the same areas of the body in which it had previously occurred which in most cases had remained darker in color. He coined the term of "fixed pigmented erythema" which is still used.

In 1898, Apolant (Ref. 6) suggested that the fixed eruption caused by antipyrine was the result of "the arrival of body fluids containing the drug at the affected site." To prove his hypothesis he prepared an ointment containing 10 percent antipyrine in lanolin. After rubbing this ointment in previously affected areas, he observed that itching occurred at these sites within 10 minutes, and that within 24 hours an erythema, exactly like the original in size but somewhat less in degree, appeared and lasted for about 3 days. Previously unaffected sites did not react to the application of the ointment.

Two articles cited in the table of antipyrine case reports warrant further discussion.

Goldman and Rockwell (Ref. 9) have reported a case of a 47-year-old male Negro who was admitted to the hospital with a 7-day history of sore lips and penis, fever and chills, loss of appetite and headache. The patient had ingested 10 days before admission a marketed OTC cold remedy containing 3.9 g antipyrine (60 gr). His temperature on admission was 102° F and both his lips and anterior portion of the penis were edematous and denuded with crusting and bleeding.

Ulceration of the buccal mucosa and erythematous, pigmented lesions on the hands and body were noted. Ten days later the patient improved and was asymptomatic. To prove the hypersensitivity, 0.2 g (3 gr) antipyrine was administered to the patient. The patient responded with a fever for 4 days, severe abdominal pain and pruritus of the perianal region and in the pigmented lesions on the hands.

A week later the patient was given 100 mg cortisone at 2 p.m. and 4:00 p.m., and 0.2 g antipyrine was administered at 5 p.m. followed by an additional dose of 50 mg cortisone at 5:30 p.m. Only a minimal pruritus in the hands was reported by the patient. This is another case in which hypersensitivity to antipyrine was proved first with a challenge dose of antipyrine and then the reaction was prevented by the concurrent administration of cortisone.

Kennedy et al. (Ref. 10) have reported 28 cases, all Negroes, of dermatitis medicamentosa following the use of a marketed OTC cold preparation containing antipyrine. Kennedy et al. comment that at that time (1959) druggists in New Orleans and elsewhere in Louisiana were reporting an increasing amount of sales of the marketed OTC antipyrine-containing cold preparation. This increase in sales was reflected in the increasing number of reactions to the marketed OTC antipyrine-containing cold product observed at the New Orleans Charity Hospital. The authors then cite the following: "Over the last year, there has seldom been a time when at least one patient with dermatitis medicamentosa from this cause was not under treatment on the dermatological wards. The seriousness of the condition is shown not only by the fatal case in the series but by the fact that the average period of hospitalization was 14 days."

All the cases reported by Kennedy et al. were black and 21 out of 28 were males. Seventeen patients had taken the marketed OTC antipyrine-containing cold product in the past but only nine patients gave a history of previous reactions. The history and clinical picture were the same in all cases of these series. Kennedy et al. cite: "The typical onset included generalized pruritus, burning of the mouth and throat, sometimes choking sensations and sometimes pain referred to the genitourinary system. The mucosa of the eyes, mouth and genitalia was involved, and large, pigmented bullous lesions of the type seen in erythema multiforme, appeared over the body, particularly on the neck, trunk, thighs and genitals. All the patients were acutely ill. Fever was frequently 102° F or higher."

In this series, there was no correlation between the size of the dose and the severity of the reaction. In the single fatal case reported, the patient took half-a-glassful but another patient had taken one full bottle followed 5 days later by another bottle and survived, although he had a serious reaction. Patch tests were performed on five patients of this series either with antipyrine alone or with the liquid marketed OTC antipyrine-containing cold preparation. Three out of five patients responded positively to either antipyrine alone or the marketed OTC antipyrine-containing liquid cold preparation. One of the patients on whom a positive response was not elicited was receiving prednisone at the time the tests were carried out.

The severity of the symptoms in the patients of this series discouraged experimental administration of the marketed OTC antipyrine-containing cold product or antipyrine alone to the subjects. However, one patient who had been released after 22 days hospitalization for severe eruptions and had been warned not to use this medication or anything containing antipyrine again, provided unwittingly an experimental demonstration of this reaction. He took a compound containing 100 mg antipyrine as well as sodium salicylate and caffeine. After taking two doses of this drug the patient had an immediate burning sensation over the entire body and had blisters on the limbs, back, penis and mouth, the same areas that had been affected in the first episode that required hospitalization. The reaction was so severe that he required hospitalization again.

This series is the largest found in the literature concerning the toxicity of antipyrine and seems to show without any doubt that all the reported reactions are indeed due to antipyrine hypersensitivity.

Early toxicologic experiments with various species of animals, as reviewed by Greenberg (Ref. 1), revealed stimulation of the central nervous system, followed by depression, with oral doses of the order of 500 mg/kg or larger. The oral lethal dose of antipyrine in several species was reported to be 1,000 mg/kg or more. If this could be extrapolated to man, it would provide a wide margin of safety with respect to the acute toxicity of antipyrine. Because of species differences, this is rarely possible.

However, this does not preclude the occasional hypersensitivity reaction summarized in the table of antipyrine case reports above, which is of concern to the Panel.

Thus the main concern of the Panel is that there is an association between the use of antipyrine and the occurrence of fixed pigmented erythemia of the skin (so-called Brocq Skin Eruption). Skin eruptions have also been reported following the use of such drugs as quinine, phenacetin, aspirin, acetaminophen, phenophthalein, barbiturates, antihistamines, etc. (Ref. 13). However, the reactions with these drugs are not reported to be as severe as the reactions with antipyrine (Refs. 14 through 18).

In summary, the Panel finds that such reactions are relatively rare following the use of antipyrine. The exact incidence cannot be determined at this time. In spite of the fact that the annual world consumption of antipyrine is estimated at 900 tons the number of cases of adverse reactions reported is rare.

Antipyrine has been said to have fewer side effects than aspirin. It is said not to interfere with the blood clotting mechanism as does aspirin, and there is no evidence that antipyrine causes hepatotoxicity as does acetaminophen when used in large doses (Refs. 1 and 3). The Panel believes that this compound should be studied further to determine its risk to benefit ratio because it represents an antipyretic-analgesic with a long duration of action chemically distinct from acetaminophen or the salicylates and could be an alternative in patients who do not tolerate other analgesic drugs.

(3) *Proposed dosage.* Adult oral dosage is limited to a single 975 mg dose in 24 hours while symptoms persist for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (*a*) "Do not exceed recommended dosage".

(*b*) "If skin rash appears discontinue use and consult a physician."

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for analgesic drugs. (See part III, paragraph C. below—Data Required for Evaluation.) Data to demonstrate safety should include epidemiological studies which take into consideration the con-

cerns of the Panel. Interested drug manufacturers should consult with the Food and Drug Administration as to the design of such studies. The studies should consider pharmacogenetic factors and include several racial groups.

(6) *Minority statement of the Panel.* The minority of the Panel concludes that antipyrine is unsafe and should be in Category II.

The extensive review of adverse reactions described in this document above includes analysis of the literature. Thirty-six patients with fixed pigment erythema have been reported. The severe skin disease reported in 28 black patients in New Orleans and the predominance of blacks in the other case reports suggested that future studies of toxicity must be done in this target population. As these studies may lead to serious illness in the study group and since other analgesics are available at present, the risk to benefit ratio of such a study of antipyrine toxicity is extremely high. This type of prospective toxicity study should be required if the drug is to move from Category III to Category I. The minority of the Panel feels that such a study has a high risk to benefit ratio and therefore would place antipyrine in Category II.

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c. *Salicylamide.* The Panel concludes that there are insufficient data to determine that salicylamide is either safe or effective when used in combination as an OTC analgesic in the currently marketed dosage of 97.2 to 400 mg. The Panel finds that salicylamide when used alone at a higher dosage (1,000 mg every 4 hours while symptoms persist not to exceed 6,000 mg in 24 hours for not more than 10 days) may be effective but has not been demonstrated to be safe for OTC use. Therefore, the Panel recommends that salicylamide not be made available for OTC use at the higher dosage range until suitable studies have been completed to show both safety and effectiveness. In addition, the Panel has also considered the use of salicylamide in combination as an OTC analgesic adjuvant elsewhere in this document. (See part VI. paragraph B.5. below—Salicylamide.)

(1) *Effectiveness.* Salicylamide is currently marketed as an OTC analgesic-antipyretic agent. It is used primarily in a wide variety of OTC analgesic combination products and in cold preparations as an analgesic agent. The amount per dosage unit ranges from 97.2 to 400 mg salicylamide in such combinations. It has also been used in sedative products for its slight hypnotic properties.

Until a few years ago, it was marketed as a single ingredient in a suspension dosage form for use as an OTC antipyretic for pediatric use in the treatment of mild fever at a dose of 100 mg every 3 to 4 hours for each year of age. Since then, the product has been reformulated. The salicylamide was removed from the product and replaced with acetaminophen.

Salicylamide is not a salicylate but the amide congener of salicylic acid. However, it is often included in the salicylate class. It does not have the chemical properties of the salicylates and is not hydrolyzed to salicylic acid in the body as are aspirin and the other salicylates (Ref. 1). It also does not form salts of salicylic acid. Salicylamide was first tested for analgesic activity in 1947 when Hart compared it with aspirin in rats (Ref. 2).

Because of the unique characteristics of the drug, the Panel has divided the discussion into the following sections:

(i) *Biolavailability (pharmacokinetics).* Recent pharmacokinetic studies indicate that many of the discrepancies found in the earlier published clinical evaluations of salicylamide preparations, which are discussed below, can be explained in part by the unusual absorption and metabolism characteristics of this drug. (See part III. paragraph B.3.c. (1) (ii) (b) below—Clinical studies.)

Contrary to many other drugs, it is important to note that salicylamide, which is the parent (free, unmetabolized) active drug, can be almost completely metabolized to inactive metabolites during its transit from the gastrointestinal lumen through the gastrointestinal mucosa and hepatic circulation before it is even absorbed into systemic circulation (blood) to become available for therapeutic action. This initial absorption (transit) of the drug before it becomes available in the systemic circulation is called the absorptive phase. The rapid rate of elimination noted by earlier authors is due to the metabolism of the drug during the absorptive phase by intestinal and/or liver drug conjugating enzyme systems. In the absorptive phase, salicylamide is metabolized principally to glucuronide and sulfate conjugates by intestinal and primarily hepatic metabolizing systems.

The rate and extent of salicylamide metabolism by these systems during the absorptive phase is saturable, i.e., the metabolizing capacity is limited by available metabolizing sites and enzymes and therefore greatly dependent on both the dose and dosage form, e.g., solution, suspension or tablet, administered. Hence, the complete metabolism of an administered oral dose of salicylamide can occur very rapidly during this absorptive phase with use of a commercial dosage form of the drug, i.e., tablets. Since the drug is poorly water-soluble (approximately 0.2 percent), the small amount available for the absorptive phase at any one time from tablet dissolution is metabolized as quickly as it is absorbed from the gastrointestinal lumen and the first pass through the liver, leaving little circulating active (unmetabolized) salicylamide available for therapeutic action.

The metabolism, at low doses, is so extensive that virtually no active (unmetabolized) drug is available for absorption into the systemic circulation for distribution to the site(s) of therapeutic action. The rapid metabolism of salicylamide, i.e., its metabolism before the drug even reaches the circulatory system, makes the availability of active (unmetabolized) salicylamide dependent on the metabolic rate. At low doses and with the usual dosage form (tablets) from which the drug has been shown to be slowly released, the concentrations of intestinal and hepatic enzymes can be sufficient to completely metabolize salicylamide, leaving little or no free drug available to be absorbed into the systemic circulation (Ref. 3). The metabolism of salicylamide is therefore dose-dependent and dosage-form-dependent during the absorptive phase (initial transit). However, as indicated, the capacity for the intestinal and hepatic enzymes to metabolize salicylamide is limited (saturable) (Ref. 4). The rate and extent of salicylamide metabolism

by these enzymes is dose-dependent because a limit to metabolism by these enzymes (saturation of the enzyme systems) can be reached. To overcome this limit, a high dose, termed the "breakthrough dose" is needed. A "breakthrough" dose is a dose that contains, in addition to a sufficient amount of salicylamide to overwhelm the metabolizing limits of the intestinal and hepatic enzymes, a quantity of salicylamide that will break through this metabolizing barrier and allow active (unmetabolized) drug to reach the systemic circulation intact. Studies have shown that very small increases in the dose above the "breakthrough" does result in profound increases in systemic availability of active (unmetabolized) salicylamide. Studies indicate that both intestinal and hepatic sites of salicylamide metabolism are saturated (limited) at doses higher than the breakthrough doses. The slow drug-releasing dosage form (tablets) in which salicylamide is available is also a factor which needs to be considered in determining a "breakthrough" dose.

It is possible that a dosage form which would release the active ingredient slowly either purposefully as in a timed-release form or accidentally through improper formulation as in a tablet, would fail to saturate the metabolic enzymes even though each dosage unit contained a breakthrough dose. The failure to release adequate active ingredient at a rate sufficient to overwhelm these enzymes would result in no free drug emerging from the liver to the systemic circulation and therefore in no therapeutic efficacy. For this reason, the formulation of each drug product must ensure a proper rate of release.

Several earlier workers noted that the pharmacologically active (unmetabolized) salicylamide is rapidly eliminated from the body by hepatic metabolism (Refs. 5 and 6) to the corresponding glucuronide and sulfate conjugates (Refs. 7 through 12). These water soluble conjugates of salicylamide are considered to be pharmacologically inactive and are rapidly eliminated by the kidney (Refs. 11 and 12).

Very little active (unmetabolized) salicylamide can be detected in the plasma or urine after usual oral single doses of 300 to 600 mg. Most earlier blood level studies, therefore, measured only total drug (active drug plus metabolites). It is now clear that for a drug with nonlinear metabolism, i.e., the rate of metabolism is not linearly related to the dose, like salicylamide, analytical methods measuring the concentrations of total drug alone provide no information on the bioavailability (systemic availability) of the parent drug, i.e., the amount of unmetabolized drug reaching the systemic (general) circulation after oral administration.

Levy and Matsuzawa (Ref. 13) demonstrated that the metabolism of salicylamide was saturable since changes in the ratio of the amounts of sulfate and glucuronide conjugates appearing in the urine occurred with different doses and different dosage forms.

Evidence that salicylamide is extensively metabolized during the absorptive phase in man was demonstrated in a study which compared both active drug (unmetabolized salicylamide) and total drug (active drug plus metabolites) in plasma following oral and intravenous administration of a 300 mg dose. Free (active) drug was greatly reduced but not the metabolities following oral administration. Over 90 percent of the active drug was metabolized during the absorptive phase. Additional studies comparing different dosage forms at the same dose show that metabolizing enzyme systems are saturable during absorption and the bioavailability is dependent on the dose and dosage form given (Refs. 13 and 14).

In studies where active (unmetabolized) salicylamide in plasma is measured and can be distinguished from the conjugated, inactive (metabolized) drug by sensitive assay procedures, it seems that the levels are indirectly influenced by the dose given (Ref. 14) as illustrated in the following table:

Dose-related effects—peak plasma concentration (micrograms per millimeter) of active (unmetabolized) salicylamide following single oral dose given in solution

	Dose		
	300 mg	1,000 mg	2,000 mg
Subject A	0.2	1.0	9.8
Subject B	[1]0	.9	13.8
Subject C	[1]0	1.0	[2]19.0

[1] Plasma levels could not be detected.
[2] Patient was sedated.

These data show that the doses usually used in combinations produce negligible plasma levels. As the dose is increased from 1,000 to 2,000 mg, inordinate increases in the peak plasma concentration (10 to 20 fold) are observed. Based on other information (Refs. 13 and 15) these workers concluded that with smaller doses (300 to 600 mg) the drug is metabolized almost completely during the absorptive phase. But at higher doses, termed the "breakthrough dose", the metabolism system becomes saturated resulting in a decrease in the fraction of the dose metabolized and an increase in active (unmetabolized) salicylamide reaching the systemic circulation (Ref. 14). It is important to note that these dose dependent effects on systemic availability of active (unmetabolized) drug would not be evident if only total drug was measured in plasma or urine (Refs. 13 through 15).

Dosage formulation also can influence the systemic availability and plasma blood levels of active drug (free salicylamide). In a study of five subjects (Ref. 14), each given 1,200 mg salicylamide in a noncommercial aqueous solution, commercial suspension and tablet, the maximum active (unmetabolized) salicylamide plasma concentration reached by the suspension was greatly reduced (2 μg/ml), the tablet reached a higher level (3 μg/ml) and greater area under the plasma time curve but took a longer time for the peak concentration to be reached, whereas the solution provided the highest plasma level (13.8 μg/ml), a significantly greater area under the plasma time curve. The following table summarizes the peak plasma concentrations of free drug reached with each dosage form:

Dosage form related effects—comparison of peak plasma concentrations following administration of 1,200 mg of different dosage forms

Dosage form	Microgram per milliliter
Solution, aqueous	[1]13.8
Tablet (commercial)	[1]3.0
Suspension (commercial)	[1]2.0

[1] Peak plasma concentration active (unmetabolized) drug (mean of 5 subjects).

Comparison of total drug in plasma and urine for each dosage form clearly shows that differences between dosage forms are not due to decreased absorption but are due to increased metabolism during absorption of the more slowly released drug from the solid dosage forms.

The salicylamide suspension was quite viscous and the slow release resulted in drastically reduced plasma levels. It is significant that this formulation was used in early clinical trials and illustrates the difficulties in assessing clinical effects of this drug unless its pharmacokinetic characteristics are well understood and sufficient data collected to assess systemic availability (Ref. 15).

Therefore, the Panel concludes that it is obvious that the pharmacokinetic characteristics of saturable metabolism during the absorptive phase account for earlier difficulties in establishing a safe and efficacious dosage and standard for bioavailability studies. Based upon current understanding, the Panel finds that this remains to be done.

(ii) *Effectiveness as a single ingredient.* (*a*) *Analgesia in animals.* Analgesic potency evaluations of salicylamide in animal studies have indicated that a wide range can be demonstrated when compared to aspirin. Hart reported salicylamide to be six times as potent as aspirin in rats subjected to heat stimulus (Ref. 2). McKenzie found salicylamide to be three to four times more potent than acetanilid in mice (Ref. 16), and salicylamide has been reported to be at least equal or better in several other animal studies (Ref. 12).

(*b*) *Clinical studies.* Salicylamide has been shown to have greater analgesic effects in animals than aspirin. However, studies in humans with pathologic pain have shown that salicylamide does not have any superiority over aspirin in doses below 600 mg and is indistinguishable from placebo (Ref. 17). Beaver (Ref. 17) has suggested a number of possible explanations for this lack of correlation between the effect of salicylamide on experimental pain in animals and the clinical response to this agent in humans. A possible explanation could be the lack of anti-inflammatory activity of salicylamide (Refs. 17 and 18) or alternatively that the lack of effective analgesia in

man by salicylamide may be due to its rapid absorption, early peak blood levels, extensive metabolism and rapid excretion (Refs. 9, 10, and 17). In five healthy subjects administered 2,000 mg salicylamide, peak serum levels were seen 1 hour after administration and 50 percent of the total dose was excreted in the urine by the end of 4 hours postdosing (Ref. 9).

Clinical studies on the efficacy of salicylamide in man have produced conflicting results. Many of these discrepancies can be explained on the basis of current knowledge of dose dependent absorption and deficiencies in experimental design including the following: Use of rheumatoid and musculoskeletal pain to determine analgesic effect even though salicylamide has no anti-inflammatory activity (Refs. 8 and 14); use of doses below the "breakthrough dose" (300 to 600 mg)—because of the extensive metabolism during the absorptive phase, doses of 600 mg or less would not be expected to have any significant clinical effect; use of dosage forms which have slow drug release characteristics; decreased systemic availability; failure to use more than one dosage level; and failure to show sensitivity of method.

Clinical studies in humans have not demonstrated any superiority of salicylamide over aspirin. Several studies used low doses and could not distinguish the drug from placebo. Studies employing higher doses have established analgesic activity. Litter et al. (Ref. 19) reported an analgesic effect of salicylamide in 90 of 118 subjects (75 percent) with a variety of arthritic diseases. The total daily doses found to cause analgesia in these rheumatic patients varied from 3,000 to 24,000 mg. An average of 2,000 mg every 4 to 6 hours was needed to show a moderate to marked analgesic effect in 75 percent of the patients.

Wallenstein and Houde (Ref. 20), and Wallenstein, Houde and Beaver (Ref. 21) compared aspirin, salicylamide and acetaminophen, using 600 mg doses, with placebo, in 27 patients with chronic pain due to advanced cancer. Each patient received at least one dose of each drug and replicated data was obtained on 17 patients. Hourly reports of changes in pain intensity for a 6-hour period after the administration of each drug were tabulated. They found aspirin and acetaminophen significantly different from placebo but not from each other. However, over the 6-hour observation period, salicylamide did not show any superiority over placebo, but was "somewhat" more effective than placebo, 1 hour after administration only. This difference in the activity of salicylamide was explained by the rapid metabolism of salicylamide to an inactive compound resulting in a very brief duration of action.

Batterman and Grossman evaluated 73 subjects in a double-blind study comparing 600 mg salicylamide with 600 mg aspirin taken every 4 hours for 1 to 3 weeks. Most of the subjects had pain due to osteoarthritis and/or musculoligamentary spasm or strain. They concluded that salicylamide was not an effective analgesic or antirheumatic medication (Ref. 22). This study has several experimental deficiencies and has been criticized by several authors (Refs. 23 and 24). In addition to the single borderline dose used, the poor choice of patient population (pain due to osteoarthritis), and the poor choice of a standard which also has anti-inflammatory effects, this study also failed to statistically distinguish aspirin from placebo.

In view of the contradictory conclusions reported in the literature regarding the degree of clinical response to salicylamide as an analgesic in man, some of which are a result of poor experimental design, the Panel recommends further well-controlled clinical studies be done to demonstrate adequate and consistent analgesic activity. This compound has unique properties that make it mandatory to clearly delineate the dosage form relation and the dose effects on systemic availability during such studies using analytical methods and pharmacokinetic studies which measure active (unmetabolized) salicylamide in plasma.

(2) *Safety.* The Panel concludes that salicylamide is ineffective in currently recommended doses of 300 to 600 mg and has not been adequately tested for safety and should be placed in Category III. In addition at doses that may be effective, i.e., 1,000 mg every 4 hours not to exceed 6,000 mg in 24 hours for not more than 10 days, safety has not been established for OTC use. The central nervous system effects of drowsiness and dizziness and gastrointestinal upset are common adverse effects reported when "higher doses are used". Other toxic manifestations in dosages that can produce analgesia, such as hepatic effects in children and damage to blood formation following chronic use are sufficiently serious to warrant additional study.

Goodman and Gilman described gastric irritation in 10 percent of cases, drowsiness or dizziness in 10 and 20 percent of cases, respectively (Ref. 25), with dosages of 2.000 mg, 3 times daily required to reach therapeutic plasma levels. Batterman and Grossman noticed side effects in 31 percent of patients taking 600 mg of salicylamide every four hours from one to three weeks which were evenly distributed between gastrointestinal and central nervous system manifestations (Ref. 22).

Three cases of purpura attributed to salicylamide have been reported. Stettbacher in 1950 reported a 48-year-old woman who had taken a total of 144 g in 3 months and developed epistaxis, severe bruising and bleeding. Examination revealed thrombocytopenia, depression of myeloid elements and maturation arrest of megakaryocytes in the bone marrow (Ref. 26).

Greig reported two cases of "black and blue" areas caused by effects on the blood clotting mechanism (thrombocytopenic purpura) in 1955 (Ref. 27). One woman took a total of 300 g orally in 50 days and developed the usual signs and symptoms consisting of bruising and bleeding. The second case was also a woman who had taken a prescribed dose and developed these signs and symptoms. Bone marrow examination showed hypocellularity with hypoplasia of all elements in both women.

Very large doses of salicylamide can produce toxic effects similar to those of the salicylates including ringing of the ears, ecchymoses, hemorrhagic lesions, leucopenia and thrombocytopenia. Barr and Penna (Ref. 14) also describe hypotensive effects in large doses but do not delineate the exact dose.

In an unpublished study submitted to the Panel dealing with the use of salicylamide (Ref. 28), W. S. Anderson reported his observations of 57 infants and children in Childrens Hospital in Washington, D.C. All of these infants and children were hospital patients and many were admitted because of fever and an accompanying respiratory illness. Thirty patients were given salicylamide every 4 hours for 4 days. Patients up to 5 years of age received 120 mg/dose and those over 5 years of age received 600 mg/dose. Since the ages of the patients are not specified, the Panel assumes that they are all below 12 years of age. They were compared with 27 patients who received aspirin at half of the salicylamide dosage. Salicylamide had "practically" no antipyretic or analgesic action. Anderson noted a mild sedative reaction. In addition, however, five patients with no evidence of renal disease had a significant blood urea nitrogen rise after 4 days. Another five patients with no demonstrable liver disease had a cephalin flocculation that increased from 0 to 3+ in two patients and from 0 to 4+ in three patients after 4 days indicating an adverse effect on liver function. Anderson found these effects only in the salicylamide treated groups. He concluded that there was no correlation between the rise in the blood urea nitrogen and the change in the cephalin flocculation.

It would seem from this study that the toxic manifestations occurred in a significant number of children and warrants further studies of this drug in children. At this time only this unpublished report of hepatic toxicity has been reported and in this case a causal relationship was not established. There is no reason to believe that 12-year-olds would react to the drug differently than an adult. Similar doses to infants and adults by the same investigators did not produce toxicity.

Signs of hepatic dysfunction have not been reported in other studies reviewed by the Panel. However, there is no indication that liver function tests were actually done in these studies. Because of the lack of current information on possible hepatic effects, the Panel recommends that suitable hepatic function tests be required in the Category III testing protocols for salicylamide.

On the basis of available reports, the Panel recommends further studies as to the toxic effect of therapeutic doses on liver and kidney function. It would also be advisable to clarify what, if any, effect formulation has on toxic manifestations.

Although salicylamide in large doses can produce gastric distress, it has no direct irritant effect on gastrointestinal mucosa. Studies on direct mucosal irritation involving a variety of analgesic agents have shown that salicylamide, unlike the salicylates, has no erosive effect on the gastric mucosa (Ref. 7). Salicylamide does not cause occult bleeding (Ref. 12). Salicylamide has not been associated with clinically significant massive gastrointestinal bleeding or peptic ulcer (Ref. 12). The Panel concludes that in contrast to salicylates, the gastric distress observed following large oral doses of salicylamide is not symptomatic of serious gastrointestinal dysfunction and represents no serious risk.

Allergic reactions to salicylamide are not common. It has been claimed that salicylamide does not show cross-sensitivity with aspirin although the definitive studies establishing this claim are said to be lacking (Ref. 12). Salicylamide has no effect on bleeding time (Ref. 29), prothrombin time and is not highly protein bound.

CONCLUSIONS AND RECOMMENDATIONS

The Panel concludes that most earlier published clinical studies, relating to dosage, dosage form and effectiveness are inconclusive. Deficiencies of some earlier studies were largely due to the fact that it has been only recently recognized that salicylamide undergoes extensive metabolism during the absorption process. The extent of metabolism and thus the systemic availability of the pharmacologically active (unmetabolized) parent drug is greatly dependent on both the dose and the release characteristics of the dosage form used.

The Panel notes that the lack of therapeutic effects or toxicities observed in some earlier studies were likely a consequence of the properties of the dosage form used rather than the intrinsic pharmacologic effects of the drug itself.

The Panel concludes that currently recommended doses of 300 to 600 mg are probably ineffective when salicylamide is used as a single analgesic (or antipyretic) agent.

Doses of 600 to 1,000 mg may be effective depending on the characteristics of the dosage form which should be individually evaluated for each product. The true incidence and nature of adverse effects at this dosage level is not well established and must also be characterized by a well-designed study.

Studies to establish safety and/or effectiveness must include an assessment of the systemic availability of the unmetabolized parent drug. Pre and postdrug assessments of organ functions, which have been identified in the literature, are needed including those for CNS, gastrointestinal, hematopoietic and hepatic functions.

(3) *Proposed dosage.* No marketed product containing salicylamide alone was submitted to the Panel. Currently marketed products submitted contain 97.2 to 250 mg salicylamide per dosage unit in combination with other active ingredients.

The Panel finds that salicylamide at a higher dosage (1,000 mg every 4 hours while symptoms persist not to exceed 6,000 mg in 24 hours for not more than 10 days) may be effective but has not been demonstrated to be safe for OTC use. However, the Panel recommends that salicylamide not be made available for OTC use at the higher dosage range until suitable studies have been completed to show both safety and effectiveness.

For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

In addition, the Panel has also considered the use of salicylamide as an OTC analgesic adjuvant elsewhere in this document. (See part VI. paragraph B.5. below—Salicylamide.)

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness and safety will be required in accordance with the guidelines set forth below for analgesic drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

Additional information from carefully planned clinical studies is required in order to establish effective dosage, select formulations that provide suitable bioavailability of active drug, and determine the nature and true incidence of adverse effects when effective doses and dosage forms are used. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage and dosage formulation prior to testing.

(6) *Combination products containing salicylamide combined with acetaminophen or salicylamide combined with aspirin.* The Panel concludes that there is insufficient information to determine the safety and effectiveness of salicylamide as an adjuvant in combination with acetaminophen or aspirin, and therefore classifies such combinations as Category III. The Panel has discussed the role of salicylamide as an adjuvant elsewhere in this document. (See part VI. paragraph B.5. below—Salicylamide.)

Salicylamide is a frequent component of analgesic mixtures. The average amount in these combinations is only about 200 mg which on the basis of previous discussion would appear to be ineffective.

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d. *Salsalate (salicylsalicylic acid)*. The Panel concludes that there are insufficient data to determine that salsalate is either safe or effective as an OTC analgesic in the recommended dosage of 500 to 1,000 mg every 4 hours while symptoms persist not to exceed 6,000 mg in 24 hours for not more than 10 days.

(1) *Effectiveness.* Salsalate, also known as salicylsalicylic acid, is more closely related to the nonacetylated salicylates than it is to aspirin (an acetylated salicylate). However, unlike most of the other salicylates reviewed by the Panel, this ingredient is highly insoluble (Refs. 1 and 2). In fact, Beaver notes that salsalate seems to hydrolyze slowly in the stomach, which may result in slow or incomplete absorption (Ref. 3).

Although salsalate is discussed in several standard medical texts, little work has been done on this ingredient (Refs. 2 and 4).

In one uncontrolled, unpublished study, salsalate was compared to aspirin on the basis of analgesic effect on "nervous headaches" in 30 subjects (Ref. 5). Aspirin was given at a dose of 600 mg and salsalate at a dose of 1,000 mg. Aspirin not only had a faster onset of analgesia, but the authors also concluded that it showed a slight superiority in degree of pain relief. However, they felt this difference in degree of pain relief was not significant. While it is likely that salsalate might be an effective analgesic, the Panel concludes that, because of its insolubility and slow absorption, at best it is only ⅔ as potent as aspirin.

(2) *Safety.* Salsalate (salicylsalicylic acid) is an ester of two salicylic acid molecules that hydrolyzes to yield the parent compound and thus it is considered by some to be pharmacologically indistinct from salicylic acid. However, there appears to be no justification in the literature for such a simplistic view of the pharmacokinetic and pharmacologic properties of this compound. Following the early work of Hanzlik and Presho in 1925 (Ref. 6), there were apparently no additional published studies on plasma levels until the study of Rubin in 1965 (Ref. 7). The study of Hanzlik and Presho (Ref. 6) indicates that a significant amount of unhydrolyzed drug reaches the systemic circulation since 10 to 20 percent is excreted in the urine unchanged.

The study of Rubin (Ref. 7) indicates that salsalate, when absorbed intact, will be measured as one salsalate molecule by the ferric chloride assay that is usually used to assay serum salicylates, and therefore, would not usually be detected by usual blood level studies. The study of Rubin (Ref. 7) suggests that a significant amount of salsalate is absorbed intact and hydrolyzes slowly to salicylic acid. Of concern to the Panel are the great variations in resulting plasma levels of salicylic acid following multiple doses given 4 times daily. After 2 days of dosing, serum salicylate levels ranged from 4 mg/100 ml to 24 mg/100 ml, and from 2 mg/100 ml to 42 mg/100 ml after 8 days of dosing. The prolonged time to reach plateau levels after multiple dosing indicates that salsalate has a greater half-life of elimination than salicylic acid.

Furthermore, the half-life appeared to be quite variable among the subjects in this study. Additional data are needed to better characterize the pharmacokinetics of salsalate. There are no data on the pharmacologic properties of the salsalate ester. Based upon the significant differences in pharmacologic effects produced by salicylic acid and its acetyl ester, aspirin, one can make no assumption that salsalate and salicylic acid have equal effects. Nordqvist et al. (Ref. 8) compared the kinetics of salsalate, aspirin and sodium salicylate following single doses. Significant differences were observed in the elimination rate constant and volume of distribution of salsalate which were both larger than that of aspirin or sodium salicylate.

Additional blood level data was submitted to the Panel in a submission (Ref. 9) to provide evidence of comparable bioavailability. A crossover study comparing 650 mg aspirin, salsalate and 650 mg calcium carbaspirin was described. Sufficient information was not given on the specifics of the analytical procedure used. However, the Panel could not determine if the serum levels following salsalate administration represented the parent compound or the hydrolysis product, salicylic acid. Therefore, additional information is needed on its bioavailability.

The Panel has outlined procedures to use salicylate blood level data only when salicylic acid and aspirin are the compounds which are absorbed from various salts or other dosage forms which hydrolyze in the gastrointestinal tract to the parent drug. When other potentially toxic or inactive substances are also absorbed, bioavailability studies alone are not sufficient to establish safety and effectiveness in lieu of adequate toxicology studies. The Panel concludes that there is insufficient information on this product to allow evaluation at this time. Additional pharmacokinetic studies permit analysis of both parent (unhydrolyzed) drug and salicylic acid in plasma. The elimination rate constants for both parent drug and metabolite should be determined over the full dosage range. If a significant amount of the ester is absorbed, toxicology data may be needed.

Unlike aspirin and the other acetylated salicylates, salsalate has not been associated with reactions causing asthmatic attacks in susceptible people. In addition, salsalate, as well as the other nonacetylated salicylates, are not known to affect the platelet adhesiveness involved in the clotting mechanism. However, this ingredient in large doses may have an effect on another aspect of the clotting mechanism (hypoprothrombinemic effect). The caution concerning bleeding should be addressed to that population which is exposed to large doses of this salicylate. The one study available at this time is that of Leonards consisting of a double-blind investigation involving twelve subjects (Ref. 10). In this particular investigation, comparisons were made of gastrointestinal blood loss associated with the ingestion of placebo, salsalate, aspirin and a combination of the latter two. Blood loss was measured by a method employing the measurement of radioactively-labeled red blood cells of normal subjects. Salsalate did not produce any bleeding above the normal control values. Aspirin produced a blood loss of 4.8 ml on the average per day. The combination tablet resulted in a 1.2 ml average daily blood loss, and the lactose placebo tablet a 0.6 ml daily blood loss.

(3) *Proposed dosage.* Adult oral dosage is 500 to 1,000 mg every 4 hours while symptoms persist not to exceed 6,000 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for analgesic active ingredients. (See part III. paragraph B.1 above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of salsalate per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing salsalate differs per dosage unit from the established standard of 325 mg sodium salicylate per dosage unit. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing salsalate be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 500 mg salsalate per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg per tablet of the established standard of 325 mg sodium salicylate per tablet".

As noted previously a decrease in occult bleeding does not mean that salsalate does not have the other gastroin-

testinal and blood clotting side effects of aspirin or the other salicylates.

While the evidence is not complete, it seems to indicate that the severity and incidence of adverse reactions, either prior to or after absorption, would be comparable to that of aspirin and the other salicylates discussed previously in this document. Until studies show that salsalate has different absorption characteristics and these characteristics are correlated with greater safety, all indications, limitations and warnings for the nonacetylated salicylates would be equally applicable here.

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for analgesic drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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CATEGORY III LABELING

The Panel concludes that the Category I labeling claims are sufficiently broad to encompass the various specific types of pain, e.g., "body aches", "muscle aches", etc. All other labeling claims relating to pain are unsupported by scientific data or sound theoretical reasoning and are classified Category II. (See part III. paragraph B.1. above—Category I Labeling and part III. paragraph B.2. above—Category II Labeling.)

In addition, the Panel has examined the submitted labeling claims for buffered and highly buffered aspirin products and has classified the following as Category III labeling which may be included on the principal display panel: a. "Provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label", and b. "Faster to the bloodstream than plain aspirin". The Panel has discussed the above Category III labeling elsewhere in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

Although buffering agents are not included in the formulation of choline salicylate, some of its currently marketed labeling claims are similar to the claims submitted for highly buffered aspirin. The similarity in labeling claims is undoubtedly due to the fact that choline salicylate, like highly buffered aspirin, is marketed in a liquid dosage form. The Panel has reviewed these claims for choline salicylate and has classified the following as Category III labeling: "May be taken on an empty stomach and may prevent the stomach distress that aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label". The basis for this classification is discussed elsewhere in this document. (See part III. paragraph 1.d.(2) above—Safety.)

C. Data Required for Evaluation

The Panel finds the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in accord with the present state of the art and do not preclude the use of any advances of improved methodology in the future.

1. *Considerations in designing an experimental protocol for testing analgesic drugs. General Principles.* The important considerations concerning the design and interpretation of analgesic assays are as follows (Refs. 1 and 2): a. The appraisal of real analgesic power must be based on the capacity of the agent to relieve pain present as a consequence of disease or trauma in as much as the pain experience of man consists of perception of the natural painful stimuli together with the psychic modification of these stimuli (Ref. 3).

b. Animal screening tests and most methods employing experimental pain in normal human volunteers have failed to predict with any consistency the clinical performance of analgesic drugs, particularly those used for OTC medication.

c. The most successful efforts to quantitate pain in the clinical situation have been those that have accepted the patient's own reports as appropriate indices of the pain experience and of the relief resulting from analgesic administration. Various criteria for analgesia may be used successfully, but whichever is used should be well defined, and sleep should not be confused with analgesia.

2. *Determination of the patient population.* A large number of appropriate subjects with different types of pain should be studied for the analgesic effect of mild analgesics. The subjective response variable change in pain intensity or pain relief are the usual effects studied. The majority of subjects should be those who have at least moderate pain. Subjects who have pain due to inflammatory conditions should be differentiated from those who have pain from other conditions. When several doses of drug are studied or if a combination of several ingredients is being studied, a number of groups is required, that is, at least four groups. Such a study should preferably use separate large groups of perhaps at least 30 subjects per group since intergroup comparisons have statistical advantages. A well-planned crossover study, however, would also be acceptable.

Determination should be made that the randomization procedure balances out the variables not otherwise controlled in the patient selection. This can be determined by analyzing the distribution of age, sex, type of pain, weight, height, etc. within each of the treatment groups. In any case, full reporting of the subject's characteristics is necessary to allow for the adequate interpretation of results. Furthermore, all exclusions from the experimental protocol should be stated.

Allowance must be made for the placebo response in a well-designed clinical study. In a population of patients, administration of a placebo will give a degree of pain relief and generate a time-effect curve that looks very similar to many of the curves generated by the mild analgesics. However, the active compound will yield significantly more relief.

Much has been written about the placebo responder. The response of patients to an inert compound or a placebo complicates the evaluation of analgesics. It is known that response to placebo is not an abnormal response but a response to be expected. Some believe that the degree of placebo response among the population is in some respects a measure of the rapport that the investigator has with the patients in the population. There is nothing gained from determining who responds to a placebo and from eliminating them from the analysis of the data of the analgesic study. Furthermore, it has been shown that the patients responding to placebo are not necessarily consistent within themselves. That is, if they respond positively to placebo in one trial, in the next trial they may or may not respond positively to a placebo, and therefore it is impossible in the clinical setting to define the placebo responders.

3. *Test parameters for study.* a. *General considerations.*—Regardless of the parameters studied to evaluate the effectiveness of an analgesic ingredient, the following considerations should be incorporated into the design of the study: (1) Patients should be allocated to treatment groups in such a way as to avoid bias.

(2) A double-blind technique should be used.

(3) Consideration should be given to the type of pain present in the patient populations used in the various studies, since conflicting reports could arise from the fact that certain of the mild analgesics owe some, or most of their effects to actions directed at relieving the cause of the pain, e.g., anti-inflammatory.

(4) Suitable controls should be introduced; graded doses of an analgesic

standard and possibly a placebo as well.

(5) Studies employing graded doses of the test drug are more meaningful. If with increasing dose an increased effect is demonstrated, this verifies the sensitivity of the method. The studies with graded doses of the test drug compared to the standard drug permit determination of relative potency and 95 percent confidence limits which otherwise are difficult to assess (Ref. 4).

(6) The scoring of pain and/or relief should be done frequently during the expected duration of action of the test drug. Retrospective evaluation of drug effect has often proved to be virtually meaningless.

(7) Results of single dose studies should not be extrapolated to predict the effect of the chronic use of a drug.

(8) Prior to carrying out an analgesic assay, the appropriate statistical analysis should be defined.

Unless the foregoing points have been observed, any statistical analysis would only impart a false sense of confidence in the results.

b. *Use of blood levels in evaluation of analgesic effectiveness.*—In the case of salts or similar variants of an analgesic, e.g. aspirin, for which effectiveness has been established, crossover bioavailability studies may be used to establish effectiveness. In these studies blood levels produced by the salt or other variant are compared with those of the established analgesic, after administration of similar dosage forms. Comparable blood levels of the parent compound and major active metabolites may be equated with effectiveness.

4. *Data interpretation.* To establish Category I status for a Category III compound requires at least two studies by independent investigators which conform to the guidelines included above for compounds for which safety is unquestioned. If the compound is placed in Category III for reasons of safety at least two 3-month safety studies by independent investigators should be required. These studies should include at least 90 subjects, placebo and known drug controls, and involve 4 times daily or other recommended intervals of administration of the test drug in question to controlled subject populations in whom side effects can be checked daily and complete blood counts, urinalysis, stool, blood and organ function tests can be checked weekly or more often if necessary. If a pharmacogenetic link is suspected a target population should be selected.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

5. *Safety evaluation.* An evaluation of the safety of an analgesic ingredient should be based on the usual animal studies and observations in man relevant to the various organs and systems, such as the gastrointestinal system, the kidneys, the effect on the cardiovascular system, particularly the effect on the clotting mechanism, etc. In addition, the hepatic system and the potential for teratogenicity should be considered.

6. *General guidelines for reclassification of Category III combinations to Category I.* a. Combinations must demonstrate at least as much analgesic effectiveness as a 650 mg (10 gr) dose of aspirin.

b. Combinations must be at least as safe as the recommended 650 mg (10 gr) single dose of aspirin or the recommended maximum 24-hour dose of 4,000 mg of aspirin.

c. Each component must make a statistically significant contribution to the total effect. For instance, this could be determined by factorially designed studies. They might be of the form: 650 mg aspirin, 650 mg aspirin plus 60 mg caffeine, 60 mg caffeine, and placebo. The analysis must show caffeine in combination to have a significant effect to justify its continued inclusion in combinations.

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IV. ANTIPYRETIC AGENTS

A. GENERAL DISCUSSION.

Antipyretics are used to reduce the body temperature when it is above the normal value of 98.6° F (37° C). The OTC antipyretics are intended primarily for the symptomatic reduction of fever. If the fever is over 103° F (39.5° C), persists for more than 72 hours, or recurs, measures in addition to antipyresis should be considered. The Panel concludes that to specify a specific temperature in the label warning would not be meaningful. A specific temperature above the normal value of 98.6° F (37° C) that would be symptomatic of a disease state requiring the diagnosis and treatment of a physician cannot be established by the Panel.

The Panel does not believe that a fever secondary to an undiagnosed condition should be allowed to persist for more than 3 days. The Panel recognizes the long standing use of OTC analgesic-antipyretic products without any specific limitation on the use of them as antipyretics. In most instances, the labeling contains a general warning statement, not specific to fever, for use up to 10 days. In view of the marketing experience with the 10 day warning, the Panel recommends that all future labeling be readily distinguishable and clearly limit use of antipyretic products to 3 days (72 hours) in the presence of fever. The Panel recommends that labeling of antipyretic products include the warning: "If fever persists for more than 3 days (72 hours), or recurs, consult your physician".

The Panel believes that it is important to differentiate in the labeling between the use of the product as an antipyretic and its use as an analgesic. It may be that some antipyretics have a relative potency which is less than one would predict from their analgesic relative potency. So far the Panel has found only one antipyretic ingredient for which relative potency has been computed in man. For this reason, the Panel recommends that the labeling on all preparations containing analgesic-antipyretic ingredients list the same dose for antipyretic use as that required for the analgesic effect since our present state of knowledge is uncertain as to the optimal dose for antipyretic effect.

The question has properly been raised whether a fever should be treated at all. This subject has been argued at length and the Panel recognizes that not every fever requires immediate treatment. In children especially, febrile convulsions are a concern to the pediatrician and to the parent.

There are some disadvantages to antipyretic therapy, for instance, in the patient who has just been started on an antibiotic for the treatment of an infection, the response to the antibiotic can be judged by the reduction in fever as the infection is brought under control. Some physicians argue that by giving an antipyretic, the one sign, reduction in body temperature, which can be followed easily to determine the effectiveness of the antibiotic therapy has been obscured. It is also possible that in patients with undiagnosed disease, the febrile course may be of diagnostic importance because of its particular characteristics. In a febrile child, a progressively rising temperature indicates to the physician that things are not going well and additional examination, diagnostic procedures, treatment or perhaps hospitalization may be necessary. These arguments for and against antipyretic treatment have been discussed by Done (Ref. 1).

The Panel finds that antipyretics fill a real need in the OTC management of symptomatic relief of fever. The Panel believes that there is a suitable target population that can benefit from the use of such OTC products. However, since fever may indicate a serious illness, a physician should be consulted if fever persists for more than 3 days (72 hours).

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B. CATEGORIZATION OF DATA.

1. *Category I conditions under which antipyretic agents are generally recognized as safe and effective and are not misbranded.*

CATEGORY I ACTIVE INGREDIENTS

The Panel has classified the following antipyretic active ingredients as generally recognized as safe and effective and not misbranded:

Aspirin	Choline salicylate
Acetaminophen	Magnesium salicylate
Calcium carbaspirin	Sodium salicylate

a. *Aspirin.* The Panel concludes that aspirin is a safe and effective OTC anti-

pyretic when taken in the recommended dosage of 325 mg to 650 mg every 4 hours while fever persists not to exceed 4,000 mg in 24 hours for not more than 3 days.

(1) *Effectiveness.* In animals, as well as in man, aspirin has proven to be an effective antipyretic. Although many clinical studies are poorly designed and the evidence is often anecdotal, there are well-documented and carefully analyzed studies showing that aspirin is a potent antipyretic agent (Refs. 1 through 10). The most carefully conducted study is that of Seed (Ref. 6) who demonstrated significant dose-effect curves.

Although it has been suggested by Steele et al. (Ref. 5) that there is a therapeutic advantage to giving aspirin in combination with acetaminophen for antipyresis (Ref. 5), the study has been criticized by Harden (Ref. 11) as well as by Wolman (Ref. 12). The Panel agrees with the criticism of Harden and Wolman and finds that the study of Steele et al. (Ref. 5) is not designed to study this interaction. Furthermore, there is no advantage to giving these drugs in combination for their antipyretic effect. The drugs in this study were used alone and at the same dosage in the combination. The increased effect observed with the combination may be due to merely the increase in dosage because of the presence of both drugs. Statistically, there is no way of calculating the interaction in this study in order to determine if the combined effect represents simple addition, potentiation or indeed even antagonism.

(2) *Safety.* The safety of aspirin has been discussed earlier in this document. (See part III. paragraph B.1.a.(2) above—Safety.)

(3) *Dosage.* (i) *For products containing 325 mg (5 gr) per dosage unit.* (*a*) *Standard schedule.*—Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while fever persists not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 487.5 mg (7.5 gr) every 4 hours while fever persists not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while fever persists not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while fever persists not to exceed 1,625 mg (25 gr) in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 243.8 mg (3.75 gr) every 4 hours while fever persists not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while fever persists not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(*b*) *Nonstandard schedule.*—Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *For products containing 80 mg (1.23 gr) per dosage unit.* Children 11 to under 12 years oral dosage is 480 mg (7.38 gr) every 4 hours while fever persists not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while fever persists not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while fever persists not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while fever persists not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 3 days. Children 2 to 4 years oral dosage is 160 mg (2.46 gr) every 4 hours while fever persists not to exceed 800 mg (12.3 gr) in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(iii) *For products containing more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) per dosage unit.* Adult oral dosage is more than 325 mg (5 gr) but not more than 842 mg (12.96 gr) initially, followed by more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) every 3 hours while symptoms persist not to exceed 3,789 mg (58.32 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(iv) *For products containing more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) per dosage unit.* Adult oral dosage is more than 421 mg (6.48 gr) but not more than 970 mg (14.92 gr) initially, followed by more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) every 4 hours or 842 mg (12.96 gr) but not more than 970 mg (14.92 gr) every 6 hours while symptoms persist not to exceeed 3,880 mg (59.68 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(v) *For products containing more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) per dosage unit.* Adult oral dosage is more than 485 mg (7.46 gr) but not more than 1,000 mg (15.38 gr) initially, followed by more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) every 3 hours or 970 mg (14.92 gr) but not more than 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(vi) *For products containing more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) per dosage unit.* Adult oral dosage is more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (*a*) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

(*b*) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(*c*) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(ii) *Standard aspirin dosage unit.* In the previous discussion on "standard strength" dosage forms, the Panel made clear the need to indicate both the quantity of aspirin per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing aspirin differs per dosage unit from the established standard of 325 mg (5 gr) aspirin per dosage unit. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that all products containing aspirin be clearly labeled as containing aspirin on the principal display panel. In addition, labeling shall state in metric units and secondarily in apothecary units the quantity of aspirin per dosage unit. As previously stated, such labeling will not only benefit all consumers but will alert those individuals having sensitivity to aspirin.

(*a*) *Products containing the standard aspirin dosage unit.* The Panel recommends that products containing only 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) aspirin per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(*b*) *Products containing aspirin in an amount different than the standard aspirin dosage unit.* While the Panel recommends that products contain only 325 mg (5 gr) aspirin per dosage unit, if the Food and Drug Administration is unable to implement this recommendation, the Panel recommends that products containing an amount of aspirin other than 325 mg (5 gr) aspirin per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg (X gr) aspirin per dosage unit compared to the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount "X" of

aspirin for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

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(10) Simila, S., S. Keinanen and K. Kouvalainen, "Oral Antipyretic Therapy," *European Journal of Pediatrics*, 121:15–20, 1975.

(11) Harden, L. B., "Oral Antipyretic Therapy," *American Journal of Diseases in Children*, 126:563–564, 1973.

(12) Wolman, I. J., "Oral Antipyretic Therapy," *American Journal of Diseases in Children*, 126:564, 1973.

b. *Acetaminophen.* The Panel concludes that acetaminophen is a safe and effective OTC antipyretic when taken in the recommended dosage of 325 to 650 mg every 4 hours while fever persists not to exceed 4,000 mg in 24 hours for not more than 3 days.

(1) *Effectiveness.* A number of studies have been done on the antipyretic effects of acetaminophen (Refs. 1 through 6). Acetaminophen has been shown to be effective. However, there has been no assay in which the relative antipyretic potency of acetaminophen compared to aspirin has been computed. An examination of the data in the studies by Eden and Kaufman (Ref. 2), Cornely and Ritter (Ref. 3), Colgan and Mintz (Ref. 4), and Hunter (Ref. 5) seem to indicate that acetaminophen is a less potent antipyretic than aspirin. However, if one examines the recent study by Tarlin et al. and constructs mean temperature lowering curves, the total effect of acetaminophen and aspirin appear to be comparable (Ref. 6), while the data of Steele et al. (Ref. 8) indicate a slight superiority for acetaminophen. However, since only one dose of acetaminophen and the same mg dose of aspirin were compared in these later two studies, it is impossible to make a statement on relative potency since dose-effect curves were not defined.

(2) *Safety.* The safety of acetaminophen has been discussed earlier in this document. (See part III. paragraph B.1.b.(2) above—Safety.)

(3) *Dosage.* (i) *For products containing 325 mg (5 gr) per dosage unit.* (a) *Standard schedule.*—Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while fever persists not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 487.5 mg (7.5 gr) every 4 hours while fever persists not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while fever persists not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while fever persists not to exceed 1,625 mg (25 gr) in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 243.8 mg (3.75 gr) every 4 hours while fever persists not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while fever persists not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Nonstandard schedule.*—Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *For products containing 80 mg (1.23 gr) per dosage unit.* Children 11 to under 12 years oral dosage is 480 mg (7.38 gr) every 4 hours while fever persists not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while fever persists not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while fever persists not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while fever persists not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 160 mg (2.46 gr) every 4 hours while fever persists not to exceed 800 mg (12.3 gr) in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(iii) *For products containing 500 mg (7.69 gr) per dosage unit.* Adult oral dosage is 500 mg (7.69 gr) to 1,000 mg (15.38 gr) initially, followed by 500 mg (7.69 gr) every 3 hours or 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (a) "Do not exceed recommended dosage because severe liver damage may occur".

(b) "Do not take this product for the treatment of arthritis except under the advice and supervision of a physician".

(ii) *Standard acetaminophen dosage unit.* In the previous discussion on "standard strength" dosage forms, the Panel made clear the need to indicate both the quantity of acetaminophen per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing acetaminophen differs per dosage unit from the established standard of 325 mg (5 gr) acetaminophen per dosage unit. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that all products containing acetaminophen be clearly labeled as containing acetaminophen on the principal display panel. In addition, labeling shall state in metric units and secondarily in apothecary units the quantity of acetaminophen per dosage unit.

(a) *Products containing the standard acetaminophen dosage unit.* The Panel recommends that products containing only 325 mg (5 gr) acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(b) *Products containing acetaminophen in an amount different than the standard acetaminophen dosage unit.* While the Panel recommends that products contain only 325 mg (5 gr) acetaminophen per dosage unit, if the Food and Drug Administration is unable to implement this recommendation the Panel recommends that only nonstandard dosage units of 500 mg (7.69 gr) be recognized for acetaminophen in addition to the standard dosage unit of 325 mg (5 gr). The Panel recommends that products containing 500 mg (7.69 gr) of acetaminophen per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of 500 mg (7.69 gr) acetaminophen per dosage unit compared to the established standard of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

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(8) Steele, R. W., F. S. H. Young, J. W. Bass and H. C. Shirkey, "Oral Antipyretic Therapy: Valuation of Aspirin—*Acetaminophen* Combination," *American Journal of Diseases of Children*, 123:204-206, 1972.

c. *Calcium carbaspirin.* The Panel concludes that calcium carbaspirin is a safe and effective OTC antipyretic when taken in the recommended dosage of 414 to 828 mg every 4 hours while fever persists not to exceed 4,968 mg in 24 hours for not more than 3 days.

(1) *Effectiveness.* The Panel concludes that calcium carbaspirin is effective, not based on controlled clinical studies, but on the fact that the absorbed moiety is aspirin, discussed fully above, and that adequate bioavailability has been established demonstrating an effect similar to aspirin (Refs. 1 and 2). (See part III paragraph B.1.c. above—Calcium carbaspirin.)

(2) *Safety.* The safety of calcium carbaspirin has been discussed earlier in this document. (See part III. paragraph B.1.c. (2) above—Safety.)

(3) *Dosage.* Adult oral dosage is 414 to 828 mg every 4 hours while fever persists not to exceed 4,968 mg in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 621 mg every 4 hours while fever persists not to exceed 3,105 mg in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 517.5 mg every 4 hours while fever persists not to exceed 2,587.5 mg in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 414 mg every 4 hours while fever persists not to exceed 2,070 mg in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 310.5 mg every 4 hours while fever persists not to exceed 1,552.5 mg in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 207 mg every 4 hours while fever persists not to exceed 1,035 mg in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (*a*) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

(*b*) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(*c*) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(ii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of calcium carbaspirin per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing calcium carbaspirin differs per dosage unit from the established standard of 325 mg (5 gr) aspirin. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing calcium carbaspirin be clearly labeled on the principal display panel: "Equivalent to X mg (X gr) per dosage unit of the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount of "X" of equivalent analgesic effectivness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 414 mg calcium carbaspirin per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg (5 gr) per tablet of the established standard of 325 mg (5 gr) aspirin per tablet".

REFERENCES

(1) Levy, G., "Comparison of Dissolution and Absorption Rates of Different Commercial Aspirin Tablets," *Journal of Pharmaceutical Sciences*, 50:388-392, 1961.
(2) OTC Volume 030050.

d. *Choline salicylate.* The Panel concludes that choline salicylate is a safe and effective OTC antipyretic when taken in the recommended dosage of 435 to 870 mg every 4 hours while fever persists not to exceed 5,220 mg in 24 hours for not more than 3 days.

(1) *Effectiveness.* A number of studies have been done on the antipyretic effects of choline salicylate.

Broh-Kahn reported on the results of a cooperative study involving 1,200 patients (Ref. 1). He did show statistically significant blood salicylate levels after the administration of choline salicylate. However, the information on its antipyretic effect is largely anecdotal.

Hunt studied the antipyretic effect of choline salicylate and found it to be an active antipyretic (Ref. 2), however, there was no direct comparison with a drug such as aspirin.

Leary again demonstrated the rapid absorption of choline salicylate and the appearance of salicylate in the plasma (Ref. 3). The major evidence for the antipyretic efficacy of choline salicylate other than the demonstration of effective blood levels is the study by Tupper (Ref. 4). This is not a controlled study but does demonstrate the temperature-lowering effect following the administration of choline salicylate.

These studies show that the drug is effective. However, they were not designed to determine whether they are more or less potent than an equivalent mg dose of aspirin and so its relative antipyretic potency cannot be determined based upon the studies.

(2) *Safety.* The safety of choline salicylate has been discussed earlier in this document. (See part III. paragraph B.1.d.(2) above—Safety.)

(3) *Dosage.* Adult oral dosage is 435 to 870 mg every 4 hours while fever persists not to exceed 5,220 mg in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 652.5 mg every 4 hours while fever persists not to exceed 3,262.5 mg in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 543.8 mg every 4 hours while fever persists not to exceed 2,719 mg in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 435 mg every 4 hours while fever persists not to exceed 2,175 mg in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 326.5 mg every 4 hours while fever persists not to exceed 1,632.5 mg in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 217.5 mg every 4 hours while fever persists not to exceed 1,087.5 mg in 24 hours for not more than 3 days. Children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(ii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of choline salicylate per tablet, teaspoonful or other dosage unit as well as the quantity by which a particular product containing choline salicylate differs per dosage unit from the established standard of 325 mg sodium salicylate per dosage unit. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing choline salicylate be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For ex-

ample, a product containing 435 mg choline salicylate per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg per tablet of the established standard of 325 mg sodium salicylate per tablet".

REFERENCES

(1) Broh-Kahn, R. H., "Choline Salicylate: A New, Effective and Well-Tolerated Analgesic, Anti-inflammatory, and Antipyretic Agent," *International Record of Medicine*, 173:217-232, 1960.

(2) Hunt, W. D., "Choline Salicylate As An Antipyretic and Analgesic In Pediatric Practice," *Clinical Medicine*, 69:2688-2693, 1962.

(3) Leary, J. F., "Preliminary Pharmacological Comparison of Choline Salicylate with Acetylsalicylic Acid," *International Record of Medicine*, 173:259-261, 1960.

(4) Tupper, J. A., "Choline Salicylate in Pediatric Practice, Trial of a New Soluble Analgesic," *Northwest Medicine*, 62:122-124, 1963.

e. *Magnesium salicylate.* The Panel concludes that magnesium salicylate is safe and effective as an OTC antipyretic in the recommended dosage of 325 to 650 mg every 4 hours while fever persists not to exceed 4,000 mg in 24 hours for not more than 3 days.

(1) *Effectiveness.* The effectiveness of magnesium salicylate has been discussed earlier in this document. Although the Panel found no controlled clinical antipyretic study of magnesium salicylate, adequate studies showing bioavailability have been done (Ref. 1) and there is no reason to believe it a less effective antipyretic than sodium salicylate. (See part III. paragraph B.1.e.(1) above—Effectiveness.)

(2) *Safety.* The safety of magnesium salicylate has been discussed earlier in this document. (See part III. paragraph B.1.e.(2) above—Safety.)

REFERENCE

(1) OTC Volume 030042.

(3) *Dosage.* Adult oral dosage is 325 to 650 mg every 4 hours while fever persists not to exceed 3,900 mg in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while fever persists not to exceed 2,437.5 mg in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while fever persists not to exceed 2,031.5 mg in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while fever persists not to exceed 1,625 mg in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while fever persists not to exceed 1,219 mg in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while fever persists not to exceed 812.5 mg in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See Part IV. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(ii) *For products containing more than 50 mEq of magnesium in the recommended daily dosage. Warning.* "Do not take this product if you have kidney disease except under the advice and supervision of a physician".

(iii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of magnesium salicylate per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing magnesium salicylate differs clinically per dosage unit from the established standard of 325 mg sodium salicylate per dosage unit. (See Part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing magnesium salicylate be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsules. For example, a product containing 325 mg magnesium salicylate per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg per teaspoon of the established standard of 325 mg sodium salicylate per tablet".

f. *Sodium salicylate.* The Panel concludes that sodium salicylate is a safe and effective OTC antipyretic when taken in the recommended dosage of 325 to 650 mg every 4 hours while fever persists not to exceed 4,000 mg in 24 hours for not more than 3 days.

(1) *Effectiveness.* Although sodium salicylate is an effective antipyretic, it is probably only 0.6 times as effective as aspirin. In a controlled study, Seed investigated the antipyretic effects in patients with chronic cancer and associated infectious processes. He determined that sodium salicylate in this population was 0.6 times as potent as aspirin (Refs. 1 and 2). This is the only controlled study in which an assay was carried out so that the relative potency of one antipyretic as compared with the standard, aspirin, could be determined.

(2) *Safety.* The safety of sodium salicylate has been discussed earlier in this document. (See part III. paragraph B.1.f. (2) above—Safety.)

(3) *Dosage.* (i) *For products containing 325 mg per dosage unit.* (a) *Standard schedule.* Adult oral dosage is 325 to 650 mg every 4 hours while fever persists not to exceed 3,900 mg in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while fever persists not to exceed 2,437.5 mg in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while fever persists not to exceed 2,031.5 mg in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while fever persists not to exceed 1,625 mg in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while fever persists not to exceed 1,219 mg in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while fever persists not to exceed 812.5 mg in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Nonstandard schedule.* Adult oral dosage is 325 mg to 975 mg initially, followed by 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *For products containing more than 325 mg but not more than 421 mg per dosage unit.* Adult oral dosage is more than 325 mg but not more than 842 mg initially, followed by more than 325 mg but not more than 421 mg every 3 hours while symptoms persist not to exceed 3,789 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(iii) *For products containing more than 421 mg but not more than 485 mg per dosage unit.* Adult oral dosage is more than 421 mg but not more than 970 mg initially, followed by more than 421 mg but not more than 485 mg every 4 hours or 842 mg but not more than 970 mg every 6 hours while symptoms persist not to exceed 3,880 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(iv) *For products containing more than 485 mg but not more than 500 mg per dosage unit.* Adult oral dosage is more than 485 mg but not more than 1,000 mg initially, followed by more than 485 mg but not more than 500 mg every 3 hours or 970 mg but not more than 1,000 mg every 6 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(v) *For products containing more than 500 mg but not more than 650 mg per dosage unit.* Adult oral dosage is more than 500 mg but not more than 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning:* "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(ii) *For products containing 0.2 mEq (5 mg) or higher of sodium per dosage unit.* The labeling of the product contains

the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq (5 mg) or higher.

(iii) *For products containing more than 5 mEq (125 mg) sodium in the maximum recommended daily dosage. Warning.* "Do not take this product if you are on a sodium restricted diet except under the advice and supervision of a physician".

The Panel recommends that all products containing sodium salicylate be clearly labeled as containing sodium salicylate on the principal display panel.

(a) *Products containing the standard sodium salicylate dosage unit.* The Panel recommends that products containing only 325 mg sodium salicylate per dosage unit be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg sodium salicylate per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(b) *Products containing sodium salicylate in an amount different than the standard sodium salicylate dosage unit.* While the Panel recommends that products contain only 325 mg sodium salicylate per dosage unit, if the Food and Drug Administration is unable to implement this recommendation, the Panel recommends that products containing an amount of sodium salicylate other than 325 mg sodium salicylate per dosage unit be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg sodium salicylate per dosage unit compared to the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of sodium salicylate for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

REFERENCES

(1) Seed, J. C., "A Clinical Comparison of the Antipyretic Potency of Aspirin and Sodium Salicylate," *Clinical Pharmacology and Therapeutics*, 6:354–358, 1965.

(2) Seed, J. C. and F. S. Acton, "Clinical Trials of Antipyretic Drugs," *Clinical Pharmacology: International Encyclopedia of Pharmacology and Therapeutics*, 1:297–308, 1965.

CATEGORY I LABELING

The Panel recommends the following Category I labeling for antipyretic active ingredients to be generally recognized as safe and effective and not misbranded as well as any specific labeling discussed in the individual ingredient statements:

a. *Indications.* "For the reduction of fever".

b. *Warnings.* (1) "If fever persists for more than 3 days (72 hours), or recurs, consult your physician".

(2) *For products containing salicylates.* (i) "Take this product for the treatment of arthritis only under the advice and supervision of a physician".

(ii) "Stop taking this product if ringing in the ears or other symptoms occur".

(iii) *For products intended for oral administration as a solid dosage form, e.g., tablets.* (a) "Adults: Drink a full glass of water with each dose".

(b) "Children under 12 years: Drink water with each dose".

(iv) *"Caution:* Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

(v) *"Caution:* Do not take this product if you are presently taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout or arthritis except under the advice and supervision of a physician".

The Panel recognizes that there are few, if any, OTC products marketed exclusively as antipyretics. The vast majority of products are labeled combinations of antipyretics-analgesics.

The Panel finds that some antipyretic-analgesics have a lower antipyretic relative potency when compared to aspirin (the standard) than the relative potency of their analgesic effects. The Panel finds that there are few well-controlled antipyretic clinical trials. Since the major reason for taking antipyretic-analgesics is usually pain relief, the inclusion of antipyretic dosage information on the labeling of these products showing dosage schedules at variance from the dosage based on analgesic efficacy would be confusing to the public. Therefore, the Panel recommends that future labeling of effective antipyretics follow the labeling used for single entities and combinations in the labeling sections of analgesics, except for the duration of use which should be no more than 3 days for antipyretic use. (See Part III.—ANALGESIC AGENTS.)

2. *Category II conditions under which antipyretic agents are not generally recognized as safe and effective or are misbranded.*

CATEGORY II ACTIVE INGREDIENTS

The Panel has classified the following claimed antipyretic active ingredients as not generally recognized as safe and effective or are misbranded:

Acetanilid	Phenacetin
Iodopyrine	Quinine

a. *Acetanilid.* The Panel concludes that acetanilid is an effective OTC antipyretic when taken in the recommended dosage of 200 to 300 mg but is not safe for OTC use.

(1) *Effectiveness.* No suitable designed clinical assays on acetanilid have been reported in the literature. Nevertheless, it is recognized that acetanilid is an effective antipyretic agent.

In the *AMA Drug Evaluations*, acetanilid is listed as having historical interest being the first coal tar analgesic-antipyretic introduced into medicine (Ref. 1). However, it is stated that there is "no justification for using acetanilid in preference to less toxic and equally effective mild analgesics."

(2) *Safety.* The Panel concludes after a review of the literature that this drug is not safe for OTC use.

The safety of acetanilid has been discussed earlier in this document. (See part III. paragraph B.2.a.(2) above—Safety.) Woodbury in 1970, summarized the case against this drug and stated that acetanilid is definitely more toxic than phenacetin or acetaminophen (Ref. 2). Severe methemoglobinemia occurs and possibly sulfhemoglobinemia. The dose required to produce these changes varies from one individual to another, and there is some evidence that dependence on the drug may occur (Ref. 3).

Acetanilid has practically disappeared from use since it is rapidly converted to aniline which causes methemoglobinemia (Ref. 4). Furthermore, it has been implicated in the production of hemolysis in glucose-6-phosphate dehydrogenase deficient individuals who form a significant proportion of the target population (Ref. 5).

(3) *Evaluation.* The Panel concludes because of the high incidence of toxic effects and the relative unfavorable margin of safety that the risks from use outweigh any benefit and therefore classifies acetanilid not safe for use as an OTC antipyretic.

REFERENCES

(1) "Mild Analgesics," in "AMA Drug Evaluations," 1st Ed., American Medical Association, Chicago, pp. 177–188, 1971.

(2) Woodbury, D. M., "Analgesic-Antipyretics, Anti-inflammatory Agents, and Inhibitors of Uric Acid Synthesis," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, Macmillian Co., New York, pp. 332–333, 1970.

(3) Gross, M., "Acetanilid: A Critical Bibliographic Review," Hillhouse Press, New Haven, 1946.

(4) Goth, A., "Medical Pharmacology," 4th Edition, The C. V. Mosby Co., St. Louis, 1968.

(5) Williams, H. E., "Genetic Disorders" in "Clinical Pharmacology," Edited by Melmon, K. L. and H. F. Morrelli, The Macmillan Company, New York, pp. 535–546, 1972.

b. *Iodopyrine.* The Panel finds that there are no data to demonstrate effectiveness but there are data showing it not safe and therefore concludes that iodopyrine is not safe and not effective for use as an OTC antipyretic.

(1) *Effectiveness.* No studies were found concerning the effectiveness of this iodide salt of antipyrine for use as an OTC antipyretic. The lack of demonstrated effectiveness for use of iodopyrine as an OTC analgesic has been discussed earlier in this document. (See part III. paragraph B.2.c.(1) above—Effectiveness.)

(2) *Safety.* The safety of iodopyrine has been discussed earlier in this document. (See part III. paragraph B.2.c.(2) above—Safety.) The Panel concludes that iodopyrine is not safe for use as an OTC antipyretic.

(3) *Evaluation.* The Panel finds that iodopyrine is not safe for OTC use because of the significantly high availability of iodide following oral administration and increased likelihood of iodism. Accordingly, the Panel concludes that the risks from use of iodopyrine outweigh any possible benefit and classifies the ingredient unsafe for use as an OTC antipyretic.

c. *Phenacetin.* The Panel concludes that phenacetin is an effective OTC antipyretic but not safe for OTC use because of the high potential for abuse, the high potential for harm to the kidney

and the possibility of hemolytic anemia and methemoglobinemia resulting from abuse (Ref. 1), and the lack of compensating benefits of the drug. The benefit to risk ratio of phenacetin compounds compares unfavorably with other single agents and combination antipyretic preparations available to target populations.

(1) *Effectiveness.* The antipyretic effect of phenacetin has been investigated by Mintz (Ref. 2). He studied the comparative antipyretic effects expressed in percent of initial temperature and found that aspirin was more effective than phenacetin. He studied these compounds in 20 febrile children under the age of 5 years who were given a single standard dose of 60 mg phenacetin per year of age and compared them with 20 febrile children given aspirin in a standard dose of 65 mg per year of age. Rectal temperatures were taken ½, 1, 2, 3 and 4 hours following the administration of drugs. Aspirin was more effective than phenacetin in lowering the body temperature whether it was expressed in percent of initial temperature or whether it was expressed in terms of the average temperature. The author concludes that half doses of aspirin are as effective as full doses of phenacetin. Thus, phenacetin appears to be half as effective as aspirin in terms of its antipyretic effects.

(2) *Safety.* The safety of phenacetin has been discussed earlier in this document. (See part III, paragraph B.2.d.(2) above—Safety.)

(3) *Evaluation.* The Panel concludes that because of the high potential for abuse, the high potential for harm to the kidney and the possibility of hemolytic anemia and methemoglobinemia resulting from abuse, the risks from the use of phenacetin outweigh any benefit and therefore classifies phenacetin not safe for OTC use as an antipyretic.

REFERENCES

(1) Woodbury, D. M., "Analgesic-Antipyretics, Anti-Inflammatory Agents, and Inhibitors of Uric Acid Synthesis," *in* "Pharmacologic Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan Co., New York, 1970.

(2) Mintz, A. A., "Antipyretic Effect of Acetophenetidin," *Clinical Medicine*, 71:865–870, 1964.

d. *Quinine.* The Panel concludes that quinine is an effective OTC antipyretic but that it is not safe for OTC use.

(1) *Effectiveness.* The Panel notes that Rollo states, "The antipyretic effect of quinine is not very prominent except in cases of malaria. The striking effect in this disease is due to its specific antimalarial action. The weak antipyretic effect that quinine has in other febrile conditions seems to be due to mainly peripheral general inhibitory effect on metabolism and suppression of skeletal muscle activity" (Ref. 1).

(2) *Safety.* The safety of quinine has been discussed earlier in this document (See part III. paragraph B.2.e.(2) above—Safety.)

(3) *Evaluation.* The Panel concludes that because of the high incidence of hypersensitivity in the effective antipyretic dosage, the risks from the use of quinine outweigh any benefit, and therefore, classifies quinine not safe for use as an OTC antipyretic.

REFERENCE

(1) Rollo, I. M., "Drugs Used in the Chemotherapy of Malaria," *in* "The Pharmacologic Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The Macmillan Co., New York, p. 1119, 1970.

CATEGORY II LABELING

The Panel has examined the submitted labeling claims for antipyretics alone and for combination products with nonantipyretic ingredients and has placed certain claims into Category II. These Category II claims have been categorized by the Panel as claims that are unsupported by scientific data or by sound theoretical reasoning, claims that are not clearly defined or clinically recognized, claims that require prior diagnosis and care of a physician, claims that are misleading or specifically contraindicated, and claims that contain modifying adjectives associating fever with illnesses.

Several of the claims considered by the Panel are Category II claims for one or more of the above reasons. An individual claim may include one, several or all of the reasons for classifying a claim as Category II. Therefore, it is difficult to outline an individual claim under one specific reason. All the reasons mentioned above including unacceptable claims related to product performance have been clearly defined elsewhere in this document. (See part III. paragraph B.2.a. above—Category II Labeling.)

The Panel has classified the following labeling claims as Category II claims: "fever of colds and flu," "reduce fever in simple headaches, minor muscular aches, neuritis, neuralgia", "reduces temperature and calms the fretfulness and discomfort of fever, the kind that comes with inoculations, common colds and teething", "fever accompanying colds or the flu", "fever discomfort", "for fever from colds, flu, inoculations, minor ailments, headache, sore throat due to colds, tonsillectomy, teething", and "hay fever".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.*

CATEGORY III ACTIVE INGREDIENTS

The Panel has concluded that the available data are insufficient to permit final classification of the following claimed antipyretic active ingredients listed below. The Panel believes it reasonable to provide 3 years for the development and review of such data. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 3 years, however, the ingredients listed in this Category should no longer be marketed in OTC products:

Aluminum aspirin
Antipyrine
Salicylamide
Salsalate (salicylsalicylic acid)

a. *Aluminum aspirin.* The Panel concludes that aluminum aspirin is safe but that there are insufficient data to determine effectiveness as an OTC antipyretic in the recommended dosage of 365 mg to 730 mg every 4 hours while fever persists not to exceed 4,380 mg in 24 hours for not more than 3 days.

(1) *Effectiveness.* The Panel recommends that if bioavailability studies show that aluminum aspirin produces blood levels comparable to those achieved with aspirin then it should be accepted as an effective OTC antipyretic and classified as Category I for this use.

The Panel recommends alternatively that if two clinical trials as described below show that aluminum aspirin is an effective antipyretic it should be placed in Category I for this use. (See part IV. paragraph C. below—Data Required for Evaluation.)

(2) *Safety.* The safety of aluminum aspirin has been discussed earlier in this document. (See part III. paragraph B.3.a.(2) above—Safety.)

(3) *Proposed dosage.* Adult oral dosage is 365 to 730 mg every 4 hours while fever persists not to exceed 4,380 mg in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 365 mg every 4 hours while fever persists not to exceed 1,825 mg in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 305 mg every 4 hours while fever persists not to exceed 1,525 mg in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 215 mg every 4 hours while fever persists not to exceed 1,075 mg in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 180 mg every 4 hours while fever persists not to exceed 900 mg in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 120 mg every 4 hours while fever persists not to exceed 600 mg in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* (*a*) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

(*b*) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(*c*) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(ii) *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of aluminum aspirin per tablet, teaspoon or other dosage unit as well as the quan-

tity by which a particular product containing aluminum aspirin differs per dosage unit from the established standard of 325 mg (5 gr) aspirin. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing aluminum aspirin be clearly labeled on the principal display panel: "Equivalent to X mg (X gr) per dosage unit of the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 414 mg aluminum aspirin per tablet (dosage unit) shall be labeled. "Equivalent to 325 mg (5 gr) per tablet of the established standard of 325 mg (5 gr) aspirin per tablet".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for antipyretic drugs. In addition, the following information is needed: Bioavailability studies of aluminum aspirin in man must show comparable blood levels of salicylates to those following administration of the standard. aspirin, as detailed below. (See part IV. paragraph C. below—Data Required for Evaluation.)

b. *Antipyrine.* The Panel concludes that there are insufficient data to determine the safety and effectiveness of antipyrine as an OTC antipyretic when, as recommended, the dosage is limited to a single 975 mg dose in 24 hours while symptoms persist for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(1) *Effectiveness.* As far as effectiveness is concerned, not a single controlled clinical study has been found in which the effectiveness of antipyrine as an antipyretic has been evaluated.

The effectiveness of antipyrine as an analgesic has been discussed earlier in this document. (See part III. paragraph B.3.b.(1) above—Effectiveness.)

(2) *Safety.* The safety of antipyrine has been discussed earlier in this document. (See part III. paragraph B.3.b.(2) above—Safety.)

(3) *Proposed dosage.* Adult oral dosage is limited to a single 975 mg dose in 24 hours while symptoms persist for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warnings.* (*a*) "Do not exceed recommended dosage".

(*b*) "If skin rash appears, discontinue use and consult a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for antipyretic drugs. (See part IV. paragraph C. below—Data Required for Evaluation.) Data to demonstrate safety should include epidemiological studies which take into consideration the concerns of the Panel. Interested drug manufacturers should consult with the Food and Drug Administration as to the design of such studies. The studies should consider pharmacogenetic factors and include several racial groups.

c. *Salicylamide.* The Panel concludes that there are insufficient data to determine that salicylamide is either safe or effective when used in combination as an OTC antipyretic in the currently marketed dosage of 97.2 to 400 mg. The Panel finds that salicylamide when used alone at a higher dosage (1,000 mg every 4 hours while fever persists not to exceed 6,000 mg in 24 hours for not more than 3 days) may be effective but has not been demonstrated to be safe for OTC use. However, the Panel recommends that salicylamide not be made available for OTC use at the higher dosage range until suitable studies have been completed to show both safety and effectiveness. In addition, the Panel has also considered the use of salicylamide in combination as an OTC analgesic adjuvant elsewhere in this document. (See part VI. paragraph B.5. below—Salicylamide.)

(1) *Effectiveness.* Controlled studies in animals and in children comparing the effects of aspirin and salicylamide have been carried out (Refs. 1 through 4), but their interpretation has been subject to much discussion. Upon reviewing the papers, it appears that the best estimate is that as an antipyretic salicylamide is about half as potent as aspirin. This compound probably has a threshold dose which must be exceeded before any antipyretic effect is seen.

(2) *Safety.* The safety of salicylamide has been discussed earlier in this document. (See part III. paragraph B.3.c.(2) above—Safety.)

(3) *Proposed dosage.* No marketed product containing salicylamide alone was submitted to the Panel. Currently marketed products submitted contain 97.2 to 250 mg salicylamide per dosage unit in combination with other active ingredients.

The Panel finds that salicylamide at a higher dosage (1,000 mg every 4 hours while symptoms persist not to exceed 6,000 mg in 24 hours for not more than 3 days) may be effective but has not been demonstrated to be safe for OTC use. However, the Panel recommends that salicylamide not be made available for OTC use at the higher dosage range until suitable studies have been completed to show both safety and effectiveness.

For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

In addition, the Panel has also considered the use of salicylamide as an OTC analgesic adjuvant elsewhere in this document. (See part VI. paragraph B.5. below—Salicylamide.)

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness and safety will be required in accordance with the guidelines set forth below for antipyretic drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(6) *Combination products containing salicylamide combined with acetaminophen or salicylamide combined with aspirin.* The Panel concludes that there is insufficient information to determine the safety and effectivenes of salicylamide as an adjuvant in combination with acetaminophen or aspirin, and therefore classifies such combinations as Category III. The Panel has discussed the role of salicylamide as an adjuvant elsewhere in this document. (See part VI. paragraph B.5. below—Salicylamide.)

Salicylamide is a frequent component of analgesic mixtures. The average amount in these combinations is only about 200 mg which on the basis of previous discussion would appear to be ineffective.

REFERENCES

(1) Vignec, A. J. and M. Gasparik, "Antipyretic Effectiveness of Salicylamide and Acetylsalicylic Acid in Infants: A Comparative Study," *Journal of the American Medical Association*, 167:1821–1826, 1958.

(2) Bass, A., "Antipyretic Effectiveness of Aspirin and Salicylamide," *Journal of the American Medical Association*, 168:1684–1685, 1958.

(3) Woodbury, R. A., "Toxicity and Antipyretic Activity of Salicylamide and Aspirin," *Journal of the American Medical Association*, 168:1259–1260, 1958.

(4) Borovsky, M. P., "Antipyretic Activity of Acetylsalicylic Acid and Salicylamide Suspension in Pediatrics; a Comparative Clinical Evaluation in Two Hundred Six Cases," *American Journal of Diseases of Children*, 100:23–30, 1960.

d. *Salsalate (salicylsalicylic acid).* The Panel concludes that salsalate (salicylsalicylic acid) is safe but that there are insufficient data to determine effectiveness as an OTC antipyretic in the recommended dosage of 500 to 1,000 mg every 4 hours while fever persists not to exceed 6,000 mg in 24 hours for not more than 3 days.

(1) *Effectiveness.* The Panel concludes that while this compound probably has antipyretic properties there is no clinical evidence to support this. The Panel recommends that if a clinical trial shows this compound to be an effective antipyretic, that it be classified as Category I for this use.

(2) *Safety.* The safety of salsalate has been discussed earlier in this document. (See part III. paragraph B.3.d.(2) above—safety.)

(3) *Proposed dosage.* Adult oral dosage is 500 to 1,000 mg every 4 hours while fever persists not to exceed 6,000 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antipyretic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the

following specific labeling: *Analgesic equivalence value.* In the previous discussion on "standard strength" dosage forms the Panel made clear the need to indicate the quantity of salsalate per tablet, teaspoon or other dosage unit as well as the quantity by which a particular product containing salsalate differs per dosage unit from the established standard of 325 mg sodium salicylate per dosage unit. (See part II. paragraph E. above—Standard Dosage Unit and Analgesic Equivalence Value.)

The Panel recommends that products containing salsalate be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule. For example, a product containing 500 mg salsalate per tablet (dosage unit) shall be labeled, "Equivalent to 325 mg per tablet of the established standard of 325 mg sodium salicylate per tablet".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for antipyretic drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

CATEGORY III LABELING

The Panel concludes that the Category I labeling claims are sufficiently broad to encompass the various types of fever due to "cold", etc. All other labeling claims relating to fever are unsupported by scientific data or sound theoretical reasoning and are classified Category II. (See part IV. paragraph B.1. above—Category I Labeling and part IV. paragraph B.2. above—Category II Labeling.)

In addition, the Panel has examined the submitted labeling claims for buffered and highly buffered aspirin products and has classified the following as Category III labeling which may be included on the principal display panel: a. "Provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label", and b. "Faster to the bloodstream than plain aspirin". The Panel has discussed the above Category III labeling elsewhere in this document. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.) All other claims for buffered aspirin products are classified as Category II.

Although buffering agents are not included in the formulation of choline salicylate, some of its currently marketed labeling claims are similar to the claims submitted for highly buffered aspirin. The similarity in labeling claims is undoubtedly due to the fact that choline salicylate, like highly buffered aspirin, is marketed in a liquid dosage form. The Panel has reviewed these claims for choline salicylate and has classified the following as Category III labeling: "May be taken on an empty stomach and may prevent the stomach distress that aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label". The basis for this classification is discussed elsewhere in this document. (See part III. paragraph B.1.d.(2) above—Safety.)

C. DATA REQUIRED FOR EVALUATION

The Panel finds the protocols recommended in this document for the studies required to bring a Category III drug into Category I in accord with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Considerations in designing an experimental protocol for testing antipyretic drugs. General principles.*—The important considerations concerning design and interpretation of antipyretic assays are as follows: The effect of antipyretic drugs in reducing fever is nonspecific and does not influence the cause of the underlying disease. In fact, the cause of the patient's illness may be obscured by relief of symptoms and the reduction of fever by the use of antipyretic drugs. However, when OTC antipyretic ingredients are used, it should only be for the symptomatic relief of fever and not for the treatment of a disease as discussed by the Panel earlier in this document. (See part IV. paragraph A. above—General Discussion.) Therefore, in antipyretic assays, the patient population should be varied as described below.

2. *Determination of the patient population.* The clinical studies should be carried out in several populations of patients, such as patients with hyperpyrexia (fever) secondary to cancer and associated infections, hyperpyrexia in children with acute infectious diseases, and hyperpyrexia in adults with acute infectious diseases.

3. *Test parameters for study.* a. *General considerations.*—(1) These studies should be carried out under double-blind conditions using graded doses of active and standard compounds and possibly a placebo.

(2) The patient treatments should be allocated under a randomized scheme to distribute bias evenly.

b. *Method of study.*—The antipyretic effect of the drug should be evaluated by obtaining the patient's temperature at least every hour for 4 to 6 hours. The difference between the postdrug temperature and the predrug temperature can be used to calculate "the degree minutes" of lowering of the temperature. From the temperature lowering effect of the drug, a total and peak score can be obtained and analysis of variance or other suitable statistical analysis should be done on on these data.

4. *Data interpretation.* If significant dose-effect curves are obtained, parallel line assay can be done and the relative potency and fiducial limits of the test compound to the standard compound computed (Ref. 1).

To establish Category I status for a Category III ingredient, the number of studies required for compounds for which safety is unquestioned, and the number and types of studies required for compounds questioned because of safety, will be the same as outlined for Category III analgesic ingredients. (See part III. paragraph C. above—Data Required for Evaluation.)

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

5. *Safety evaluation.* An evaluation of the safety of an antipyretic ingredient should be based on the same studies and observations discussed earlier in this document for the safety evaluation of analgesics. (See part III. paragraph C.5. above—Safety evaluation.)

REFERENCE

(1) Seed, J. C. and F. S. Acton, "Clinical Trials of Antipyretic Drugs," *International Encyclopedia of Pharmacology and Therapeutics*, 16:297–308, 1965.

V. ANTIRHEUMATIC AGENTS

A. GENERAL DISCUSSION

1. *Introduction.* An antirheumatic agent reduces joint inflammation and relieves muscle tenderness and swelling. These agents are used in the treatment of arthritis and the rheumatic diseases. Arthritis is man's oldest known chronic illness. In the discussion that follows below, the Panel will describe arthritis and other rheumatic diseases.

As will be noted, the Panel has found aspirin, calcium carbaspirin, choline salicylate, magnesium salicylate and sodium salicylate acceptable antirheumatic agents. However, the Panel concludes that these drugs should be used in the treatment of rheumatic diseases only under the advice and supervision of a physician. There are many reasons for the Panel taking this position. The reasons will be elaborated upon in greater detail below. Basically, each person with symptoms of the more common rheumatic diseases, e.g., joint and muscular aches, pains and stiffness, and joint swelling should seek the advice of a physician for proper diagnosis of the specific cause of the symptoms and for identification of the exact rheumatic disease involved. Each rheumatic disease is a distinct disease entity with a different cause and a different prognosis, and more importantly, each disease requires a different method of treatment.

As pointed out by the National Institute of Arthritis, Metabolism and Digestive Diseases (Ref. 1), "If you have arthritis, do not try to treat yourself. All forms of arthritis must be treated by a qualified physician."

The Panel recognizes the remarkable properties of aspirin, its salts, and other salicylates in relieving pain and reducing inflammation. However, as pointed out by the Arthritis Foundation (Ref. 2), each individual is different; in a leaflet prepared for arthritis sufferers describing the use of aspirin the following is stated:

You are an individual, not quite like anyone else. Your arthritis is not quite like anyone else's arthritis. How such aspirin you need for your disease, and how much you can tolerate, is for a qualified physician to decide. You make a serious mistake when you act as your own doctor and try to figure out your own dosage schedule.

On the basis of the above, and other data described below, the Panel concludes that the use of OTC antirheumatic agents for the treatment of the symptoms of specific rheumatic diseases requires prior diagnosis by a physician and the establishment of a suitable treatment program, which may include not only OTC antirheumatic drugs, but also prescription medications (e.g. gold, phenylbutazone, indomethacin, hydroxychloroquine, corticosteroids, etc.), physical therapy, exercise, devices (braces, splints, crutches, etc.) and reconstructive surgical procedures. The Panel is concerned that any labeling conditions promoting the use of OTC products for the treatment of rheumatic diseases mislead the consumer who attempts to self-diagnose and self-treat a serious disease. Terms such as "arthritis", "rheumatism", "pain of arthritis", "pain of rheumatism", "minor aches and pains of arthritis", "minor aches and pains of rheumatism", "minor pain of arthritis", "minor pain of rheumatism", "low back pains", "bursitis" and "lumbago" are clearly conditions that should be diagnosed by a physician prior to treatment. Most importantly, there is a potential hazard from self-diagnosis and self-medication. Even with all the precautions the Panel has recommended for OTC drug labeling, there is the unfortunate hazard of an inadequate treatment program with progression of the disease and permanent disability. The advice of a physician is essential for a complete treatment program.

For example, aspirin, the most commonly used OTC antirheumatic agent, can have serious side effects when taken at the high dosages required for effective anti-inflammatory activity. Prover diagnosis and controlled treatment by a physician is essential. Aspirin is only a safe OTC drug when taken at the recommended analgesic daily dosage for the recommended time period (10 days). It is the Panel's conclusion that labeling and advertisements for aspirin-containing products which make antirheumatic claims leave the general impression in the mind of the consumer that aspirin is an innocuous drug and is completely effective when used for this purpose.

In addition, present OTC antirheumatic labeling and advertising has given consumers the impression that arthritis is a "minor" disease. No allusion is made to the progressive, disabling degeneration that occurs if rheumatic diseases are not properly diagnosed and treated. Consequently, such misleading labeling and advertising may cause the affected individual to delay consulting a physician until the disease has progressed to a degenerative state that results in permanent physical disability. It is important that the individual see a physician in the early stages of rheumatic disease in order to attempt to prevent possible progressive degeneration.

The mistaken notion that joint aches and pains can be self-treated is instilled in the consumer by current labeling of OTC antirheumatic products and by misleading advertising. In addition, the consumer is led to believe that there is no distinction between the joint aches and pains of different individuals. The impression is given that all aches, pains and stiffness of joints are medically the same and that all individuals with these "minor" symptoms can self-medicate with OTC antirheumatic products with benefit to their condition.

Many of these OTC products contain the term "arthritis" in their trade name. The advertisements of these products leave the consumer with the false idea that all joint aches, pains and stiffness are both "minor" and due to a single disease entity when in fact these same symptoms are present in individuals who have many different rheumatic diseases. As will be discussed in detail below, many of these rheumatic diseases are very serious and are not amenable to treatment with the OTC antirheumatic products. Although the pain associated with some rheumatic diseases can be relieved, their serious clinical features, which if untreated often lead to progressive degeneration and debilitation, may be unaffected by these products. Also, those inflammatory rheumatic diseases that can be treated with these products often require a much higher daily dosage and more prolonged treatment than is required for the relief of pain alone.

There are no labeling claims, i.e., indications for use, for OTC antirheumatic drugs that are suitable for OTC marketed products. Labeling claims are limited to professional labeling (labeling of the products for health professionals but not for the general public). There is no suitable OTC dosage schedule nor directions for use that could be included on OTC marketed products. Each person should have the proper daily dosage adjusted on an individual basis by a physician.

Because of the widespread current OTC use of aspirin and other salicylates in treating rheumatic diseases, the Panel recommends that all OTC products containing salicylates contain the warning, "Take this product for the treatment of arthritis only under the advice and supervision of a physician". The Panel is of the opinion that such a warning is necessary to inform the consumer not to self-diagnose and self-medicate for arthritis. In addition, the Panel concludes that the nonsalicylate, acetaminophen, is not an effective OTC antirheumatic as discussed elsewhere in this document. (See part V. paragraph B.2.a. below—Acetaminophen.) Therefore, the Panel recommends that all OTC products containing acetaminophen contain the warning, "Do not take this product for the treatment of arthritis except under the advice and supervision of a physician".

In the discussion that follows, the basis for the Panel's concern for the protection of the consumer will become quite obvious.

The term rheumatism is derived from the Greek word *rheumatismos* which designated mucus (catarrh) as an evil humor that was thought to flow from the brain to the joints and other portions of the body, producing pain (Ref. 3). Rheumatic diseases includes diseases of a wide variety that involve the joints and/or para-articular structures. The rheumatic diseases are associated with pain and stiffness of the musculoskeletal system and include diseases of the connective tissue.

Arthritis, which is one of the oldest known diseases, is the general term used when the joints themselves are the major cause of the rheumatic disease. However, the disease involves much more than just aches and pains around a joint. In fact, inflamed joints may be only one manifestation of the many different diseases that can be termed arthritis. "In some of these conditions rheumatic complaints occur irregularly or constitute only a minor problem whereas in others joint disease may play an important role in the patient's illness" (Ref. 4). Other types of rheumatic diseases involve muscles, tendons, ligaments, or bursae and are referred to as rheumatism. According to the National Health Examination Survey conducted by the National Center for Health Statistics of the Department of Health, Education, and Welfare, more than 16 million people in the United States believed they had "arthritis" (Refs. 5, 6, and 7).

2. *Classification of rheumatic diseases.* In this discussion, the Panel has referred to the classification of rheumatic diseases as proposed by the Nomenclature and Classification Committee of the American Rheumatism Association and officially adopted by that society in 1963 (Ref. 4).

The common property shared by most of the diseases and syndromes is that of an involvement of the joints (chiefly the synovial joints) and/or para-articular structures. The three most common diseases in the U.S. are osteoarthritis, rheumatoid arthritis and gout. Each disease is different, with different causes and different prospects for recovery depending upon the specialized treatment used. To illustrate the wide variety of known rheumatic diseases, many of which produce similar symptoms requiring diagnosis by a physician, the Panel has included the American Rheumatism Association's classification of rheumatic diseases (Ref. 4) in the following table:

CLASSIFICATION OF THE RHEUMATIC DISEASES

I. POLYARTHRITIS OF UNKNOWN ETIOLOGY

A. Rheumatoid arthritis
B. Juvenile rheumatoid arthritis (including Still's disease)
C. Ankylosing spondylitis
D. Psoriatic arthritis
E. Reiter's syndrome
F. Others

II. "CONNECTIVE TISSUE" DISORDERS (ACQUIRED)

A. Systemic lupus erythematosus
B. Progressive systemic sclerosis (scleroderma)
C. Polymyositis and dermatomyositis
D. Necrotizing arteritis and other forms of vasculitis (polyarteritis nodosa, hyper-

sensitivity angiitis, Wegener's granulomatosis, Takayasu's (pulseless) disease, Cogan's syndrome and giant cell arteritis (including "polymyalgia rheumatica)).
E. Amyloidosis
F. Others (See also rheumatoid arthritis, I. A. above; Sjogren's syndrome, VI. G. below.).

III. RHEUMATIC FEVER

IV. DEGENERATIVE JOINT DISEASE (OSTEOARTHRITIS, OSTEOARTHROSIS)

A. Primary
B. Secondary

V. NONARTICULAR RHEUMATISM

A. Fibrositis
B. Intervertebral disk and low back syndromes
C. Myositis and myalgia
D. Tendinitis and peritendinitis (bursitis)
E. Tenosynovitis
F. Fasciitis
G. Carpal tunnel syndrome
H. Others (see also shoulder-hand syndrome, VIII. C. below)

VI. DISEASES WITH WHICH ARTHRITIS IS FREQUENTLY ASSOCIATED

A. Sarcoidosis
B. Relapsing polychondritis
C. Schönlein-Henoch purpura
D. Ulcerative colitis
E. Regional enteritis
F. Whipple's disease
G. Sjogren's syndrome
H. Familial Mediterranean fever
I. Others (See also psoriatic arthritis, I. D. above)

VII. ASSOCIATED WITH KNOWN INFECTIOUS AGENTS

A. Bacterial (gonococcus, meningococcus, pneumococcus, streptococcous, staphylococcus, salmonella, brucella, streptobacillus moniliformis (Harverhill fever), mycobacterium tuberculosis, treponema pallidum (syphilis), treponema pertenue (yaws), and others (see also rheumatic fever, III. above.)).
B. Rickettsial
C. Viral (Rubella, Mumps, Viral hepatitis, and Others)
D. Fungal
E. Parasitic

VIII. TRAUMATIC AND/OR NEUROGENIC DISORDERS

A. Traumatic arthritis (the result of direct trauma)
B. Neuropathic arthropathy (charcot joints), syphilis (tabes dorsalis), diabetes mellitus (diabetic neuropathy), syringomyelia, myelomeningocele, congenital insensitivity to pain (including familial dysautonomia) and others
C. Shoulder-hand syndrome
D. Mechanical derangement of joints
E. Others (see also degenerative joint disease, IV above; carpal tunnel syndrome, V. G. above.).

IX. ASSOCIATED WITH KNOWN OR STRONGLY SUSPECTED BIOCHEMICAL OR ENDOCRINE ABNORMALITIES

A. Gout
B. Chondrocalcinosis articularis ("pseudogout")
C. Alkaptonuria (ochronosis)
D. Hemophilia
E. Sickle cell disease and other hemoglobinopathies
F. Agammaglobulinemia (hypogammaglobulinemia)
G. Gaucher's disease
H. Hyperparathyroidism
I. Acromegaly
J. Thyroid acropachy
K. Hypothyroidism
L. Scurvy, hypovitaminosis C)
M. Hyperlipoproteinemia type II (xanthoma tuberosum and tendinosum).
N. Fabry's disease (angiokeratoma corporis diffusum or glycolipid lipidosis).
O. Hemochromatosis
P. Others (See also inherited and congenital disorders, XII. below.)

X. NEOPLASMS

A. Synovioma
B. Primary juxta-articular bone tumors
C. Metastatic malignant tumors
D. Leukemia
E. Multiple myeloma
F. Benign tumors of articular tissue
G. Others (See also hypertrophic osteoarthropathy, XIII. I. below.)

XI. ALLERGY AND DRUG REACTIONS

A. Arthritis due to specific allergens (e.g., serum sickness)
B. Arthritis due to drugs
C. Others (see also systemic lupus erythematosus, II, A. above for drug-induced lupus-like syndromes, e.g., hydralazine and procainamide syndromes; hypersensitivity angiitis, II. D. above).

XII. INHERITED AND CONGENITAL DISORDERS

A. Marfan syndrome
B. Homocystinuria
C. Ehlers-Danlos syndrome
D. Osteogenesis imperfecta
E. Pseudoxanthoma elasticum
F. Cutis laxa
G. Mucopolysaccharidoses (including Hurler's syndrome)
H. Arthrogryposis multiplex congenita
I. Hypermobility syndromes
J. Myositis (or fibrodysplasia) ossificans progressiva
K. Tumoral calcinosis
L. Werner's syndrome
M. Congenital dysplasia of the hip
N. Others (See also arthropathy associated with known biochemical or endocrine abnormalities, IX. above.)

XIII. MISCELLANEOUS DISORDERS

A. Pigmented vidonodular synovitis and tenosynovitis
B. Behcet's syndrome
C. Erythema nodosum
D. Relapsing panniculitis (Weber-Christian disease)
E. Avascular necrosis of bone
F. Juvenile osteochondritis
G. Osteochondritis dissecans
H. Erythema multiforme (Stevens-Johnson syndrome)
I. Hypertrophic osteoarthropathy
J. Multicentric reticulohistiocytosis
K. Disseminated lipogranulomatosis (Farber's disease)
L. Familial lipochrome pigmentary arthritis
M. Tietze's syndrome
N. Thrombotic thrombocytopenic purpura
O. Others

3. *Incidence of rheumatic diseases.* Many different population studies have been conducted to determine the incidence of rheumatic diseases. However, as pointed out by Hollander (Ref. 3):

> Large scale surveys are inaccurate because they depend on answers to set questions, permitting guesswork by the people surveyed. Smaller population samplings, with strict diagnostic criteria and medical examination, are far more accurate but represent such a local segment that doubt is thrown on the projection of the figures to cover the general population. In spite of the handicaps, the realization that rheumatic diseases form a tremendous segment of chronic disability all over the world has become more widespread in recent years.

The impact of these diseases in the U.S. is discussed elsewhere in this document. (See part V. paragraph A.5. below—Economic and social impact of rheumatic diseases in the U.S.)

On the basis of a U.S. survey (Ref. 7), Hollander (Ref. 3) further states that:

> From the National Health Survey figures it appears that 26 percent of those having rheumatic disease were definitely limited in their activities, and 10 percent were grossly disabled. This means that more than a million persons are rendered unemployable by arthritis and rheumatism.
>
> About 27 million work days are lost annually because of arthritis. About 1 in every 5 chronically housebound invalids had arthritis. Arthritis and rheumatism were the second greatest cause of chronic limitation of major activity with a relative incidence of 16 percent. Heart disease, with an incidence of 17 percent, was the only disease group exceeding arthritis.
>
> Although arthritis cripples a tremendous number of persons each year, it kills relatively few. There is no other group of diseases which causes so much suffering by so many for so long. Because of the tendency to cripple without killing, arthritis and rheumatism belong at the head of the list of chronic diseases from the standpoint of social and economic importance.

The Panel finds that the insidiousness of this group of diseases makes it all the more important that extraneous factors be eliminated so as not to result in delayed diagnosis or treatment. Factors which allude to arthritis as a "minor disease", such as the misrepresentation that the alleviation of symptoms, e.g., joint and muscle pain or stiffness with "extra strength aspirin" or other salicylates will control the disease, are clearly misleading.

According to the Arthritis Foundation (Ref. 8), the incidence of the most common rheumatic diseases in the United States during 1974 (the latest figures available) is as follows:

Incidence of rheumatic diseases in the United States during 1974

Rheumatic disease:	*Number of persons (millions)*
Osteoarthritis	12
Rheumatoid arthritis	5
Gout	1
Systemic lupus erythematosus	.4 to 0.5
Juvenile rheumatoid arthritis	0.25

Since the above listed diseases are the most prevalent, the Panel has included a more detailed description of their clinical features and the recommended treatment program below. As will be evident from the discussion, adequate treatment requires the advice and supervision of a physician.

4. *Comments on the more common rheumatic diseases in the U.S.* a. *Osteoarthritis.*—(1) *Clinical features*—Osteoarthritis (degenerative joint disease) is a very common disease especially among elderly individuals. It probably begins as degeneration of joint cartilage in all people by the end of their second decade of life. It is rarely accompanied by evidence of inflammation in and around the joints, yet pain and swelling of the joint are present due to destruction of

cartilage and misalignment of the joint. This condition which is very common among elderly individuals is an ubiquitous condition which increases in frequency with aging.

The joints most frequently involved are those of the distal interphalangeal joint (joint near fingernail), first carpometacarpal joint (joint at base of thumb), hips and knees. Degenerative disease of the hip alone is estimated to be present in at least 175,000 Americans age 65 or older (Ref. 9). The lower spine and spine of the neck may also be involved frequently.

Twenty-three percent of those persons having osteoarthritis have moderate or severe disease (Ref. 10).

Clinical features of the disease (Ref. 11) include pain, crunching sounds (crepitus) with crunching feeling in the joint, atrophy of the surrounding muscles, limitation of motion, malalignment of the extremity and changes in the shape of the joint which are detectable on physical examination. Tenderness to palpation may be observed, but signs of inflammation are relatively uncommon, except for fluid in the joint which may be present after episodes of trauma following overly vigorous usage of the involved joint.

The *Primer on the Rheumatic Diseases* has described the clinical features as follows (Ref. 11):

> Special forms of degenerative disease involve particular joints in a characteristic manner.
>
> (Bony nodes, termed Heberden's nodes, are common.) These consist of a deforming bony protuberance at the margins and on the dorsal surface of the distal interphalangeal joints (joint next to the nail) of the fingers, and are often associated with flexion and angulation of the distal phalanx. Local pain and tenderness with some warmth may be present early in the course of their development. Heberden's nodes are more frequent in women, tend to occur in families, and are often associated with degenerative changes in other joints, although the association is not invariable. Involvement of the proximal interphalangeal finger joints (Bouchard's nodes) is not at all uncommon in osteoarthritis, and may give rise to confusion with rheumatoid arthritis.
>
> Degenerative disease of the hip, although less common than knee disease, is the most disabling form of osteoarthritis * * *. Pain on motion or weightbearing is the main complaint, and this generally becomes progressively more severe and is often referred to the groin or to the medial (inner) side of the knee. Later, the pain may become continuous, and be especially difficult to bear at night. On physicial examination there is a global loss of range of motion of the involved hip * * *.
>
> The changes (in the knee) may involve the softening of the posterior surface of the patella (knee cap) (chondromalacia patellae) as well as the weight-bearing surfaces of the femoral and tibial condyles. The former is often observed in young persons and is considered by many to be related to trauma. Degenerative disease of the knees is commonly observed in older women and is associated with loss of motion, crepitus, and flexion deformity.
>
> Degenerative disease of the spine affects two distinct articular systems: The apophyseal articulations in the vertebral arch (and, in the case of the cervical vertebrae, between the vertebral bodies) which are diarthrodial joints; and the intervertebral articulations which constitute an amphiarthrosis known as a symphysis.

Symptoms of osteoarthritis of the spine include localized pain and stiffness and radicular pain (nerve root pain). Spontaneous remissions and exacerbations occur. Spasm of back muscles is common.

The prognosis of osteoarthritis is extremely variable. "Involvement of the distal interphalangeal joints of the hands may be associated with a moderate amount of pain but usually leads to little limitation of the essential function unless fine finger motion is occupationally required" (Ref. 12). Involvement of certain joints may be associated with moderate to severe pain, stiffness and limitation of motion localized to that particular area. In this regard, osteoarthritis is not a benign disease. Involvement of the hip or knee may lead to marked disability as the disease progresses. In a study of osteoarthritis of the hip, the average time from onset of pain to almost complete loss of motion in 400 patients reviewed was 8 years with a range of 18 months to 23 years (Ref. 12).

As pointed out by Dr. Roland W. Moskowitz in his chapter on osteoarthritis in Hollander and McCarty's textbook on *Arthritis and Allied Conditions*, 8th Ed. (Ref. 12), "Active treatment may retard disease progression and is of further value in protecting contralateral joints which may be exposed to increased stress." Thus, it is apparent that such active treatment as described below is denied to patients who self-medicate for a long period of time for the relatively minor symptoms, such as pain and stiffness, without consulting a physician and, therefore, are subject to disease progression which may be prevented by proper medical management.

(2) *Treatment.* The management of osteoarthritis is dependent on the anatomic patterns involved and the degree of joint deformity. There is no specific remedy, but disability can be minimized. The principal objectives of treatment are the relief of pain, restoration of joint function, and the prevention of avoidable disability and progression of the disease. Diagnosis by a physician and continued medical supervision in preventing the development of unnecessary disability is therefore essential. Since the degree of disability and the extent of joint involvement varies among patients, the treatment must be individualized by a physician.

Orthopedic surgical management is often effective in severe cases. This is the only rheumatic disease affecting a large portion of the population in which aspirin is used as an analgesic rather than as an anti-inflammatory agent. The proper medical management includes not only analgesic therapy but such modalities as physical therapy, orthopedic devices, weight reduction if necessary and possible orthopedic reconstructive surgery which may be extremely effective in severe hip disease. Many patients accept pain as inevitable. Many individuals, who self-medicate for degenerative disease of the hip, could be totally relieved of the pain and disability they endure, and in addition, prevent degenerative changes if they went to a physician for treatment of their arthritis.

(i) *Drugs.* No medication has been shown to retard the development or progression of degenerative joint disease (Ref. 13). Pharmacologic agents play a relatively minor role in the management of osteoarthritis. As has been noted in the *Primer on the Rheumatic Diseases* (Ref. 14):

> It remains to be determined whether drug therapy can slow the development or progression of early degenerative joint disease, although there are some interesting preliminary findings from experimental studies.
>
> Aspirin, in moderate dosage (0.6 gm 3 to 5 times a day) is helpful in conjunction with rest and physical measures, especially when inflammation due to traumatic synovitis is present. Agents with greater risk of toxicity are rarely justified, particularly since they would have to be used on a long-term basis. Since osteoarthritis is generally a noninflammatory disease, the use of an anti-inflammatory agent, such as aspirin would seldom be justified except for use in the relief of pain. Individuals with joint pain who self-medicate with analgesics to relieve their pain may delay consulting a physician and thus unwittingly contribute to the progressive degeneration of their joint disease.

The *Primer on the Rheumatic Diseases* (Ref. 14) also notes that:

> Corticosteroids should not be used with the exception of intra-articular injections which may provide relief of symptoms for several weeks and permit graded exercises to be started with less discomfort. Repeated injections of corticosteroids should be avoided, however, as the course of the degenerative process is not changed and may even be accelerated, since these agents have been found to inhibit the synthesis of proteinpolysaccharide by articular cartilage.

It has been stated by Christian (Ref. 13):

> It remains to be determined whether drug therapy can slow the development of progression of early degenerative joint disease, although there are some interesting preliminary findings from experimental studies. Salicylates seem to prevent the development of degenerative changes in scarified cartilage in rabbits and there is an extract of calf costal cartilage which has been shown to stimulate cartilage proteinpolysaccharide synthesis.

(ii) *Physical measures and surgical management.* The use of drugs is only one method of treatment. Osteoarthritis is treated by several methods in an attempt to relieve pain, restore joint function and prevent avoidable disability or progression of the disease. The Panel refers to the statement in the *Primer on the Rheumatic Diseases* (Ref. 14), "It is helpful to emphasize the value of continued medical supervision in preventing the development of unnecessary disability." Hence, the disability that results from the disease can be minimized by a physical therapy program and by orthopedic surgical treatment. The two general goals in the design of a physical medicine program for degenerative joint disease are minimizing the forces of work and weightbearing that apply to af-

fect joints, and maintenance of normal joint alignment and motion.

Christian (Ref. 13) recommends that:

General physical measures include daily periods of rest and support during recumbency, particularly in spondylosis (patients with spine involvement) in which case a firm mattress with underlying board is needed. When weight-bearing joints are affected, local support is often of great value, including the use of canes, crutches, or other mechanical devices. Avoidance of unnecessary walking and stair-climbing, wearing of proper shoes, restoration of arch, or building up of one side of a shoe to shift the line of weight-bearing often prove helpful. Correction of abnormal posture is desirable, although this is more effective before advanced disease has developed. Weight reduction is advised when indicated, although not often accomplished. Local measures include heat and specific exercises designed to avoid or correct muscle atrophy, since weakness aggravates joint instability and contributes to disability. Traction is useful when there is muscle spasm, particularly for hip or cervical vertebral disease. Patients with the latter are often relieved by wearing a cervical collar.

It is clear to the Panel that these measures will not be undertaken unless the patient is under medical care. A self-medicating patient will obviously not receive adequate treatment for his/her disease even though their pain may be relieved by OTC doses of analgesics.

As has been described in the *Primer on the Rheumatic Diseases* (Ref. 14):

In adults, surgical treatment is often necessary for the relief of persistent pain and the correction of serious deformity. Obviously, many considerations influence the selection of patients and the type of operative procedure. It is important to note that the patient must be able to cooperate physically and emotionally with the necessary postoperative rehabilitation if a good end result is to be achieved. Surgical treatment of osteoarthritic joints includes (1) debridement; (2) arthrodesis (joint fusion); (3) arthroplasty (the formation of a prosthetic articulating surface); (4) osteotomy (a general term for section of bone to alter weight-bearing surfaces); and (5) total joint replacement. Specific procedures usually have predictable end-results with respect to pain relief, mobility, stability, and deformity, and the procedure is selected with this knowledge in mind. Thus, intertrochanteric osteotomy for osteoarthritis of the hip is indicated in the case of early disease when relatively good motion (at least 60° to 70° of flexion) is present. With replacement arthroplasty using metallic prosthesis, or with the recently developed and highly encouraging total hip replacement, pain relief is often obtained with good stability and mobility. Surgery for knee disease is perhaps less well defined, but there are patients who benefit markedly from high tibial osteotomy, patellectomy and debridement, interposition arthroplasty, or arthrodesis. Rarely does spondylosis of the thoracic or lumbar spine require surgical intervention. Occasionally, however, resection of cervical osteophytic spurs or cervical arthrodesis is necessary to relieve impingement on nerve roots or the spinal cord.

(3) *Summary and conclusions.* Osteoarthritis is an extremely common rheumatic disease affecting more than 6 percent of the U.S. population. Hip disease alone affects 175,000 Americans aged 64 or older. The Panel concludes that self-medication with analgesics by these patients is undesirable because they will thus deny themselves proper medical management. Self-medicating patients will not receive proper treatment for their disease because they will not receive treatment such as physical therapy and orthopedic surgery. Such management by physicians may arrest further disease progression whereas patients who self-medicate, only relieve their joint pain temporarily, while allowing their diseased joint to progressively degenerate.

b. *Rheumatoid arthritis.* (1) *Clinical features.*—The second most common rheumatic disease is rheumatoid arthritis which affects 3 percent of the female population and 1 percent of the male population (Ref. 15). The disease occurs in both adults and juveniles. Juvenile rheumatoid arthritis begins before the age of 16 and can occur as early as 6 weeks of age. The disease is characterized by inflammation of the synovial joints (moveable joints which possess a cavity and are lined by a synovium or joint lining which is a specialized connective tissue). Inflammation of the synovium results in pain, swelling, tenderness and may lead to limitation of the motion of the joint. The cartilage of the joint may become eroded by the inflamed proliferating synovium and this process may eventually lead to severe destruction of the joint.

The clinical features of the disease are described in the *Primer on the Rheumatic Diseases* (Ref. 16) as follows:

Rheumatoid arthritis is defined clinically by joint involvement but this is often preceded by constitutional symptoms alone, and, in children particularly, by "unexplained" high fever. In the majority of cases the onset is insidious, with aching and stiffness often poorly localized to joints. This followed by the gradual appearance of frank articular inflammation in the form of pain, swelling, redness, warmth, and tenderness. Stiffness of the joints, particularly noticeable on awakening in the morning, is a regular and often prominent early complaint.

The characteristic morning stiffness of patients with rheumatoid arthritis is very common in these patients. The Panel concludes that advertisements which promise relief from morning stiffness may give these consumers the belief that the OTC dosage of aspirin is the recommended therapy for their symptoms. The Panel is concerned that both the labeling and mass media advertising (through television and magazines), primarily directed toward women and the elderly, give the consumer the misleading impression that aspirin in the OTC dose is the therapy of choice for individuals with rheumatoid arthritis. Consumers are deluged with such advertisements daily on a massive scale, leading to a general misconception in the minds of many patients with rheumatoid arthritis that aspirin in OTC doses is as effective for rheumatoid arthritis, as it is for headaches and minor pains, and that this is a disease which is easily managed by an OTC product without medical supervision. As will be discussed below, the Panel's recommended OTC analgesic dosage of aspirin provides inadequate management for rheumatoid arthritis. (See part V. B.1.a. below—Aspirin.)

The Arthritis Foundation in its *Primer on the Rheumatic Diseases* (Ref. 16) gives the following additional description of the clinical features of rheumatoid arthritis:

In adults joint symptoms usually originate in the hands and feet. Rheumatoid arthritis also attacks the large peripheral joints, including the knees, ankles, wrists, and elbows; in some cases virtually all the peripheral junctures may be involved, including the jaw, the spine (intervertebral facetal joints), and even such fine structures as the cricoarytenoid joints of the larynx.

Tenosynovitis (inflammation of the tendon sheath) is common, most frequently affecting the extensor and flexor tendon sheaths about the wrists. Inflammation of the latter structures is often associated with the development of the carpal tunnel syndrome (median neuropathy).

Although often spotty in the initial distribution of affected joints, rheumatoid arthritis tends to be bilaterally symmetrical. A monoarticular onset, usually one knee, is noted in some instances; there may be a history of prior trauma to the joint. In these patients, particular attention must be given to the differential diagnosis, which includes especially infectious arthritis and gout.

Thus, it is important for the patient with pain and some swelling in one knee to see a physician rather than to self-medicate. Although a delay of 10 days may not lead to serious consequences in a patient with rheumatoid arthritis, this patient may actually have infectious arthritis which needs immediate therapy with antibiotics to prevent spread of the infection and destruction of the cartilage (which can occur during the recommended 10 days of self-medication for OTC indications). Changes observable by x-ray can occur 3 weeks after the onset of infectious arthritis consisting of loss of cartilage and erosion of bone (Ref. 17). Since these changes can be seen by x-ray within only 3 weeks, it is quite likely that subtle changes occur within the first week of the disease.

As has also been stated in the *Primer on the Rheumatic Diseases* (Ref. 16):

The period from the onset of symptoms to the time the patient consults a physician is highly variable. When there are only mild constitutional complaints and stiffness limited to the hands, it is understandable why a patient may not seek medical advice; indeed she may dose herself with aspirin, or the symptoms may disappear spontaneously Swelling and pain of the larger joints, however, are likely to lead to prompt medical attention. Evaluation by the physician in the early stages of the disease is important in order to exclude other diagnostic possibilities, to begin a relationship with the patient that will be especially helpful in management in the event of prolonged active disease, and to prescribe appropriate conservative measures at the stage in which improvement and even remission is likely to occur in the majority of cases.

The Panel concurs with the above statement regarding the need for evaluation by a physician in the early stages of the disease. Since self-medicating patients may, in some instances, experience relief of pain, they may tend to con-

tinue to self-medicate intermittently for a prolonged time at intervals for 10-day periods as stated in the OTC labeling. In the early stages of the disease, the OTC dosage may give relief of pain for the period of time (10 days) it is taken. The patient will be relieved of pain but will not be taking aspirin at the dosage required for anti-inflammatory action. During this period of intermittent self-medication, the patient will not seek out a physician because the pain will have been relieved. The Panel is also aware that at least three-quarters of the patients with rheumatoid arthritis who have the symptoms of the disease for less than 1 year will improve for a time, and that 15 to 20 percent may show a complete remission (Ref. 18). Such remission would only tend to reinforce the belief by the consumer that aspirin and the salicylates are completely effective for this disease. Clearly, it is the Panel's conclusion that the patient should be seen by a physician so that an adequate dosage of aspirin or other salicylate can be recommended along with appropriate physical therapy or other measures discussed above. The Panel concurs with the statement "Evaluation by the physician in the early stages of the disease is important" * * * (Ref. 16) and considers that self-medication is to be avoided even at the early stages of the disease.

The patient should not self-medicate because an adequate physical examination and history of the disease should be made by a physician. In addition, the physician will perform certain laboratory tests at the time of the first visit in order to establish the severity of the disease and to rule out other diseases.

The patient is clearly unable to perform a physical examination on himself or herself. The physician will search for nodules near the elbow which are characteristic of rheumatoid arthritis. The physician will perform a thorough evaluation of all joints for swelling, heat, synovial thickening, deformities, and note the range of motion of all joints. All the findings will be recorded for future reference, and laboratory tests may be needed. Mild anemia and an elevated erythrocyte sedimentation rate are often observed with active rheumatoid arthritis. A number of tests to rule out systemic lupus erythematosus may be employed since this disease not infrequently has an onset similar to rheumatoid arthritis. If fluid is present within the knee or another single large joint, analysis of the fluid may be done to rule out infection. The physician inserts a needle into the knee and withdraws fluid which can be examined for crystals typical of gouty arthritis and a culture can be obtained to determine whether or not the swollen knee is due to an infection of the joint.

Clearly, the patient with a single swollen knee cannot determine the cause of the swelling. The most common diseases are those discussed above, i.e., osteoarthritis and rheumatoid arthritis. These two conditions cannot be distinguished by the patient. Since the treatment of the two diseases, the prognosis, and the management are different, it is to the patient's advantage to seek medical advice rather than to self-medicate. Since infectious arthritis is frequently present as a single swollen knee, the patient may be harmed by self-medicating for even 10 days.

The Panel concurs with the following statements made in the *Primer on the Rheumatic Diseases* (Ref. 18):

> Clearly, the major concern on the part of the patient as well as the physician is not for a mild arthritis that lasts a few weeks or months and leaves no impairment. Rather, the difficult problem is recurrent or sustained disease, in which, over the course of a few to many years, there is an increasingly serious and permanent disturbance in joint function. At sites of involvement one finds swollen, boggy joints that are the result of intra-articular effusion, edema of periarticular structures, and particularly the overgrowth of the hyperplastic synovial membrane and variable degrees of periarticular fibrosis.
>
> The joint deformities which develop in rheumatoid arthritis are thought to originate in muscle spasm, the flexors maintaining involuntary contraction with accompanying extensor relaxation, such as occurs reflexly with injury of the extremity. Inflammation and subsequent fibrosis in the capsule, ligaments, and musculotendinous apparatus lead to fixed deformity. Subluxation, or the slipping of one articular (joint) surface past the other, is usually preceded by erosion of cartilage and bone and destruction of supporting soft tissues, particularly ligaments and joint capsule. Among the most characteristic deformities in the hand are an ulnar drift or deviation of the fingers, subluxation (dislocation) of the metacarpophalangeal joints, and enlargement of the proximal interphalangeal joints. More disabling is the "boutonniere" deformity in which the flexed proximal interphalangeal joint is forced through the extensor hood like a button through the buttonhole.
>
> Any diarthrodial joint (moveable joint) may be affected in rheumatoid arthritis. Rheumatoid (and other) effusions of the knee may be complicated by the development of large popliteal cysts, (Baker's cyst) that often extend into the calf. . . . Serious, indeed life-threatening, complications may occur from involvement of the atlanto-axial (one of the neck) joints leading to subluxation and spinal cord compression with sensory and/or pyramidal tract signs and disease of the cricoarytenoid joint of the larynx, which, when fixed with the vocal cords abducted, can cause laryngeal obstruction.

The joints most frequently involved are those at the fingers, knees, wrists, feet, ankles, shoulders, elbows and hips although any joint may be affected. The course and prognosis depend on several factors. Laboratory tests are often required.

The *Primer on the Rheumatic Diseases* also makes the following observations (Ref. 19):

> The combination of typical joint deformities, subcutaneous nodules, and high titers of rheumatoid factor is diagnostic of rheumatoid arthritis and constitutes classic disease. After observing a patient with active rheumatoid arthritis for several months, the physician (can) evaluate the prognosis and discuss this cautiously yet realistically with the patient . . . A poor prognosis, in respect to joint function includes persistent disease of more than one year's duration, age below 30 when the patient is first seen by a physician, sustained disease, and the presence of subcutaneous nodules and high titers of rheumatoid factor.

With regard to the long-term outlook for patients followed for periods of many years, based on the course of cases seen in various arthritis clinics, the *Primer on the Rheumatic Diseases* notes that about 50 percent of the patients are in the "stationary" or "improved" categories after 10 years (Ref. 19).

It also goes to note that:

> Without an improvement by this time, there is little likelihood that one will occur, and thereafter more patients begin to appear in the "worse" category. Nevertheless, it should be noted that in observations extending for 10 to 15 years, 50 percent to 70 percent of the patients remained capable of full-time employment and that after 15 to 20 years those completely incapacitated constituted only about 10 percent of the group.

(2) *Treatment.* In planning a treatment program for the patient with rheumatoid arthritis the *Primer on the Rheumatic Diseases* states that the physician should be guided by the following factors (Ref. 20):

> (1) the status of joint function, particularly range of motion, with respect to the apparent duration of the disease; (2) degree of disease activity, from slight, with mild complaints confined to a few joints, to most severe, with extra-articular manifestations, especially vasculitis; (3) the age, sex, occupation, and family responsibilities of the patient, and her or his response to the disease; (4) the results of previous treatment. Assessment of these variables guide the physician in deciding on the most appropriate course of action, in being conservative or more vigorous, and in considering the advisability of surgical intervention. In judging the stage of disease and the degree of the patient's disability in estimating and reporting response to treatment, it is helpful to utilize criteria for the classification of progression of rheumatic arthritis and of functional capacity developed for these purposes by a committee of the American Rheumatism Association.

(See part V, paragraph A.2. above—Classification of rheumatic diseases.)

The Panel believes that conservative measures should be used at the outset of treatment and continued as long as indicated. In addition, the Panel concurs with the following statement made in the *Primer on the Rheumatic Diseases* (Ref. 19):

> When discussing the nature of the disease with the patient who has had arthritis of a few weeks' to months' duration the prudent physician avoids promises of quick relief or cures, and usually refrains from prescribing any antiarthritis medication except aspirin. This is a strong opinion, and clearly a personal one, but appears to be the prevailing view of those experienced physicians who have treated patients with this disorder for many years. There is no cure for rheumatoid arthritis, there is no certain way to arrest the disease or produce a remission, and there is no evidence that the more potent drugs can relieve symptoms fully and regularly. On the other hand, there is ample evidence that if such agents temporarily ameliorate joint complaints, severe rebound of inflammation may occur when they are withdrawn.

The Panel has heard expert testimony of physicians brought to the Panel by the drug industry (Ref. 20). It was stated

by industry spokesmen that arthritic patients will be better off self-medicating than going to a physician because the physician will treat them with corticosteroids. However, the Panel concurs with the statement in the *Primer on the Rheumatic Diseases*, prepared by leading rheumatologists of the American Rheumatic Association, that "the prudent physician avoids promises of quick relief or cures, and usually refrains from prescribing any antiarthritis medication except aspirin" (Ref. 18). The use of corticosteroids in the treatment of rheumatic diseases is limited to specific indications. The hazards of the indiscriminate use of corticosteroids in the treatment of arthritis has been well documented over the past 15 years.

Proper therapy includes the use of aspirin in adequate doses to control the inflammation of the synovial membrane. As noted in the *Primer on the Rheumatic Disease* (Ref. 21), "Aspirin is the mainstay of therapy." In addition, the Panel concurs with the following statement (Ref. 21):

> Adults should take a total of at least 3.6 gm of aspirin per day, in divided doses after each meal and before bedtime; often 4.8 gm per day or more will be tolerated without gastrointestinal symptoms, loss of auditory acuity, or tinnitus. With active disease aspirin should be taken on a regular daily basis rather than at will. There is considerable variation from person to person in the plasma level of salicylate produced by a constant quantity of aspirin so that it is misleading to think in terms of a "standard" dose. If need be, each patient should be given increasing amounts of aspirin to tolerance (tinnitus). In general, younger individuals show a much higher tolerance to the side effects of aspirin than do the elderly.

In order to achieve anti-inflammatory efficacy, a higher daily dose and a much more prolonged administration is required than that which is required for analgesic efficacy. Since the dose and duration of therapy should be regulated by a physician, and in addition, because the dose is higher and the duration of medication is longer than that for analgesic use, the side effects are more significant. However, it should be noted that one side effect of overdosage, tinnitus (ringing of the ears), is used by physicians in the management of patients with rheumatoid arthritis in order to provide the patient with the necessary anti-inflammatory levels of salicylate. This unique safety feature of salicylates, particularly aspirin, was discussed in more detail above. (See part III, paragraph B.1.a. (2) above—Safety.)

Clearly, OTC dosages of 12 tablets daily are rarely capable of achieving anti-inflammatory levels of salicylates. Thus, it is unwise for patients to self-medicate with aspirin for rheumatoid arthritis since not all individuals will achieve adequate anti-inflammatory levels of serum salicylate when following the OTC dosages. Since the majority of such individuals will achieve analgesic levels, their pain will be relieved but at the same time the inflammation in their joints will not be suppressed. The Panel concludes that intermittent self-medication, for intermittent periods of 10 days, over the course of a few months using different OTC preparations (especially trying out those labeled with the word "Arthritis") will result in continued disease activity. The Panel emphasizes that this may lead to destruction of the cartilage by the inflamed synovium which could have been suppressed if the patient had received earlier medical therapy by a physician, as described above, including adequate individualized amounts of aspirin.

In addition to using aspirin, the physician has additional measures that the patients will follow. Clearly, these will not be followed if the patient is self-medicating. For example, periods of rest during the day are helpful. Complete inactivity should be avoided, however, unless severe disease exists with markedly painful swollen joints. Lightweight splints or shells may be used. The majority of patients will respond with improvement to these conservative measures. In the case of those patients who continue to have persistent complaints, the physician may recommend drugs, such as chloroquine or hydroxychloroquine. Gold salts may be recommended.

The *Primer on the Rheumatic Diseases* (Ref. 21) notes that:

> At all stages of the disease * * * physical measures must be considered in the comprehensive program of management. Local application of heat by means of moist compresses or infrared irradiation, followed by directed exercises, is often helpful in relieving joint pain and muscle spasm. These exercises are designed to preserve the range of motion of joints and to strengthen muscles.
>
> The cooperative efforts of professional personnel trained in rheumatology, orthopedic surgery, and rehabilitation medicine have proven to be of great value in providing a truly comprehensive and maximally effective approach to the care of the patient with rheumatoid arthritis. Many other health care specialists, including physiotherapists, occupational therapists, and social service workers, play an important role. Joint inflammation may persist with incapacitating symptoms despite careful application of the measures described above. When this occurs, hospitalization may be warranted so that therapy can be continued with maximum intensity.

At this stage in the disease, some physicians will use corticosteroids at a low dose in addition to aspirin. Immunosuppressive therapy is reserved for patients with progressive deformities, disease activity and incapacity. Various surgical procedures have also been used for correcting or compensating for joint damage.

It is clear that the management of patients with rheumatoid arthritis is a complicated therapeutic situation which must include the family physician or internist. These physicians may request consultation in the complicated patient with a rheumatologist and/or orthopedic surgeon. This is clearly not a disease which can be controlled by self-medication.

(3) *Summary and conclusions.* Rheumatoid arthritis is a chronic disease, in which inflammation of the moveable joints is frequently combined with a variety of manifestations (Ref. 22). As an inflammatory disease which is accompanied by pain, the use of aspirin or other salicylates at very high dosage levels as analgesics and as anti-inflammatory agents is the mainstay of therapy. The treatment of rheumatoid arthritis requires the administration of aspirin or other salicylates on a regular daily basis at high dosage levels that will achieve an anti-inflammatory therapeutic effect. Such daily dosages are higher and require more prolonged use than is needed for analgesic effectiveness. Individuals with inflamed joints who self-medicate with aspirin or other salicylates to relieve the pain without consulting a physician will probably self-administer OTC daily dosages which will achieve analgesia but will not produce an anti-inflammatory effect. Such individuals will suffer continuous deterioration of their inflamed joint condition unless they consult a physician for proper diagnosis and treatment. The daily dosage of aspirin or other salicylates needed to reach an anti-inflammatory effect may vary between patients but is frequently far above the OTC analgesic dosage level. Only a physician can individualize the salicylate dosages needed for anti-inflammatory effectiveness.

c. *Gout.* (1) *Clinical features.* Another common condition is a rheumatic disease associated with a biochemical abnormality, i.e., gouty arthritis. Acute gouty arthritis is more prevalent among males (Ref. 23).

The *Primer on the Rheumatic Diseases* (Ref. 24) has described gout and its clinical features as follows:

> Gout is a disease of ancient lineage which is characterized by recurrent episodes of violent arthritis associated with the presence of monosodium urate monohydrate crystals in the synovial fluid (fluid in the joint space), and in many cases, the eventual appearance of gross uratic deposits called tophi (deposits of uric acid crystals) in and about the joints, in the kidneys and in certain subcutaneous sites. Gouty arthritis a complication of prolonged hyperuricemia (high blood uric acid levels), the origin of which has been found to be markedly diverse. Hyperuricemia is the result of a heritable error of metabolism leading to overproduction and/or retention of uric acid due to abnormalities in purine biosynthesis and/or renal excretion of uric acid. Acute gout is a type of arthritis in which the onset of joint inflammation is very rapid, and, typically, maximal pain and swelling are reached in several hours. The affected joint tends to be exquisitely painful and tender, and there is generally considerable periarticular swelling and erythemia. This feature together with the low-grade fever and leukocytosis which often accompany the attack frequently give rise to the mistaken impression of cellulitis or thrombophlebitis.
>
> In the United States uric acid stones (calculi) represent about 10 percent of all urinary calculi. Such stones occur in approximately 15 to 20 percent of all patients with gout. Patients with gout have a higher frequency of arterial hypertension (high blood pressure) and kidney malfunction than do nongouty individuals and are often found to have nephrosclerosis. Pyelonephritis associated with urate deposits in the medulla of the kidney and obstruction by stone may contribute to the renal disease.

Since the patient with joint inflammation due to gout cannot self-diagnose and self-medicate, the diagnosis and

treatment of gouty arthritis must clearly be carried out by a physician.

(2) *Treatment.* Treatment of this form of arthritis is based firstly on an accurate diagnosis. Once the physician has made the diagnosis, treatment is aimed at 1) immediate control of the acute joint inflammation and 2) prevention of future attacks and the long term reduction in hyperuricemia so as to prevent formation of uratic deposits and promote resolution of those tophi already present (Refs. 24 and 25). With the medications currently available it is possible to achieve both of these objectives and to attain normal levels of uric acid in the blood in the vast majority of gouty subjects. The maintenance of normal serum uric acid levels and prevention of tophaceous gout require long treatment which is seldom successful unless the patient is well informed concerning the nature of this disease (Ref. 24).

Several drugs are used to treat gout, some of which lower the amount of uric acid in the blood. Dietary management is also important in helping to reduce the body burden of uric acid. Especially to be avoided are foods high in purines. Surgery has been used in the management of gout. Surgical excision is indicated for large bulky tophi, particularly so, if there is external drainage, infection or interference with joint function. Orthopedic surgery and other procedures may be helpful in selected cases of severe or crippling gouty arthritis.

The objectives of treatment cannot be met by the use of any of the OTC analgesics. Aspirin given in amounts of 3 g or more daily exerts a uricosuric effect (increased amount of uric acid excretion into the urine). The *Primer on the Rheumatic Diseases* notes that "Since uricosuric therapy must be continued indefinitely, however, and since the frequency of toxic reaction to the large doses of aspirin required for effective uricosuria is high, there is little indication today for the use of aspirin to control serum urate levels" (Ref. 24). Probenecid and sulfinpyrazone are prescribed for many patients with gout. It should also be made clear that smaller quantities of aspirin counteract the uricosuric effects of the agents sulfinpyrazone and probenecid and, hence, should be avoided by patients taking these drugs (Ref. 24). In addition, small doses of aspirin may lead to the inhibition of uric acid excretion resulting in elevation of serum urate levels which may bring on an attack of gout (Ref. 24).

The drugs that will effectively control acute gouty arthritis are prescription drugs. They can only be obtained with a physician's prescription. It is therefore imperative that individuals with joint inflammation that may be due to gout consult a physician for diagnosis and treatment.

(3) *Summary and conclusions.* If the patient self-medicates with OTC analgesics for painful acute attacks, which would subside within a few days without any treatment at all, he will not have seen a physician and therefore no diagnosis will have been made. With increasing numbers of attacks over the years, serious complications will arise unless proper medical management is received which is directed at lowering the serum uric acid levels. Prior to the advent of the uricosuric agents, 50 to 60 percent of patients with gouty arthritis developed visible tophi and permanent joint damage (Refs. 24 and 26). The development of tophi is correlated with the height of the serum uric acid concentration. These patients, in addition to developing severe joint destruction, may also develop renal disease due to the deposition of urate in the kidney. Renal failure is the eventual cause of death in from 22 to 25 percent of chronic gouty subjects who have not received proper medical management to reduce their uric acid levels (Refs. 27 and 28).

The Panel concludes that self-medication with OTC analgesics, such as aspirin, by individuals with joint inflammation that may be due to gouty arthritis, to alleviate pain without consulting a physician is hazardous. It delays proper diagnosis and treatment which may lead to serious complications.

d. *Arthritis associated with known infectious agents.* Arthritis may be associated with a known infectious agent. The following bacterial agents may produce arthritis: Gonococcus (gonnorhea), meningococcus, pneumococcus, *Streptococcus, Staphylococcus, Salmonella, Brucella, Streptobacillus moniliformis, Mycobacterium tuberculosis, Treponema pallidum* (syphilis), *Treponema pertenue* (yaws) and others. Rickettsial agents may also produce arthritis. Viruses such as rubella, mumps, viral hepatitis agent and others may cause arthritis. Occasionally, arthritis due to fungal and parasitic agents may occur (Ref. 29). Bacterial arthritis is caused by the invasion of the synovial membrane by living microorganisms. Infectious arthritis may present minimal signs of inflammation and need not be confined to a single joint. Between 75 and 85 percent of gonococcal infections involve two or more joints (Refs. 30 and 31).

Bacterial arthritis may cause pain in the joint which is perceived by the individual as "pain of arthritis." The individual who self-medicates for this "pain of arthritis" with aspirin may delay proper specific antibiotic therapy which would stop the arthritis and control spread of the infection to other parts of the body. For example, gonococcal arthritis may occur in a patient with gonorrhea and is a frequently occurring cause of infectious arthritis. The Center for Disease Control states that the total number of cases of gonorrhea reported to health departments in 1975 was 938,778, an increase of 7.4 percent over the number reported in 1974. When underreporting and underdiagnosis of cases are taken into consideration, the true incidence of gonorrhea is estimated at 2.6 million cases annually. From 1964 to 1973, gonorrhea cases increased 179 percent. (Ref. 31). Holmes reported that approximately 1 to 3 percent of gonorrhea patients develop arthritis (Ref. 32). The Panel therefore estimates the incidence of gonococcal arthritis in 1975 to be from 25,000 to 75,000. Since the incidence of gonorrhea is steadily increasing, the incidence of gonococcal arthritis can also be expected to increase. This type of infectious arthritis occurs most frequently in young, otherwise healthy individuals who may have no other symptoms of gonococcal infection. In most women with gonococcal arthritis, no symptom other than joint pain may be noted by the patient even though the genital tract is infected.

Any delay in the diagnosis and treatment of these patients leads to continued venereal spread of gonorrhea to other individuals. Gonococcal arthritis is usually but not always accompanied by a fever which is moderate in the majority of patients. Shaking chills rarely occur. Many patients experience migratory aches in a number of joints with variable signs of articular inflammation. In other patients, the joints first involved may clear completely as new joints are affected until the arthritis becomes particularly severe in one or more joints. Large joints are most frequently involved. Females accounted for 76.7 percent of patients in a series reported from Ben Taub General Hospital. (Ref. 33).

It is obvious that patients with gonococcal arthritis should not be encouraged to self-medicate with aspirin since they will supress pain and may also suppress signs of arthritis. This may lead to their not seeking care from a physician and therefore may lead to spread of the venereal disease to others during the period of self-medication, increased risk of gonococcemia due to self-medication, and the possibility of significant restriction of joint function due to permanent damage to the joint because of delay in diagnosis and therapy. Sharp describes two patients who had permanent damage to infected wrists due to delay in treatment for 18 and 28 days (Ref. 34). He states "* * * diagnostic studies should be completed with haste and treatment started as soon as appropriate cultures have been obtained to minimize the risk of residual articular damage." Although no severe joint damage may occur in patients with gonococcal arthritis who self-medicate with aspirin for less than 10 days, such individuals are clearly not receiving adequate treatment. Some loss of joint (cartilage) space and lytic changes in bone may be noted within 1 to 2 weeks after onset of infection. It is important that "effective treatment of septic arthritis requires early recognition, prompt arthrocentesis and the administration of an antibiotic chosen on the basis of sensitivity tests on the infection organism. Treatment should be initiated as soon as adequate cultures are obtained and altered as required after the antibiotic sensitivities are available" (Ref. 35).

e. *Other diseases*—(1) *Rheumatic fever.* Rheumatic fever is a serious illness manifested by arthritis, and involves the heart in from one-third to one-half of the patients. Involvement of the heart particularly during the acute phase of the disease may occasionally have fatal consequences. Rheumatic fever is an in-

flammatory disease which occurs as a sequel to infection with group A streptococci (Ref. 36). Salicylates are of considerable value in controlling the toxic manifestations, in contributing to the comfort of the patients, and in combating anemia and other constitutional symptoms (Refs. 37 and 38). Salicylates, usually aspirin, are given in an initial daily dose of approximately 0.1 g/kg of body weight ranging from 3 g in children to 6 to 8 g in adults, trying to achieve a plasma salicylate level of 25 to 30 mg/100 ml. (Compared to an OTC analgesic dosage limit of 4g/24 hours for aspirin). The symptoms of rheumatic fever typically appear as an acute polyarthritis (swelling and pain of the joints) which may subside in one joint after a few days only to appear in another joint (migratory polyarthritis). Fever is a frequent accompanying feature of the disease. It is entirely possible that where fever is not present or is of low grade, an individual who has unknowingly contracted rheumatic fever may treat the arthritic symptoms with OTC antirheumatic products. The illusion of having successfully treated the problem is reinforced when the symptoms disappear. When the arthritic symptoms reappear in another joint (migratory polyarthritis), aspirin or other salicylates are, again, ingested by the consumer. During this period the disease progresses to include the serious and, perhaps, permanent heart manifestations described above. It is clear that patients with this type of arthritis should be under prompt physician's care and should not self-medicate with aspirin even for 10 days.

(2) *"Connective tissue" disorders.* Another group of rheumatic diseases is the "connective tissue" disorders which are acquired rather than congenital diseases. These disorders include systemic lupus erythematosus, progressive systemic sclerosis, polymyositis, necrotizing arteritis and other forms of vasculitis and are serious disorders which may be life-threatening. These patients must be under the care of the physician and should not self-medicate. Since arthritis or muscle pain is a feature of all of these diseases, it is important that the disease be diagnosed by a physician, and such patients should not self-medicate for their "arthritis" since this will prolong the period before they eventually seek a physician's aid and are diagnosed and treated. This is particularly important since some of these patients may have severe kidney disease that is usually asymptomatic. Urine and blood chemistry studies are essential for diagnosis and subsequent assessment of the patient's status and response to treatment.

(3) *Miscellaneous diseases.* Other diseases with which arthritis may be associated include sarcoidosis, relapsing polychondritis, ulcerative colitis, and regional enteritis.

Nonarticular rheumatism involves structures around joints and includes such conditions as fibrositis, low back syndromes, myositis, tendonitis and others. These more common conditions which may be acutely painful, however, must be distinguished by a physician from other more serious and life-threatening conditions as described above. For example, gonococcal arthritis may be associated with tendonitis due to infection with gonococci. Myositis may occur in systemic lupus erythematosus and polymyositis and gout may involve bursa leading to acute bursitis.

A variety of miscellaneous disorders also involve joints and should also not be treated by self-medication. These include villonodular synovitis, Behcet's Syndrome, erythema nodosum, avascular necrosis of the bone and others.

Serious traumatic and neurogenic disorders involving joints should also be treated under the care of a physician. Diseases other than gout with known or strongly suspected biochemical or endocrine abnormalities in which joint disease occurs include hemophilia, sickle cell anemia, hyperparathyroidism, acromegaly, hypothroidism, scurvy and other disorders. Clearly, self-medication with analgesics may lead to a delay or lack of proper diagnosis and therapy in these serious and, in many cases, curable disorders. Neoplasms (cancers) involving the joints include leukemia and multiple myeloma as well as primary neoplasm of the synovium (synovioma), and self-medication is clearly to be discouraged in these patients. Indeed, self-medication may lead to delay in diagnosis.

5. *Economic and social impact of rheumatic diseases in the U.S.* The rheumatic diseases cause a large segment of chronic disability in the U.S., and in fact, all over the world. In this country alone, the three most common of these diseases, i.e., rheumatoid arthritis, osteoarthritis and gout afflict over 18 million individuals. When all rheumatic diseases are considered, it is evident that these diseases afflict well over 10 percent of the U.S. population. Hence, over 20 million Americans suffer from discernible symptoms of some form of rheumatic disease.

Of even greater importance to the Panel is a statement in a 1973 advisory committee report (Ref. 39) to the Arthritis Foundation where it was concluded that most individuals with rheumatic diseases are not receiving medical care. They stated:

> Of the more than 20 million individuals afflicted with rheumatic diseases, well over 12 million are not receiving medical care, even though many of these experience some degree of disability.
>
> Since early accurate medical diagnosis and appropriate treatment can often prevent or delay the appearance of advanced symptoms, the potential for unnecessary suffering among those not under treatment is considerable.

Further, more than 12 million victims of rheumatic diseases are under age 65 and more than 3 million are under age 45. In 1969, these diseases caused victims to spend a total of more than 70 million days in bed. Among normally employed individuals, more than 14 million days were lost from work due to rheumatic diseases. The number of days lost from work does not include the many lost by those who are so disabled that they are no longer employed, nor does it include the days lost by housewives and students (Ref. 38).

In a survey described by Hollander (Ref. 3), conducted during 1957 to 1959, 30,000 persons were found to be unable to work because of arthritis for a minimum of 6 months. These individuals became eligible for Social Security benefits. Of these, 78 percent were over 50 years of age, and 20 percent were women. Osteoarthritis was present in 56 percent and rheumatoid arthritis in 27 percent.

Rheumatoid arthritis seldom causes death directly, but is still the greatest cause of crippling deformity from disease. These patients form a great proportion of the population attending arthritis clinics because of the long duration and severity of the process.

The Panel believes that early diagnosis and treatment in many cases can prevent or delay the most serious and crippling symptoms of arthritis which so seriously detract from the U.S. labor force as well as causing a great deal of suffering among these same people and their families.

6. *Hazards of self-diagnosis and self-medication.* The Panel concludes that it is absolutely essential that the individual seek proper medical attention when symptoms of arthritis are present. Abnormal fatigue, muscular stiffness, painful swelling of joints or loss of joint motion are all common first signs of rheumatoid arthritis. The self-medication of these symptoms with aspirin, as promoted through OTC drug labeling or suggested through advertising, may lead to relief of pain. However, cessation of self-medication will cause the patient to note return of pain which will inevitably result in self-medication again with aspirin. The Panel is concerned that repeated "successful" self-medication may keep the patient from going to a physician and obtaining the correct diagnosis and therapy; the result being progression of the disease with possible permanent crippling. Futhermore, where infectious diseases manifest themselves as arthritis, these may also, in the early stages, be "successfully" self-treated only to result in very serious or life-threatening episodes. It is essential for the control of the disease and to prevent disability that the individual seek proper medical advice as early as possible.

Because symptomatic self-medication for arthritis of undetermined and undiagnosed etiology may lead in some instances to some relief of pain and yet allow the disease to progress, the Panel recommends that aspirin and aspirin-containing agents not be labeled for the treatment of "arthritis." The use of aspirin and aspirin-containing products as antirheumatic agents (anti-inflammatory agents) should be under the supervision of a physician because only a physician can properly diagnose the cause of the arthritis and prescribe the therapy suitable for the specific disease causing the arthritis in the individual patient. It should be noted that the principal therapeutic purpose for the use of aspirin in some rheumatic diseases is as an anti-inflammatory agent and not as an analgesic. As an anti-inflammatory agent, the dosage of aspirin is higher

and the duration of treatment is longer than when aspirin is used as an OTC analgesic for the relief of pain.

The Panel concurs with a leaflet published by the Arthritis Foundation (Ref. 2), where it is emphasized that aspirin is the best single drug for treatment of arthritis but points out that its use is widely misunderstood. In addition, it is the conclusion of the Arthritis Foundation that it is a misused drug. It is stated, "There is a special way to take aspirin for arthritis. It is not the way you take it for a headache or the common cold."

The Arthritis Foundation has published in the leaflet (Ref. 2) five important "Do's and Don'ts" pertaining to the treatment of arthritis. The Panel fully concurs with these recommendations which are as follows:

1. DO see a qualified physician for diagnosis and treatment of arthritis. Proper treatment can control the disease and prevent crippling.
2. DO take aspirin, if the doctor prescribes it, strictly according to the 'aspirin program' he gives you.
3. DON'T change your aspirin dosage schedule without first asking your physician.
4. DON'T try to diagnose your own arthritis problem or pick your own remedies from non-prescription medicines available at the local drugstore.
5. DON'T be lured by aspirin advertising into self-treatment and dosing yourself on a homemade schedule. Even though arthritis may begin with 'minor aches and pains,' it is no disease to fool around with. DO get qualified medical advice and get it early.

The Panel has recommended that all OTC analgesic-antipyretic-antirheumatic products be labeled with the warning, "Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician". The Panel concludes that even if temporary self-medication is limited to 10 days, pain may be relieved, but will recur and the disease may progress if not properly diagnosed by a physician.

7. *Labeling of antirheumatic products.* In his chapter on "Salicylate Therapy for Rheumatiod Arthritis" in *"Arthritis and Allied Conditions"*, Dr. T. B. Bayles states "All patients with active rheumatoid arthritis, mild to severe, should receive salicylates regularly in the largest tolerated dosage excluding only those with proven adverse gastrointestinal symptoms or bleeding, peptic ulcer, or allergic manifestation due to salicylates" (Ref. 33).

Suggested labeling doses for self-medication provide only analgesic effect and deprive the patient of the benefit of a physician's care as discussed above. Permanent disability may occur if self-medication occurs intermittently or over prolonged periods of time for certain types of arthritis.

In a brochure distributed by the Arthritis Foundation for patients with arthritis (Ref. 2), the following is stated:

Many ads make arthritis sound like nothing much more than a disease of "minor aches and pains". The truth is arthritis can be a serious disease. The pain can be excruciating and results can be severe crippling unless the victim starts full and proper medical treatment in the early stages. How often do aspirin advertisements tell you this? And how often do aspirin advertisements tell you that your dosage schedule should be prescribed by a doctor? Don't let advertising lead you to self-diagnosis and self-treatment for arthritis. There is more to controlling arthritis than getting wonderful "relief". Arthritis isn't a disease to fool around with. While you are dosing yourself from the medicine cabinet and staying away from the doctor, irreversible damage may be taking place in your arthritic joints.

In another more recent position by the Arthritis Foundation (Ref. 40), the following is stated:

Aspirin is frequently the drug of choice in treating the more serious forms or arthritis, but it should be prescribed by a physician in appropriate dosage for each individual patient, who should be closely monitored for side effects. Furthermore, people who have "minor aches and pains" are usually not qualified to decide whether these symptoms are just that and no more, or whether they may herald a serious form of arthritis requiring medical diagnosis and treatment.

Therefore, the Arthritis Foundation considers advertising for aspirin products which encourage arthritis sufferers to self-diagnose and self-medicate as a disservice to them. In some cases, self-diagnosis and self-medication may lead to delay in seeking medical attention until after preventable joint damage has taken place.

The Arthritis Foundation also opposes use of the word "arthritis" in aspirin brand names, because of its potential for abuse. It should not be permitted.

Arthritis suffers would be best served if the word "arthritis" were banned from aspirin product labeling and advertising, leaving the medication decisions to physicians.

The Panel strongly concurs with this statement and concludes that there should be no OTC labeling for antirheumatic indications or use of the term in product names. Therefore, the ingredients reviewed for such use have all been classified by the Panel as Category II for any OTC antirheumatic labeling claims.

The Panel recognizes that the Food and Drug Administration does not regulate the advertising of OTC drug products. However, it is the Panel's conclusion that labeling and advertisements be closely monitored by the proper authority to see that advertisements do not go beyond the limitations of the monograph and/or negate the restrictions and warnings recommended by this Panel.

8. *Conclusions.* The Panel is concerned with the continuous promotion of OTC drug products for use in the self-treatment of rheumatic diseases. The labeling and advertisements of these OTC products represent a hazard to the individual afflicted with these potentially incapacitating and crippling disease conditions. The consumer is misled into the false belief that he can self-diagnose and self-treat any joint aches and pains he may have. The labeling and advertisements make no allusions to the progressive degenerating nature of rheumatic diseases if proper medical diagnosis and appropriate treatment is not instituted early in the disease. Pain is only one of the clinical features of these diseases. It is this symptom which the labeling and advertisement belabor to the exclusion of the other more serious clinical features.

OTC analgesics, especially aspirin, are the antirheumatic agents that are used by individuals with joint pains and aches that may be due to rheumatic diseases. The daily dosage of aspirin that is sufficient to achieve an analgesic effect, is an inadequate dose to affect the inflammation of the inflammatory rheumatic diseases, such as rheumatoid arthritis. A higher daily dosage and a much more prolonged administration is required to affect the inflammation of rheumatoid arthritis. The dosage and duration of treatment should be supervised by a physician. At doses higher than the dosage recommended for OTC use, serious side effects occur. The dosage and duration of treatment must be individualized for each patient by his physician. The consumer cannot self-diagnose and self-treat for the rheumatic diseases.

There is the general impression in the minds of American consumers that aspirin is an innocuous medication and that arthritis is a minor disease. The labeling and advertising of OTC aspirin products have reinforced this mistaken impression. This disease condition is not rare and the degenerating nature of the disease if proper medical diagnosis and treatment are not instituted can have a severe debilitating effect on the individual. The labeling and advertising that downplay the seriousness of this disease do the American consumer a gross injustice.

The Panel therefore concludes that all OTC products containing salicylates contain the warning, "Take this product for the treatment or arthritis only under the advice and supervision of a physician". In addition, the Panel recommends that the term "arthritis" be removed from the product names of OTC products to avoid the false impression that the consumer can self-diagnose and self-treat rheumatic diseases.

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B. Categorization of Data

1. *Category I conditions under which antirheumatic agents are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following antirheumatic active ingredients as generally recognized as safe and effective and not misbranded:

Aspirin
Calcium carbaspirin
Choline salicylate
Magnesium salicylate
Sodium salicylate

a. *Aspirin.* The Panel concludes that aspirin is a safe and effective OTC antirheumatic when taken in the dosages recommended by a physician for specific rheumatic diseases. The dose required for antirheumatic effectiveness usually exceeds the dose recommended for analgesia (4,000 mg in 24 hours) and the duration of therapy required is longer than 10 days. The therapeutic indications require prior diagnosis by a physician and therefore suitable claims are limited to professional labeling.

(1) *Effectiveness.* The effectiveness of aspirin in the treatment of rheumatoid arthritis has been endorsed by many generations of physicians and patients. Very few controlled or uncontrolled studies have been performed to demonstrate the antirheumatic effectiveness of aspirin. However, the analgesic action of aspirin in patients with a variety of rheumatic diseases has been extensively reported.

A double-blind study was carried out by the Cooperating Clinics Committee of the American Rheumatism Association in which placebo or eight 5 gr aspirin tablets daily were taken by 441 patients with rheumatoid arthritis. The results showed that aspirin had significantly more antirheumatic effect than placebo (Ref. 1).

Fremont-Smith and Bayles reported that after withdrawal of aspirin in a total dose of from 3.6 to 7.5 g daily given in 5 divided doses, objective evidence of exacerbation of rheumatoid arthritis appeared. This was demonstrated by a significant decrease in the grip strength and increased circumference of the interphalangeal joints (Ref. 2).

Boardman and Hart measured grip strength and circumference of proximal interphalangeal joints in a double-blind study of the effectiveness of aspirin in patients with rheumatoid arthritis. The data showed that a low dose of aspirin, 2.6 g daily given in 4 equal doses, was not significantly superior to acetaminophen or placebo but a high dose of 5.3 g daily, was (Ref. 3).

Calabro and Paulus performed a double-blind crossover study comparing aspirin, salicylamide and placebo in patients with rheumatoid arthritis. Each patient took 18 tablets daily, 3 tablets every 4 hours. All tablets contained 300 mg of analgesic or placebo. The results showed a statistically significant greater improvement of objective parameters of joint inflammation in patients receiving aspirin than in those receiving either salicylamide or placebo (Ref. 4).

Aspirin is effective in the treatment of some patients with rheumatoid arthritis at a dose of 2.4 g daily in divided doses. However, most patients require more than this minimally effective dose (Refs. 5, 6, and 7).

Extensive studies by Ansell, Bywaters and Isdale have demonstrated that aspirin is effective in the suppression of juvenile rheumatoid arthritis (Ref. 8). Initial doses ranged from 1.3 g daily at age 2 years to 6 g daily for older children. Maintenance dosage ranged from 1.5 to 6 g daily.

Manifestations of acute rheumatic fever such as fever, arthritis, elevated erythrocyte sedimentation rate and c-reactive protein disappear faster in patients receiving aspirin therapy than in untreated controls (Ref. 9).

Ankylosing spondylitis should be treated with aspirin and more potent agents added only when aspirin does not suffice (Ref. 10). Godfrey, Calabro, Mills and Maltz conducted a double-blind crossover trial of aspirin and the anti-inflammatory drugs indomethacin and phenylbutazone. Each drug was used for 6 weeks. They found that indomethacin and phenylbutazone were clearly superior to aspirin in increasing the range of motion. However, aspirin proved more effective than the other two medications in 5 of the 41 patients (Ref. 11).

Psoriatic arthritis should also be treated with aspirin (Ref. 12).

Aspirin is generally recommended for treatment of fibrositis syndromes (Ref. 13).

Aspirin is helpful in the treatment of systemic lupus erythematosus, especially when arthritis is associated with the disease. A minimal dose of 2.4 g daily in four divided doses is required (Ref. 14).

Aspirin is also recommended in the treatment of osteoarthritis (Ref. 15). Harth and Bondy performed a crossover trial using objective measurements rather than relief of pain scores. This study compared the effects of 1.3 g aspirin taken 3 times daily with the effects of indomethacin 50 mg taken 3 times daily. Objective measurements of hip-muscle strength and isometric strength of knee muscles were evaluated prior to therapy and during each trial of medication. These results revealed that aspirin is effective in the treatment of osteoarthritis (Ref. 16).

EFFECTIVENESS OF OTHER FORMS OF ASPIRIN AS ANTIRHEUMATIC AGENTS

The problem of managing the adverse effects of aspirin in the gastrointestinal tract are a particular concern in patients with rheumatoid arthritis where large doses are generally employed over extended periods of time. The addition of antacids, buffering agents and enteric coating have been used among others to reduce gastrointestinal irritation. The Panel has discussed the effects of finished dosage forms on the therapeutic activity of the active ingredients elsewhere in this document. (See part II. paragraph J. above—Effects of Product Formulations on Drug Absorption and Pharmacologic Effectiveness.)

Buffered aspirin has been proven effective in the treatment of rheumatoid arthritis (Refs. 2 and 4).

Aspirin combined with magnesium and aluminum hydroxides has not specifically been shown to have antirheumatic efficacy; however, if the product contains 325 mg (5 gr) aspirin it should be considered to be as effective as aspirin at the same dosage.

A study by Batterman (Ref. 17) analyzed the analgesic but not the antirheumatic effect of aspirin plus magnesium and alminimum hydroxides on patients with arthritis.

Feinblatt et al, measured the effect of aspirin plus magnesium and aluminum hydroxides in 20 patients with arthritis of unclear etiology. The mobility improved in all but one patient (Ref. 18). Unfortunately, the exact disease and the method of measurement of limitation of joint motion were poorly described.

Sandove and Schwartz (Ref. 19) studied the analgesic effect of aspirin and magnesium and aluminum hydroxides in patients with arthritis. No attempt to measure antirheumatic efficacy was made.

An enteric-coated aspirin tablet was studied regarding its analgesic effect on patients with rheumatoid arthritis and osteoarthritis (Ref. 20).

Similarly, Giovinco (Ref. 21) studied the analgesic effect of an enteric-coated tablet on rheumatoid arthritis and osteoarthritis patients. If the enteric-coated aspirin can be shown to prove blood salicylate levels similar to that of uncoated aspirin, then it should be recommended that the coated tablet is effective as an antirheumatic agent in all diseases in which aspirin is effective.

(2) *Safety.* The safety of aspirin has been previously discussed earlier in this document. (See part III, paragraph B.1.a. (2) above—Safety.)

The Panel concludes that it is generally not safe for the general public to self-medicate for joint pain perceived as "arthritis". Since the antirheumatic daily dose is much greater than that recommended for OTC use, side effects are more severe. In addition, the duration of therapy is much longer than that recommended for OTC use, and therefore, prolonged high daily doses of aspirin are less safe.

The OTC consumer is unable to differentiate the various forms of arthritis due to the large variety of diseases associated with pain in joints. Diagnosis should be made by a physician so that appropriate and adequate treatment of the arthritis can be instituted. It is not safe for individuals to self-medicate using antirheumatic doses of aspirin.

Patients with a history of gastric or duodenal ulcers or those with symptoms of ulcers should be under the care of a physician and antirheumatic therapy prescribed by the physician. These patients are at risk of gastrointestinal hemorrhage and clearly should not be self-medicating with aspirin using antirheumatic doses for prolonged periods to control their arthritis. In addition, the daily dose of aspirin should be individualized for each patient and monitored by the physician at specific intervals. For example, only a physician can measure the efficacy of aspirin therapy in rheumatoid arthritis patients by determining diminution of swelling, increase in range of motion, decrease in joint tenderness, increased grip strength, etc. Based upon the physician's assessment of the patient the physician may increase, decrease or continue the same dose of aspirin or add additional medication. In addition, evidence of side effects such as ulcer symptoms and falling hematocrit suggesting gastrointestinal bleeding can only be noted by the physician. Patients who are to undergo surgery are told to withhold aspirin for an appropriate period prior to and after surgery. In addition, the physician may institute other therapy such as gold injections, antimalarial therapy, etc. The physician also prescribes specific physical therapy, may order such measures as splints, paraffin baths, hot packs, and change the lifestyle of the patient to include periods of rest. All of these measures cannot be prescribed unless the patient is under the care of the physician.

The Panel concludes that aspirin is safe for use as an OTC antirheumatic only under the advice and supervision of a physican.

(3) *Dosage.* There is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I professional labeling for antirheumatic active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

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b. *Calcium carbaspirin.* The Panel concludes that calcium carbaspirin is a safe and effective OTC antirheumatic when taken in the dosages recommended by a physician for specific rheumatic diseases. The dose required for antirheumatic effectiveness usually exceeds the dose recommended for analgesia (4,968 mg in 24 hours) and the duration of therapy required is longer than 10 days. The therapeutic indications require prior diagnosis by a physician and therefore suitable claims are limited to professional labeling.

(1) *Effectiveness.* No data on effectiveness as an antirheumatic agent are available. However, as discussed earlier in this document, its dissolution rate and analgesic efficacy have been studied and found to be similar in action to aspirin. (See part III. paragarph B.1.c.(1) above—Effectiveness.)

(2) *Safety.* The safety of calcium carbaspirin has been previously discussed earlier in this document. (See part III. paragraph B.1.c.(2) above—Safety.) Its safety when administered in antirheumatic doses and for prolonged periods is not known because of the significant amount of calcium that may be absorbed.

The Panel concludes that calcium carbaspirin is safe for use as an OTC antirheumatic only under the advice and supervision of a physician.

(3) *Dosage.* There is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I professional labeling for antirheumatic active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

c. *Choline salicylate.* The Panel concludes that choline salicylate is a safe and effective OTC antirheumatic when taken in the dosages recommended by a physician for specific rheumatic diseases. The dose required for antirheumatic effectiveness usually exceeds the dose recommended for analgesia (5,220 mg in 24 hours) and the duration of therapy required is longer than 10 days. The therapeutic indications require prior diagnosis by a physician and therefore suitable claims are limited to professional labeling.

(1) *Effectiveness.* A study performed in 1960 by Nevinny and Gowans (Ref. 1) described the results of the treatment of five patients with rheumatoid arthritis with liquid choline salicylate but did not describe the dose and duration of therapy. Four of the five patients showed a reduction of "systemic indexes", which are a series of subjective and objective parameters of joint inflammation (Ref. 2).

A well-designed double-blind crossover study comparing equimolar concentrations of choline salicylate and aspirin as antirheumatic agents was performed by Golden, Tesar and Schmid (Ref. 3). The amount of salicylate used was a mean of 3.6 g daily and patients took tablets of one ingredient during the first 2 weeks and then took tablets of the second ingredient during the second 2 weeks. Patients were examined weekly using the following parameters: Duration of morning stiffness; grip strength; ring size; time to complete a measured walk; and subjective pain severity. Statistical analysis showed no difference in therapeutic effectiveness between choline salicylate and aspirin.

(2) *Safety.* The safety of choline salicylate has been previously discussed earlier in this document. (See part III. paragraph B.1.d.(2) above—Safety.)

The Panel concludes that choline salicylate is safe for use as an OTC antirheumatic only under the advice and supervision of a physician.

(3) *Dosage.* There is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I professional labeling for antirheumatic active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

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(3) Golden, H. E., J. T. Tesar and F. R. Schmid, "Quantitation of Gastrointestinal Bleeding and Therapeutic Effectiveness of Choline Salicylate Compared to Aspirin in Rheumatoid Arthritis," *Arthritis and Rheumatism*, 13:319, 1970.

d. *Magnesium salicylate.* The Panel concludes that magnesium salicylate is a safe and effective OTC antirheumatic when taken in the dosages recommended by a physician for specific rheumatic diseases. The dose required for antirheumatic effectiveness usually exceeds the dose recommended for analgesia (4,000 mg in 24 hours) and the duration of therapy required is longer than 10 days. The therapeutic indications require prior diagnosis by a physician and therefore suitable claims are limited to professional labeling.

(1) *Effectiveness.* Brown (Ref. 1) conducted a double-blind study on patients with rheumatoid arthritis who received 1 g aspirin or magnesium salicylate 4 times daily for 7 days. Objective measurements of antirheumatic efficacy were studied including grip strength, morning stiffness duration, walking time and number of active joints. The results showed that magnesium salicylate is equally as effective as an antirheumatic as aspirin.

(2) *Safety.* The safety of magnesium salicylate has been previously discussed earlier in this document. (See part III. paragraph B.1.e.(2) above—Safety.)

Magnesium salicylate is contraindicated in patients requiring long-term use of the agent as an antirheumatic who have advanced chronic renal insufficiency (Ref. 1). Use of this agent in patients with advanced chronic renal insufficiency may lead to toxic levels of magnesium.

The Panel concludes that magnesium salicylate is safe for use as an OTC antirheumatic only under the advice and supervision of a physician.

(3) *Dosage.* There is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Categorv I professional labeling for antirheumatic active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *For products containing more than 50 mEq of magnesium in the recommended daily dosage. Warning.* "Do not take this product if you have kidney disease except under the advice and supervision of a physician".

REFERENCE

(1) Brown, H., "Magan-7 Day Variability Study," draft of unpublished paper is included in OTC Volume 030042.

e. *Sodium salicylate.* The Panel concludes that sodium salicylate is a safe and effective OTC antirheumatic when taken in the dosages recommended by a physician for specific rheumatic diseases. The dose required for antirheumatic effectiveness usually exceeds the dose recommended for analgesia (4,000 mg in 24 hours) and the duration of therapy required is longer than 10 days. The therapeutic indications require prior diagnosis by a physician and therefore suitable claims are limited to professional labeling.

(1) *Effectiveness.* Sodium salicylate was tested in 27 patients with rheumatoid arthritis by Hollander and Harris (Ref. 1). Patients were given 4 g (1 g 4 times daily) for at least 1 week. Antirheumatic effectiveness was measured by subjective parameters such as relief of stiffness and measurement of the erythrocyte sedimentation rate before and after 1 week of therapy. No change in the sedimentation rate was observed, while relief of stiffness occurred. The data were compared with the efficacy of para-aminobenzoic acid at a dose of 4 g daily for 1 week. Sodium salicylate was found to give substantially more relief of stiffness than para-aminobenzoic acid. The study, however, did not actually measure antirheumatic effect on an objective scale and the results, therefore, do not permit a conclusion as to the efficacy of sodium salicylate as an antirheumatic.

A similarly inconclusive study was carried out by Smith (Ref. 2) who studied the analgesic effect of sodium salicylate in doses of 0.6 to 1.3 g every 4 hours during the day. Although the drug was found to be an effective analgesic, no objective parameters of its antirheumatic efficacy were measured.

Other studies in the literature are poorly designed and describe only analgesic effect of sodium salicylate in patients with rheumatoid arthritis and

other forms of arthritis (Refs. 3, 4, and 5).

An excellent study was carried out by Dick et al., (Refs. 6 and 7) in which the antirheumatic effect of sodium salicylate was compared with that of indomethacin and placebo. The study was carried out in 13 patients with rheumatoid arthritis who entered a 3 week, double-blind trial during which they received the following three courses of treatment each lasting for 1 week: Enteric-coated sodium salicylate 1.2 g 4 times daily; indomethacin 25 mg 4 times daily; and lactose as placebo. The order of treatment was randomized. The Ritchie index (Ref. 8) was used as a measure of total articular status. This index is based on the response of the patient to firm pressure over the joint margin (0=no pain, +1= patient complains of pain, 2+=patient complains of pain and winces, 3+= patient complains of pain, winces and withdraws). The maximal score is +78. The mean intra-observer error difference (difference between observers examining this same joint) is 1.2 score units and the standard error is 1.1 score units. In addition to the Richie index, pain, tenderness, stiffness and swelling in one knee was noted (knee score). Each was noted on a 0 to +3 scale. The results revealed that the knee score was significantly higher as tested by a paired Students t test while the patients received placebo than the values obtained while the patients received either sodium salicylate (p is less than 0.001) or indomethacin (p is less than 0.001). The articular index of Ritchie was significantly higher while patients received placebo than when they were treated with either sodium salicylate (p is less than 0.001) or indomethacin. Thus, this study clearly demonstrated the antirheumatic efficacy in a well-designed study.

A similarly well-designed study was carried out by Dick, Greyson, Woodburn et al. (Ref. 7). In this study, which may be used as a model for future studies on antirheumatic efficacy, the following parameters were measured: Ritchie index (Ref. 4); grip strength (Ref. 9) (mechanical measurement of the strength of a patient's grip); measurement of circumference of finger joints using a millimeter gauge (Ref. 10); and knee score (Ref. 6).

In addition to the above, the accumulation of radioactive technetium within the knee joint after intravenous administration was studied by joint scanning. Ten patients with rheumatoid arthritis were studied in a triple crossover clincial trial using 5 g sodium salicylate daily, 100 mg indomethacin daily and placebo, each administered for 1 week. Sodium salicylate was shown to be significantly better than placebo according to articular index (Ritchie index), knee score, and technetium peak count. No significant difference was shown using joint size or grip strength. The results reveal that sodium salicylate has antirheumatic efficacy.

The effectiveness of sodium salicylate as an antirheumatic has been clearly established. The effective dose is at least 4.8 g daily in divided doses.

(2) *Safety.* The safety of sodium salicylate has been previously discussed earlier in this document. (See part III. paragraph B.1.f.(2) above—Safety.)

The long-term administration of sodium salicylate preparations may be hazardous in patients with chronic renal insufficiency or heart disease due to the sodium in the preparation.

The Panel concludes that sodium salicylate is safe for use as an OTC antirheumatic only under the advice and supervision of a physician.

(3) *Dosage.* There is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I professional labeling for antirheumatic active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling:

(i) *For products containing 0.2 mEq (5 mg) or higher of sodium per dosage unit.* The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq (5 mg) or higher.

(ii) *For products containing more than 5 mEq (125 mg) sodium in the maximum recommended daily dosage. Warning.* "Do not take this product if you are on a sodium restricted diet except under the advice and supervision of a physician".

REFERENCES

(1) Hollander, J. L. and T. N. Harris, "Combined Salicylate and Para-Aminobenzoic Acid in the Treatment of Rheumatoid Arthritis," American Journal of the Medical Sciences, 221:398–401, 1951.

(2) Smith, R. T., "Treatment of Rheumatoid Arthritis and other Rheumatic Conditions with Salicylate and Para-Aminobenzoic Acid," The Journal—*Lancet*, 70:192–196, 1950.

(3) Barden, F. W., P. S. Hill and K. J. Cuneo, "Evaluation of a Drug Therapy in Arthritis and Rheumatoid Conditions," *Journal of the Maine Medical Association*, 46:99–101, 1955.

(4) Cass, L. J., W. S. Frederik and J. D. Cohen, "Para-Aminobenzoic Acid and Salicylates in the Treatment of Arthritis," The Journal—*Lancet*, 76:42–44, 1956.

(5) Hebert, G. and N. Renzi, "Salicylate et Para-Aminobenzoate Sodium dans le Traitement De l'Artheite Rhumatoide," *Union Medicale Canada*, 86:73–75, 1957.

(6) Dick, C. et al., "Effect of Anti-Inflammatory Drug Therapy Clearance of 133Xe from Knee Joints of Patients with Rheumatoid Arthritis," *British Medical Journal*, 3: 278–280, 1969.

(7) Dick, W. C. et al., "Indices of Inflammatory Activity," *Annals of the Rheumatic Diseases*, 29:643–648, 1970.

(8) Ritchie, D. M. et al., "Clinical Studies with an Articular Index for the Assessment of Joint Tenderness in Patients with Rheumatoid Arthritis," Quarterly Journal of Medicine, 37:393–406, 1968.

(9) Wright, V., "Some Observations on Diural Variation of Grip," *Clinical Science*, 18:17–23, 1959.

(10) Boardman, P. L. and F. D. Hart, "Clinical Measurement of the Anti-Inflammatory Effects of Salicylates in Rheumatoid Arthritis," *British Medical Journal*, 4:264–268, 1967.

CATEGORY I LABELING

The use of OTC antirheumatic agents for the treatment of the symptoms of specific rheumatic diseases requires prior diagnosis by a physician and the establishment of a suitable recommended dosage. The Panel believes that any labeling conditions such as these which require medical intervention may mislead the consumer who attempts to self-diagnose and self-treat serious disease. Therefore, there are no suitable labeling claims for use on OTC marketed products. Suitable labeling claims are limited to professional labeling.

The Panel recommends the following Category I professional labeling (labeling of the product for health professionals but not for the general public) for antirheumatic active ingredients to be generally recognized as safe and effective and not misbranded as well as specific labeling discussed in the individual ingredient statements.

a. *Indications.* For rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis (degenerative joint disease), ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome and fibrositis.

2. *Category II conditions under which antirheumatic agents are not generally recognized as safe and effective or are misbranded.*

CATEGORY II ACTIVE INGREDIENTS

The Panel has classified the following claimed antirheumatic active ingredients as not generally recognized as safe and effective or are misbranded:

Acetaminophen	Phenacetin
Acetanilid	Quinine
Iodopyrine	Salicylamide

a. *Acetaminophen.* The Panel concludes that acetaminophen is not an effective OTC antirheumatic.

(1) *Effectiveness.* Acetaminophen is not considered to have effective antirheumatic properties (Refs. 1 and 2). A study by Boardman and Hart compared the efficacy of 6 g acetaminophen daily administered as 3 tablets given 4 times daily compared to placebo given in the same manner (Ref. 3). Each drug was given for 7 consecutive days, and quantitative measurements of joint size using standard jewellers' rings under double-blind controlled conditions, in addition to measurements of grip strength were made at the beginning of the study and at the end of each of the 7 day trials. All patients had classical or definite rheumatoid arthritis of at least 1 year's duration, had synovitis of the small joints of the hands, and in all patients it was possible to stop all treatment for 14 days before the trial. The results showed that there was no significant difference of joint size in patients on acetaminophen compared with placebo. Patients had a mean improvement of grip strength from 303 mm Hg on placebo to 326 mm Hg on acetaminophen. This difference was not significant ($t=0.57$, $n=26$; P is greater than 0.05).

The Panel concludes that acetaminophen is not effective as an antirheumatic.

(2) *Safety.* The Panel has discussed the safety of acetaminophen earlier in this document. (See part III. paragraph B.1.b.(2) above—Safety.)

(3) *Evaluation.* The Panel concludes because there are no data demonstrating the effectiveness of acetaminophen as an antirheumatic that the ingredient is not effective for use as an OTC antirheumatic.

REFERENCES

(1) Woodbury, D. N., "Analgesic-Antipyretics, Anti-Inflammatory Agents, and Inhibitors of Uric Acid Synthesis," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, Macmillan Co., New York, pp. 314–317, 1970.

(2) Handel, H. G. and C. Davidson, "Nonnarcotic Analgesics and Antipyretics II: Nonsalicylates and Drugs Useful in Gout," *in* "Drill's Pharmacology in Medicine," Edited by DiPalma, J. R., McGraw-Hill, New York, 1972.

(3) Boardman, P. L. and F. D. Hart, "Clinical Measurement of the Anti-Inflammatory Effects of Salicylates in Rheumatoid Arthritis," *British Medical Journal*, 4:264–268, 1957.

b. *Acetanilid.* The Panel concludes that acetanilid is not an effective OTC antirheumatic and is not safe for OTC use.

(1) *Effectiveness.* The Panel has discused the effectiveness of acetanilid earlier in this document. (See part III. paragraph B.2.a.(1) above—Effectiveness.)

The Panel concludes that acetanilid is not effective for use as an OTC antirheumatic.

(2) *Safety.* The Panel has discussed the safety of acetanilid earlier in this document. (See part III. paragraph B.2.a.(2) above—Safety.)

The Panel concludes that acetanilid is not safe for use as an OTC antirheumatic.

(3) *Evaluation.* The Panel concludes because there are no data demonstrating the effectiveness of acetanilid as an antirheumatic and because of the high incidence of toxic effects that the ingredient is not safe and not effective for use as an OTC antirheumatic.

c. *Iodopyrine.* The Panel finds that there are no data to demonstrate effectiveness and there are data showing it not safe and therefore concludes that iodopyrine is not safe and not effective for use as an OTC antirheumatic.

(1) *Effectiveness.* No studies were found concerning the effectiveness of this iodide salt of antipyrine for use as an OTC antirheumatic. The lack of demonstrated effectiveness for use of iodopyrine as an OTC analgesic has been discussed earlier on this document. (See part III. paragraph B.2.c.(1) above—Effectiveness.)

(2) *Safety.* The safety of iodopyrine has been discussed earlier in this document. (See part III. paragraph B.2.c.(2) above—Safety.) The Panel concludes that iodopyrine is not safe for use as an OTC antirheumatic.

(3) *Evaluation.* The Panel finds that iodopyrine is not safe for OTC use because of the significantly high availability of iodide following oral administration and increased likelihood of iodism. Accordingly, the Panel concludes that the risks from use of iodopyrine outweigh any possible benefit and classifies the ingredient unsafe for use as an OTC antirheumatic.

d. *Phenacetin.* The Panel concludes that phenacetin is not an effective OTC antirheumatic and is not safe for OTC use because of the high potential for abuse, the high potential for harm to the kidneys and the possibility of hemolytic anemia and methemoglobinemia resulting from abuse and the lack of compensating benefits of the drug. The benefit-risk ratio of phenacetin compounds compares unfavorably with other single agents and combination antirheumatic preparations available to target populations.

(1) *Effectiveness.* The Panel notes that "Acetaminophen and phenacetin have analgesic and antipyretic effects similar to those of aspirin. However, they have only weak anti-inflammatory effects and do not share the antirheumatic uses of the salicylates" (Ref. 1).

(2) *Safety.* The Panel has discussed the safety of phenacetin earlier in this document. (See part III. paragraph B.2.d.(2) above—Safety.)

(3) *Evaluation.* The Panel concludes because there are no data demonstrating the effectiveness of phenacetin as an antirheumatic and because of the significant high risk level with long-term use that the ingredient is not effective and not safe for use as an OTC antirheumatic.

REFERENCES

(1) Woodbury, D. M. and E. Fingl., "Analgesic-Antipyretics, Anti-Inflammatory Agents, and Drugs Employed in the Therapy of Gout," *in* "Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan, New York, p. 344, 1975.

e. *Salicylamide.* The Panel concludes that salicylamide is not an effective OTC antirheumatic.

(1) *Effectiveness.* Calabro and Paulus compared the efficacy of aspirin, salicylamide and sucrose placebo given as three 0.3 g tablets every 4 hours for 24 hours (Ref. 1). The double-blind crossover study included in each of its three phases, 8 weeks of drug-testing of aspirin, salicylamide or placebo daily, and 2 weeks of interval therapy when all patients took only 2.6 g aspirin daily. The patients were evaluated every 2 weeks using the Lansbury indices. This index evaluates five criteria: Duration of morning stiffness; time of onset of fatigue; aspirin need; grip strength; and the Westergren erythrocyte sedimentation rate. Using Lansbury's Tables, individual findings are converted to a percentage equivalent. When the percentages are added together they constitute a final score on the Lansbury systemic index. In addition, joint pain and metacarpophalangeal and metatarsophalangeal tenderness and swelling were graded from 0 to 4+. The results of this study using the subjective and objective criteria revealed that salicylamide was more effective than placebo in only two subjective parameters of the ten parameters evaluated. These were, time of onset of fatigue and the need for additional aspirin. All of the eight other parameters showed no statistically significant difference between salicylamide and placebo. Statistically significant differences between placebo and aspirin were shown by all criteria.

Batterman and Grossman (Ref. 2) studied the analgesic effect of salicylamide on patients with osteoarthritis, but did not measure antirheumatic effect.

Similarly, Litter, Moreno and Donin (Ref. 3) studied the analgesic efficacy of salicylamide on a large group of arthritic patients, but did not measure antirheumatic effects.

(2) *Safety.* The Panel has discussed the safety of salicylamide earlier in this document. (See part III. paragraph B.3.c. (2) above—Safety.)

(3) *Evaluation.* The Panel concludes from the data presented that salicylamide is not effective for use as an OTC antirheumatic.

REFERENCES

(1) Calabro, J. J. and H. E. Paulus, "Anti-Inflammatory Effect of Acetylsalicylic Acid in Rheumatoid Arthritis," *Clinical Orthopedics and Related Research*, 71:124–131, 1970.

(2) Batterman, R. C. and A. J. Grossman, "Effectiveness of Salicylamide as an Analgesic and Antirheumatic Agent," *Journal of the American Medical Association*, 159:1619–1622, 1955.

(3) Litter, M., A. R. Moreno and L. Donin, "Salicylamide: Pharmacology, Fate, and Clinical Use," *Journal of Pharmacology and Experimental Therapeutics*, 101:119–124, 1951.

CATEGORY II LABELING

The Panel has examined the submitted labeling claims for antirheumatics alone and for combination products with nonantirheumatic ingredients and concludes that there are no labeling claims suitable for OTC labeling of antirheumatic agents. Other labeling including unacceptable claims related to product performance have been clearly defined elsewhere in this document. (See part III. paragraph B.2. above—Category II Labeling.) The Panel classifies all labeling claims, including the following which are currently used in the OTC marketplace, as Category II:

a. *Claims that refer to diseases requiring prior diagnosis by a physician.* The Panel considers the use of any indication for the treatment of arthritic conditions not to be suitable for OTC labeling and recommends that such indications be deleted from the labeling of OTC antirheumatic products. Therefore, the following submitted claims are classified as Category II and should be removed from OTC antirheumatic products: "arthritis", "rheumatism", "pain of arthritis", "pain of rheumatism", "minor aches and pains of arthritis", "minor aches and pains of rheumatism", "minor pain of arthritis", "minor pain of rheumatism", "low back pains", "bursitis", "chronic minor pain of arthritis", "minor aches and pains of bursitis," and "lumbago".

b. *Claims that are unnecessarily descriptive.* The Panel has recommended

that the indications for antirheumatic OTC products be limited to professional labeling. Therefore, the Panel feels that labeling claims such as "body aches" and "minor muscle aches" are unnecessary. Such claims are included in the simple term, aches. Likewise, the claim "sore, stiff aching muscles" can be adequately described and understood by the terms, aches and pains. The consumer will not be confused by the cause of the ache but will merely treat the ache. The consumer perceives a muscle ache after exercise as an ache and will take the appropriate ingredient. Since the Panel wishes to avoid multiple descriptions of the terms, aches and pains, such descriptions as "due to fatigue" and "sore, stiff muscles" should be deleted from the labeling. The following submitted labeling claims have been classified as Category II by the Panel and should be removed from OTC antirheumatic products: "minor muscular pains and aches", "minor muscular aches", "minor muscle aches", "aches and pains due to fatigue", "sore, stiff aching muscles", "muscular fatigue", "muscular tensions", "low body ache and fatigue", "body aches", and "sprains".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.*

CATEGORY III ACTIVE INGREDIENTS

The Panel has concluded that the available data are insufficient to permit final classification of the following claimed antirheumatic active ingredients listed below. The Panel believes it reasonable to provide 3 years for the development and review of such data. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 3 years, however, the ingredients listed in this category should no longer be marketed in OTC products.

Aluminum aspirin
Antipyrine
Salsalate (salicylsalicylic acid)

a. *Aluminum aspirin.* The Panel concludes that aluminum aspirin is safe but that there are insufficient data to determine effectiveness as an OTC antirheumatic.

(1) *Effectiveness.* No data on the effectiveness of aluminum aspirin as an antirheumatic were found or submitted to the Panel.

(2) *Safety.* The safety of aluminum aspirin has been discussed earlier in this document. (See part III. paragraph B.3.a. (2) above—Safety.) No data on the safety of prolonged use of antirheumatic doses are available.

(3) *Proposed dosage.* There is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I professional labeling for antirheumatic active ingredients. (See part V. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for antirheumatic drugs. In addition, the following information is needed: Bioavailability studies of aluminum aspirin in man must show comparable blood levels of salicylates to those following administration of the standard, aspirin, as detailed below. (See part V. paragraph C. below—Data Required for Evaluation.)

b. *Antipyrine.* The Panel concludes that there are insufficient data to determine the safety and effectiveness of antipyrine as an OTC antirheumatic.

(1) *Effectiveness.* No study has been found or submitted in which the antirheumatic efficacy of antipyrine has been evaluated (Ref. 1).

The effectiveness of antipyrine as an analgesic has been discussed earlier in this document. (See part III. paragraph B.3.b.(1) above—Effectiveness.)

(2) *Safety.* The safety of antipyrine has been discussed earlier in this document. (See part III. paragraph B.3.b. (2) above—Safety.)

(3) *Proposed dosage.* There is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I professional labeling for antirheumatic active ingredients. (See part V. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for antirheumatic drugs. (See part V. paragraph C. below—Data Required for Evaluation.) Data to demonstrate safety should include epidemiological studies which take into consideration the concerns of the Panel. Interested drug manufacturers should consult with the Food and Drug Administration as to the design of such studies. The studies should consider pharmacogenetic factors and include several racial groups.

REFERENCES

(1) Woodbury, D. M. and E. Fingl, "Analgesic-Antipyretics, Anti-Inflammatory Agents, and Drugs Employed in the Therapy of Gout," *The Pharmacologic Basis of Therapeutics*, 5th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan, New York, pp. 347–348, 1975.

c. *Salsalate (salicysalicytic acid).* The Panel concludes that salsalate (salicylsalicylic acid) is safe but that there are insufficient data to determine effectiveness as an OTC antirheumatic.

(1) *Effectiveness.* No data is available either in the literature or in the submission to evaluate the efficacy of salsalate as an antirheumatic.

(2) *Safety.* The safety of salsalate (salicylsalicylic acid) has been discussed earlier in this document. (See part III. paragraph B.3.d. (2) above—Safety.)

(3) *Proposed dosage.* There is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I professional labeling for antirheumatic active ingredients. (See part V. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for antirheumatic drugs. (See part V. paragraph C. below—Data Required for Evaluation.)

CATEGORY III LABELING

The Panel recommends the Category I professional labeling for antirheumatic active ingredients. (See part V. paragraph B.1. above—Category I Labeling.)

C. DATA REQUIRED FOR EVALUATION

The Panel finds the protocols recommended in this document for the studies required to bring a Category III drug into Category I in accord with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Considerations in designing an experimental protocol for testing antirheumatic drugs. General principles.*—The important considerations concerning design and interpretation of short term antirheumatic assays are as follows: The studies should be designed to test the anti-inflammatory activity of an ingredient, separate from any other action it may have.

2. *Determination of the patient population.* Patients with appropriate inflammatory rheumatic diseases should be selected. They should be studied by disease groups. Patients with the same inflammatory rheumatic disease should be compared for the action of the ingredient in significantly reducing the signs of the rheumatic disease.

3. *Test parameters for study.* Patients should be grouped according to disease. The studies should be double-blind crossover in design with aspirin as the standard drug and the patients treatment scheme should be randomized. Objective indices of joint inflammation should be measured (Ref. 1), e.g., grip strength measured by manometer, circumference of the proximal interphalangeal joints, measurement of the time taken to walk 50 ft and the number of swollen or tender joints.

Prior to carrying out an antirheumatic assay, the appropriate statistical analysis should be defined. Unless the above points have been observed, any statistical analysis would only impart a false sense of confidence in the results.

4. *Data interpretation.* To establish Category I status for a Category III ingredient, the number of studies required for compounds for which safety is unquestioned and the number and types of studies required for compounds questioned because of safety, will be the same as outlined for Category III analgesic ingredients. (See part III. paragraph C. above—Data Required for Evaluation.)

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

5. *Safety evaluation.* An evaluation of the safety of an antirheumatic ingredient should be based on the same studies and observations discussed earlier in this document for the safety evaluation of analgesics. (See part III. paragraph C.5.—Safety evaluation.)

REFERENCES

(1) Dick, W. C. et al., "Indices of Inflammatory Activity," *Annals of Rheumatic Diseases*, 29:643–648, 1970.

VI. ADJUVANT AND CORRECTIVE AGENTS

A. GENERAL DISCUSSION

The Panel considered several nonanalgesic ingredients as "active" because they were submitted as such pursuant to the notice published in the FEDERAL REGISTER of July 21, 1972 (37 FR 14633) and the Panel classifies these as adjuvant and/or corrective agents because they may affect the activity or safety of the analgesic components(s) of the submitted preparation(s).

The Panel is of the opinion that these ingredients, which are commonly found in marketed products, can be properly reviewed as a separate group, i.e., as components of a drug delivery system. Their activity either derives from or modifies the activity of the analgesic, antipyretic or antirheumatic agents reviewed. More specifically, this group may be divided into three categories to include adjuvants, which may be directly or indirectly acting, correctives and excipients.

The components of the drug delivery system can be defined as follows:

1. *Adjuvants.* Adjuvants are agents which, in the amounts used, have no significant analgesic effect themselves but contribute to the therapeutic effect of the active agent either directly or indirectly.

a. *Direct acting.* A direct acting adjuvant is one which enhances the pharmacologic response directly by synergistic or additive effects at the site of action. For example, caffeine is added to some analgesic preparations for this purpose.

b. *Indirect acting.* An indirect acting adjuvant is one which does not have effects at the site of action, but indirectly increases the activity of the active agent(s) of the preparation by modifying the disposition (absorption, metabolism, excretion or distribution) of the active agent. Examples include benzoic acid and salicylamide, which are claimed to compete for metabolizing systems affecting the elimination (benzoic acid) or absorption (salicylamide) of aspirin. Buffering systems may act as an indirectly acting adjuvant by increasing the rate of absorption of salicylates.

2. *Correctives.* A corrective is an agent in the drug delivery system intended to reduce some undesirable effect of the therapeutically active agent. An example would be the addition of buffering agents to aspirin formulations to reduce the incidence of gastric distress.

3. *Excipients.* In the course of the manufacture of the finished dosage form, many inert ingredients are required, such as starch or other agents to aid disintegration, or magnesium stearate as a lubricant in the tableting process. Not only should these agents be inert pharmacologically but inactive from the point of view of adversely affecting the rate and extent of the absorption of the active agents. It is important to recognize that some of the agents above may have effects relating to two components, for example, buffering agents may be added to serve as an indirectly acting adjuvant to enhance absorption rate of aspirin or as a corrective to decrease the incidence of gastrointestinal adverse effects of aspirin. In these cases each effect should be considered as a separate claim since the mechanism of action and the clinical endpoint are likely to be different.

B. CATEGORIZATION OF DATA

1. *Antacid or buffering ingredients.* The Panel has classified the following as ingredients of buffering systems for use as antacids or correctives:

Aminoacetic acid (glycine, glycocoll)
Calcium carbonate
Calcium phosphate dibasic (monocalcium phosphate)
Citric acid
Dihydroxyaluminum aminoacetate (aluminum glycinate)
Dihydroxyaluminum sodium carbonate
Dried aluminum hydroxide gel
Magnesium carbonate
Magnesium hydroxide
Sodium bicarbonate
Sodium carbonate

The Panel notes that these ingredients are generally recognized as safe and effective antacid active ingredients and are identified in § 331.11 of the OTC antacid monograph.

The Panel finds that there are three major types of marketed products containing these ingredients that have been submitted to the review:

MARKETED PRODUCTS CONTAINING ANALGESIC COMBINED WITH ANTACID OR BUFFERING INGREDIENTS

Analgesic-antacid products. Products containing nonsalicylate ingredients combined with antacids.

Buffered aspirin products. Products containing aspirin combined with buffering ingredients (correctives).

Highly buffered aspirin for solution. Products containing aspirin combined with antacids.

a. *Products containing nonsalicylate ingredients combined with antacids.* One group consists of products containing analgesic, antipyretic and/or antirheumatic active ingredients combined with these antacid agents in such quantities that they can be classified as antacids pursuant to the OTC antacid monograph. Such marketed combination products are not only labeled as analgesics (for "headache," "pain", etc.) because of their analgesic ingredient(s) but are also labeled as antacids (for "heartburn", "sour stomach", etc.) because they also contain effective antacids.

The Panel concludes that such combinations are appropriate provided they contain nonsalicylate ingredients and satisfy the standards established by the Panel for combination products. (See part II, paragraph G.4.g. above—Standards for Category I combination products.) Each claimed antacid ingredient must be generally recognized as safe and effective as an antacid and be identified in § 331.11 of the OTC antacid monograph. Labeling for concurrent symptoms may include "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for acid indigestion".

b. *Products containing aspirin combined with buffering ingredients (correctives).* Another major group of marketed products contain these agents combined with aspirin. These products are identified as "buffered aspirin" if the finished product contains at least 1.9 mEq of acid neutralizing capacity per 325 mg (5 gr) aspirin. These agents are employed to reduce the local irritant effects of aspirin which have been extensively discussed earlier in this document. (See part III. paragraph B.1.a.(2)(ii) above—Adverse effects on the gastrointestinal tract.) Buffered aspirin products are labeled as an analgesic (for "headache", "pain", etc.) accounting for the recognized activity of aspirin, but in addition, are labeled with terms such as "buffering agents to help make the pain reliever more gentle to the system", or "helps prevent the stomach upset often caused by pain aspirin". The Panel has discussed such labeling more fully below. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

Buffered aspirin is defined in this document as a solid dosage form which consists of aspirin plus a sufficient quantity of alkaline buffers to significantly increase the dissolution rate of the product relative to a standard aspirin tablet without necessarily increasing the pH of the gastric fluid. The Panel recommends that specific standards be established, through appropriate testing procedures, that each product shall meet in order to be recognized as a safe and effective "buffered aspirin" preparation.

The Panel concludes that aspirin tablets may be labeled as "buffered aspirin" providing they meet the following minimum requirements: Each dosage unit contains antacid active ingredients identified in § 331.11 of the OTC antacid monograph such that the finished product contains at least 1.9 mEq of acid neutralizing capacity per 325 mg (5 gr) aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of the OTC antacid monograph.

The product should have dissolution characteristics equivalent to the buffered aspirin tablet that has been used in most comparative clinical studies (Refs. 1 through 6). The dissolution test used should be capable of detecting significant differences in the initial rate of dissolution which correlates with the in vivo rate of absorption. This problem of devising suitable dissolution methodology is likely to involve significant experimental development to establish in vitro/in vivo correlations and is therefore, beyond the scope of this Panel. The conditions of the dissolution tests should be established by the appropriate compendial and/or Governmental Agency. A tentative methodology is described below for illustrative purposes. (See part VI.

paragraph C.1.b. below—Aspirin (plain and buffered) tablet dissolution testing procedure.) While these are desirable formulation characteristics, the Panel has placed claims relative to these effects in Category III because of the potential of these statements to mislead the general public. Evaluation of individual claims is necessary to assure that the claims do not imply that increased rate of absorption has been proven to result in improved clinical effectiveness or that decreased incidence of gastric distress is significant for most people or that increased incidence of recurring gastric distress following aspirin ingestion in a small set of patients implies greater safety from serious gastrointestinal effects associated with aspirin products.

Current evidence indicates that properly formulated preparations, those meeting the proposed antacid and dissolution standards, can be expected to (1) increase the rate of absorption of aspirin relative to a plain aspirin tablet; and (2) decrease the incidence of subjective gastric intolerance in some of the relatively small percentage of persons in the general population who regularly experience gastric intolerance with OTC doses of plain aspirin tablets.

In the presence of buffers, an increase in dissolution rate of aspirin tablets has been demonstrated. Even though the amount of buffer in buffered aspirin tablets is not sufficient to markedly affect the pH of gastric fluids, it does increase the pH immediately around the dissolving particles causing an increased rate of dissolution of aspirin from the particles (Refs. 7 through 9). Since dissolution is usually the rate-limiting process for gastrointestinal absorption of salicylates given in solid dosage form, the greater dissolution rate of aspirin in the presence of buffers results in a more rapid rate of absorption (Ref. 10). However, other aspirin formulation variables, such as the tablet compression and choice of tablet excipients, can also have significant effects on the rate of dissolution of aspirin (Refs. 7 and 8). Thus, the inclusion of buffering agents alone will not necessarily result in an increase in the dissolution rate and, therefore, the absorption rate of aspirin. Buffered aspirin tablets with slower rates of dissolution than plain aspirin tablets have been reported (Refs. 7 and 8). Therefore, it is important to evaluate the actual dissolution rate of products claiming rapid absorption. The Panel believes that a suitably designed dissolution test would obviate the necessity of requiring in vivo blood level studies for all buffered aspirin products in order to establish increased absorption rate. It should be noted that a clear relationship between absorption rate and clinical effects (onset, intensity or duration of clinical effects) has not been definitively established. (See part II. paragraph J.4.e. above—Onset, duration and intensity of pharmacologic effects.)

Buffered aspirin has been claimed to reduce subjective symptoms of gastric intolerance (dyspepsia, stomach upset, gastric distress, etc.) associated with aspirin ingestion. The evaluation of this claim is difficult because the overall number of persons who regularly experience subjective symptoms of gastric distress is relatively small in the general population. However, the evidence seems to indicate that some individuals in this small subset of the general population may experience less gastric intolerance with some buffered aspirin tablets compared to plain aspirin tablets.

Sher (Ref. 1) compared buffered aspirin, unbuffered aspirin and aspirin-phenacetin-caffeine products in a prisoner population. Twenty-nine percent or 476 of the total population of 1,629 prisoners reported a previous history of gastric intolerance to aspirin products. The effects of the 3 types of aspirin products were studied in 236 of these 476 prisoners. The 236 prisoners in this "double-blind" study were selected at random. Sher claims that 94 percent of these 236 subjects had one or more complaints of gastric intolerance during the study. "Severe" reactions were encountered more often with an aspirin-phenacetin-caffeine combination (33 percent) and with aspirin alone (18.3 percent) than with buffered aspirin (3.9 percent).

Paul (Ref. 3) also claimed that buffered aspirin produced less gastric distress.

Fremont-Smith (Ref. 2) found 70 percent of patients who were intolerant to unbuffered aspirin could take buffered aspirin and 30 percent were intolerant to both forms.

Unpublished double-blind, crossover, multiple dose studies by Paul (Ref. 4) submitted to this Panel provide evidence that a buffered aspirin tablet and highly buffered aspirin tablet may produce less incidence of gastric intolerance than either unbuffered aspirin tablets or a product containing aspirin and caffeine when multiple doses are administered.

Some investigators have failed to show a difference between buffered and unbuffered aspirin in controlled studies. Batterman (Ref. 5) used a crossover double-blind technique in ambulatory and hospitalized patients who received repeated doses for 1 day, 1 week, 1 to 3 weeks and greater than 5 weeks. Intolerance increased with duration of therapy for both preparations with no significant difference between the two. There is a question whether the tablets used in this study were representative of the usual marketed preparations used in most other studies in the literature.

Cronk (Ref. 6) states that in a well-controlled study only 8 of 397 patients showed gastric intolerance with no difference between buffered aspirin or plain aspirin. Patients who experienced intolerance to regular aspirin did not complain when repeatedly given unidentified aspirin. These latter two studies did not evaluate large numbers of patients usually intolerant to aspirin and the authors did not demonstrate the sensitivity of their method.

Thus, the evidence although apparently conflicting seems to indicate that buffered aspirin produces a lower incidence of gastric intolerance in some patients but not in all patients who exhibit gastric intolerance with regular aspirin products. The number of patients who might benefit from buffered aspirin compared to standard aspirin is probably small. (See part III. paragraph B.1.a.(2)(ii) above—Adverse effects on the gastrointestinal tract.)

The results of a study on subjective gastric intolerance obtained with a given buffered aspirin product cannot necessarily be extrapolated to all other buffered aspirin products. It is not clear whether an observed decrease in gastric distress is related to the buffering effect on the pH of the microenvironment surrounding the dissolving particles, an increased dissolution rate, or both. However, it is the opinion of the Panel that claims of less gastric intolerance if valid for one buffered product would also be justified for other buffered aspirin tablets which contain the same neutralizing capacity and show similar dissolution characteristics and appropriately designed dissolution procedures as determined by this Panel.

Evaluation of individual formulations is beyond the scope of the Panel's review. It is the Panel's opinion that if a buffered aspirin formulation meets the requirements for buffer capacity and dissolution rates outlined above, the claims described below may be used. (See part VI. paragraph B.1.d. below—Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients.)

In spite of this apparent superiority in terms of blood salicylate studies there is no evidence on the basis of controlled clinical analgesic assays that buffered or highly buffered aspirin provides a more rapid onset, a greater peak intensity, or a more prolonged duration of analgesia than unbuffered aspirin (Ref. 9).

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c. *Products containing aspirin combined with antacids*—(1) *Introduction.* Highly buffered aspirin for solution contains a sufficient quantity of buffers to conform to the specifications for antacids established in the antacid monograph (21 CFR Part 331) and therefore, will increase the pH of the gastric fluid. Such products, which have a neutralizing capacity of at least 20 mEq of hydrochloric acid, have been shown to significantly decrease gastric occult bleeding that results from the direct effects of aspirin on the gastric mucosa. Such products also have the most rapid rate of aspirin absorption. The Panel notes that there is current OTC marketing of aspirin combined with antacids for use as an effervescent solution with labeling for use in the symptomatic relief of concurrent symptoms requiring both an antacid and an analgesic-antipyretic.

The Panel finds it irrational to include aspirin with any antacid preparation intended to provide claims for an antacid effect, e.g., "For the treatment of heartburn, sour stomach and acid indigestion", since aspirin in any dosage form e.g., tablet, highly buffered aspirin solution, etc., can potentiate symptoms of peptic ulcer, occult bleeding and in some predisposed individuals massive gastrointestinal bleeding. The serious adverse effects of aspirin on the gastrointestinal tract occur more frequently in individuals who have existing gastrointestinal disorders which are often characterized by the recurring gastric symptoms described above.

Therefore, the Panel concludes that it is rational to market such an aspirin product for use only as an analgesic-antipyretic and not for concurrent symptoms requiring an antacid. The Panel has identified such products as highly buffered aspirin for solution. The Panel has discussed products as highly buffered aspirin for solution. The Panel has discussed the basis for these conclusions that any potential increased analgesic benefits derived from combining aspirin and an antacid for concurrent symptoms is not justified by the increased risk of serious adverse effects in this population relative to other analgesic ingredients that are available to the target population. (See part III. paragraph B.1.a. (2)(ii) above—Adverse effects on the gastrointestinal tract.)

The highly buffered aspirin for solution products discussed above contain aspirin combined with antacid active ingredient(s) identified in § 331.11 of the OTC antacid monograph such that the finished product contains at least 20 mEq of acid neutralizing capacity per 325 mg (5 gr) aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of the OTC antacid monograph. These products shall be identified as "highly buffered aspirin for solution" or as "specially buffered aspirin" with labeling only as an analgesic and/or antipyretic.

The Panel is limiting claims for these products to "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever". In addition, claims such as "Provides ingredients that may prevent the stomach upset that plain aspirin occasionally causes", and/or "Gets to the bloodstream faster than plain aspirin", are possibly more valid for highly buffered aspirin products for solution than for buffered aspirin tablets. However, these claims would carry the same benefit to risk considerations for highly buffered aspirin for solution as for other buffered aspirin preparations and must therefore be considered as Category III.

Currently marketed highly buffered aspirin for solution preparations are claimed by the drug manufacturer to be safe for self-medication by individuals with symptoms of stomach distress, indigestion and heartburn and to be safe for occasional use for relief of concurrent symptoms requiring both an antacid and an analgesic, both for individuals with normal gastrointestinal function and those who may have peptic ulcer. The following statements have also been made by them (Refs. 1 and 2):

> Evidence is presented indicating that blood loss occurring after the ingestion of aspirin, whether occult or overt, is due to the action of unionized aspirin in altering the gastric mucosal barrier, permitting back diffusion of aspirin into the gastric mucosa. In the absence of these events there will be no blood loss from aspirin . . . data are also presented which demonstrate that blood loss occurring after the ingestion of aspirin is due not only to the action of unionized aspirin in breaking the gastric mucosal barrier but in the absense of acid there will be no blood loss from the stomach [and] The conclusion that individuals with peptic ulcer (whether or not diagnosed) are not at risk from highly buffered aspirin is founded on the demonstrated evidence that [highly buffered aspirin solution] does not initiate acute gastric erosions.

It is therefore argued by the drug manufacturer that this type of product is safe by virtue of special properties conferred by the highly buffered aqueous drug delivery form which obviates the acid-mediated local effects of aspirin on the gastric mucosa. It is alleged that aspirin contributes to both occult and massive bleeding through only these acid-mediated local effects (Refs. 1 through 4).

The Panel concludes that there is evidence that highly buffered aspirin solutions will reduce, but not eliminate the acute gastric erosions and occult blood loss produced by the local effects of aspirin in experimental animals and individuals with no predisposing gastrointestinal disease. However, there is no valid clinical evidence to support the claim that highly buffered aspirin for solution has significantly less potential to induce major gastrointestinal hemorrhage in patients with preexisting gastrointestinal lesions which the Panel believes includes mechanisms other than the acid-mediated local mechanisms involved in the production of occult bleeding in normal subjects. Major gastrointestinal bleeding produced by aspirin is frequently associated with recurring gastric distress and a history of peptic ulcer, gastritis or previous episodes of gastrointestinal hemorrhage.

Contrary to the assertions in the data submitted by the manufacturer, there is no evidence to support their arguments that aspirin acts through only one single localized mechanism. In fact, the submitted studies and references support the view that several different mechanisms may be involved in the potentiation of bleeding from acute lesions by the local and/or systemic effects of aspirin and salicylates on hemostasis as well as on mucosal blood flow. These lesions are not only caused by aspirin in the presence or absence of gastric acid but may also be caused by other factors.

The claims for highly buffered aspirin solutions have been quite controversial. The Panel in its examination of these claims has had the advantage of extensive information from recent reviews, including the conclusions of the OTC Antacid Advisory Panel's review of the evidence for this claim (Ref. 5), and also of the hearings and individual reactions to published conclusions of others (Refs. 6, 7, and 8). The Panel has also had the advantage of several new epidemiological (Refs. 9 and 10) and experimental studies (Refs. 11 through 13) not reviewed by previous groups which support the concept that major gastrointestinal bleeding involves multiple mechanisms, and that highly buffered aspirin preparations can induce bleeding.

The Panel has also reviewed all available epidemiological data implicating highly buffered aspirin solution preparations from the above point of view that several mechanisms are involved. Many of the inconsistencies in the arguments used in the drug manufacturer's submission are resolved by the concept that aspirin in any dosage form can potentiate massive bleeding in certain individuals with existing "primed" (ready to bleed or slightly bleeding) bleeding sites.

Based upon the total evidence now available to the Panel, it concludes that the evidence is insufficient to substantiate the claims that buffered or highly buffered aspirin solution is safe for use in patients who should not take regular, unbuffered (plain) aspirin. Furthermore, based upon current knowledge of high risk groups such as individuals who drink alcohol excessively, the benefit to risk ratio for individuals with symptoms of gastric distress, particularly with concomitant headache, does not warrant the use of aspirin in any dosage form. Therefore, the Panel does not recommend any exception to the current proposed labeling warning which states: "*Caution:* Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

The Panel's conclusions, which are discussed more fully below, are based in part on a thorough evaluation of all submissions that support the concurrent antacid-analgesic claims, including the

arguments relating to assumptions on the mechanism of aspirin-induced bleeding and the properties of highly buffered aspirin for solution preparations on animal and clinical experimental studies, including published and unpublished studies on occult bleeding in normal and peptic ulcer patients; on the analysis of published epidemiological studies; and on marketing experience data.

(2) *Arguments submitted to the Panel to support concurrent analgesic-antacid labeling claims for highly buffered aspirin for solution.* All arguments given in the extensive materials provided to the Panel directly relate to the following basic contentions: (i) *The acid-mediated single mechanism theory.* The first contention relates to the primary mechanism involved in the gastric damage produced by aspirin. It is asserted that massive bleeding, erosive gastritis and occult (unseen) bleeding, all result from the same (universal) gastric acid-mediated (Davenport) mechanism and only this single mechanism is involved. According to this mechanism, the presence of gastric acid is required for aspirin to produce the primary lesion involved in massive or occult bleeding. The primary lesion must be produced by the absorption of unionized aspirin into the mucosal cell and at some critical concentration increases the permeability of the gastric barrier which facilitates backflux of hydrogen ion to produce subsequent erosion and hemorrhage. This postulate is referred to by the Panel as the "acid-mediated single mechanism theory."

(ii) *The alleged distinctive properties of highly buffered aspirin for solution.* The second contention relates to proposed properties of highly buffered aspirin solutions. It is asserted that the direct effects of aspirin, and therefore gastric bleeding, are not possible with highly buffered aspirin for solution because in these solutions only sodium acetylsalicylate, which is chemically and pharmacologically distinct from aspirin, is present. Acetylsalicylate, the ionized form of aspirin, is not absorbed into the mucosal cell. Therefore, critical concentrations are not reached in the cell for local effect. Also, the gastric acid is neutralized, and therefore, hydrogen ion is not available to damage the mucosa, thus erosion and massive bleeding cannot occur.

The Panel concludes that submitted and published experimental information which is discussed in more detail below does not support any of these contentions. In the evaluation of statements in the extensive submissions to the Panel, it found that in the final analysis, the validity of the claim for use of highly buffered aspirin for solution preparations for concurrent symptoms, i.e., for use as an antacid and analgesic, is dependent on an unproven argument that there is only one single mechanism involved in massive bleeding. Virtually all other arguments in the submission are dependent upon the validity of the "acid-mediated single mechanism theory."

(3) *Data submitted to the Panel to support concurrent analgesic-antacid labeling claims for highly buffered aspirin for solution.* The acid-mediated single mechanism theory has been the basis of the additional sequence of arguments which have been used to justify the proposed use of highly buffered aspirin for solution products in individuals with stomach distress, gastritis, peptic ulcer, etc.

(i) *The allegation that occult bleeding studies demonstrate the safety of highly buffered aspirin for solution.* In the data submitted to the Panel, it is contended that since aspirin-induced massive bleeding and occult bleeding involve the same mechanism, studies of occult bleeding are adequate to establish safety relative to major (massive) gastrointestinal bleeding (Refs. 1, 2, and 3).

This assertion is the basis of the use of occult bleeding studies in normal subjects and experimental animals in place of clinical studies. The Panel finds that this assertion and the use of these studies are not consistent with available experimental evidence. Occult blood studies in normal subjects do not serve as good models for the effects of aspirin in "primed" individuals with preexisting gastrointestinal pathologies and potentially bleeding acute lesions.

(ii) *The contention of the absence of highly buffered aspirin for solution associated erosion and occult bleeding.* In the data submitted to the Panel, it is contended that because highly buffered aspirin for solution does not produce erosion or occult bleeding, it is safe for use in individuals with a history of signs and symptoms including gastric distress, gastritis, peptic ulcer or massive bleeding (Refs. 2 and 3).

All initial experimental studies with highly buffered aspirin for solution submitted to the Panel involved short-term use of the product in normal subjects or animals in which no increased occult blood loss was claimed as proof of safety for highly buffered aspirin for solution (Refs. 1 and 2). However, upon the request by the Panel for information on occult blood loss in humans or animals with existing lesions, new information was obtained showing that when preexisting lesions were present, occult blood loss after highly buffered aspirin for solution use was actually increased (Refs. 11, 12 and 14).

(iii) *The argument against aspirin-associated massive bleeding in the absence of gastric erosion.* In the data submitted to the Panel, it is contended that since aspirin-induced massive bleeding and gastric erosion occur only through acid-mediated gastric erosion, any cases of massive bleeding not involving aspirin-induced acute erosion cannot be considered to have been caused by aspirin (Refs. 3, 15, and 16).

This argument is used to dismiss the few epidemiological studies which have specifically considered highly buffered aspirin for solution preparations as a separate class and found them associated with cases of massive bleeding to the same extent as regular aspirin preparations (Refs. 15 and 16).

The Panel concludes that the studies of Brown and Mitchell (Ref. 15) and Jennings (Ref. 16), which were criticized by Langman (Ref. 17) on the basis of the above invalid argument, actually support the conclusion that highly buffered aspirin for solution like other aspirin formulations can potentiate massive bleeding from existing lesions in individuals with a variety of gastrointentinal disorders.

The Panel concludes that several types of evidence (experimental and epidemiological) clearly show that the effects of aspirin cannot be totally explained by one mechanism and that the acid-mediated acute lesion produced by aspirin is not the only mechanism by which aspirin can contribute to massive bleeding (Refs. 4, 9 through 12, 14, 18, and 19). There is good evidence that all aspirin products can precipitate bleeding from existing acute lesions.

The Panel finds that there is conclusive evidence that aspirin can and does produce acute erosions and occult bleeding by the acid-mediated mechanism, but that gastric acid is not essential for all local effects of aspirin. The Panel also concludes that in view of the evidence now available it is impossible and illogical to attempt to explain all effects of aspirin on the gastrointestinal tract by a single mechanism in which the effect must involve a lesion produced by aspirin mediated through gastric acid.

Thus, the Panel concludes that aspirin in any form can potentiate major gastrointestinal bleeding in certain individuals with new or preexisting mucosal lesions. The bleeding lesions may be either caused by aspirin in some cases, or by other factors (alcohol, stress, gastrointestinal disease) and may be simply triggered or potentiated by aspirin. This mechanism(s) explains and correlates many otherwise inconsistent clinical and experimental observations.

(4) *Analysis of data submitted to the Panel*—(i) *Evidence for and against a universal acid-mediated mechanism.* A recent submission on highly buffered aspirin for solution (Ref. 3) illustrates the sequence of invalid reasoning repetitively used to show that highly buffered aspirin for solution cannot produce massive bleeding. The argument that massive gastrointestinal bleeding must occur from erosions caused by aspirin is discussed in the submission to reinforce arguments given in previous submissions (Refs. 1 and 2). The recent submission states: "For massive gastrointestinal bleeding to occur in response to aspirin, there must be sufficient erosions of the gastric mucosa." Information is also summarized in the submission to show that aspirin can cause gastric erosions and that the direct effect of aspirin is consistent with the acid-mediated Davenport mechanism. The Panel notes that it is unwarranted to conclude that because (a) erosions are needed for bleeding, (b) aspirin causes lesions, and (c) aspirin can act through the acid-mediated Devenport mechanism, that therefore, all gastric bleeding involves erosions produced by the Davenport mechanism. Such a conclusion assumes that there is evidence that only one possible mechanism exists for each of the three observed events.

It is stated (Ref. 3) that "Dagradi et al. confirmed that aspirin is capable of causing massive gastrointestinal bleeding because of its ability to initiate acute gastric erosions". They further state that erosions will be prevented if acid is eliminated from the stomach and cite animal studies to support this statement as follows: "Evidence that there is only a single mechanism whereby aspirin may produce gastric damage and blood loss is the fact that * * * even under conditions where aspirin will produce severe hemorrhagic erosions, these erosions will be prevented from occurring if conditions are varied by eliminating the presence of acid in the stomach," citing the animal studies of Brodie and Chase (Refs. 20 and 21) and Dagle et al. (Ref. 22) and concluding that "regardless of the severity of the gastric damage or bleeding response, the presence of acid in the stomach is an essential element for this to occur" (Ref. 2).

Finally the submission (Ref. 3) quotes Cooke (Ref. 23) who reiterates the key argument that only one mechanism is involved with all adverse aspirin effects on the gastrointestinal system: "Finally, the basis of aspirin damage to the gastric mucosa, i.e., erosions, occult and overt bleeding is the presence of acid in the lumen of the stomach."

However, the animal studies of Brodie and Chase (Refs. 20 and 21) and Dagle et al. (Ref. 22) clearly show that gastric acid is not required for aspirin to produce gastric erosions.

As noted above, even if each statement regarding experimentally observed phenomena were valid, the Panel concludes that it is not valid to extrapolate that each event is causally related to each other to the exclusion of all other possible contributing or causal factors.

In the Panel's review of the data of Dagradi et al. (Ref. 24), the Panel agrees that, indeed, evidence is provided that would support the contention that aspirin may cause massive bleeding by virtue of initiating acute gastric erosions. However, this same study also provides evidence that aspirin may precipitate or potentiate bleeding from lesions that were quite unlikely to have been caused by the acute effects of aspirin.

Thus, the basic fallacy in virtually all arguments given in the submissions is the unproven, and in the Panel's opinion, highly unlikely argument that aspirin can cause massive gastric bleeding only if aspirin directly produces the acute bleeding lesion (with the further constraint that aspirin can produce the lesion only through the acid-mediated mechanism).

There are now several lines of recent evidence which strongly indicate that massive bleeding related to aspirin ingestion does not involve only one type of acute gastric erosion but several types, some of which may have been present before aspirin was administered. These potentially bleeding erosions may have been caused by a variety of initiating factors, including stress, alcohol and infection, as well as aspirin and other drugs.

Although morphologically different, these lesions have the same clinical characteristics and prognosis in cases of massive bleeding. These lesions may be chronic or acute, gastric or intestinal, and involve excessive secretion or the absence of gastric acid (Refs. 24 and 25). The feature they have in common, however, is an abraded mucosa with an exposed engorged capillary bed which by virtue of the unique vascular arrangement are very prone to an oozing type of bleeding dependent on platelet plugs for hemostasis (Ref. 26). The Panel has discussed the effects of aspirin on platelet aggregation and hemostasis elsewhere in this document. (See part III, paragraph B.1.a.(2)(i)(c) above—Relationship between systemic platelet effects and gastrointestinal bleeding.) There is now considerable evidence that the primary effects of aspirin on these lesions is a prolonged impairing effect on hemostasis involving irreversible platelet damage and there may possibly be other effects on the microcirculation, although this has not been proven.

The submission dismisses the effect of aspirin on hemostasis as a factor in massive bleeding on the basis of the study by Leonards and Levy (Ref. 27) who showed that aspirin given intravenously increased template bleeding time but did not increase occult bleeding. The lack of correlation between bleeding time and occult blood loss has also been noted by the Panel. (See part III, paragraph B.1.a.(2)(ii)(e) above—Occult bleeding.)

The use of this study as evidence to conclude that the systemic aspirin hemostatic effect does not relate to massive bleeding, again results from the unwarranted adherence to the unproven single acid-mediated mechanism theory. This conclusion is again not valid unless it is assumed that massive bleeding and occult bleeding are identical, or that the individuals studied by Leonards and Levy had preexisting lesions which predisposed them to massive bleeding episodes, and therefore, they served as realistic models to determine the effects of the increase in bleeding time on gastric bleeding from preexisting potentially bleeding sites.

The Panel reemphasizes that a study which shows no difference should not be accepted unless there is evidence that the study was properly designed relative to the question at hand and that the study had sufficient sensitivity to detect real differences if they did exist. The design of this study of occult bleeding in normal subjects is totally unrelated to the question of whether systemic aspirin effects on platelet function and thus bleeding time will potentiate bleeding in patients who have existing potentially hemorrhagic gastrointestinal lesions. Indeed, the studies of Grossman showed that intravenous aspirin caused significant gastrointestinal bleeding in only the two "primed" individuals who had preexisting lesions (Ref. 19). This information was noted in the submission but dismissed because it conflicted with their single acid-mediated mechanism theory.

The evidence supporting the potentiating role rather than the initiating role of aspirin in bleeding from existing erosions is reviewed below.

The Panel concludes that there is now significant evidence from experimental and clinical studies strongly supporting a mechanism in which aspirin can potentiate major gastrointestinal bleeding in certain individuals with preexisting mucosal lesions. The possibility that bleeding lesions may be either caused by aspirin in some cases but also may have been caused by other factors and simply triggered or potentiated by aspirin, provides a unifying mechanism that explains and correlates many otherwise inconsistent clinical and experimental observations.

(ii) *Evidence for multiple mechanisms of aspirin-induced massive bleeding.* The Panel concludes that current evidence indicates that aspirin may contribute to the increased incidence of massive gastric bleeding by direct production of the bleeding lesion and/or by potentiating bleeding from existing lesions. (*a*) *Direct production of acute mucosal lesions.* In some cases it is possible that repetitive dosing with aspirin directly produces acute erosive gastritis which becomes the bleeding lesion. Supporting evidence, discussed elsewhere in this document, is the extensive clinical and experimental data showing that aspirin reproducibly produces gastric erosions and occult bleeding in normal subjects. Massive bleeding, however, is more likely in individuals with existing gastrointestinal disease (Refs. 28, 29, and 30). (See part III, paragraph B.1.a.(2)(ii)(*g*) above—Massive gastrointestinal bleeding.) However, when a challenge dose of aspirin is given to individuals who have recently experienced massive hemorrhage following aspirin ingestion or who may have peptic ulcers which may have been produced by chronic aspirin ingestion, the occult bleeding and gastric damage produced in these individuals is frequently no different than that produced in normal control subjects (Ref. 31).

Those who contend that aspirin contributes to massive bleeding only by its direct mucosal erosive effect, claim that this is proof that there must be other modifying factors in order for local erosion and occult bleeding to progress to massive hemorrhage. For those who argue that there can be no effect of aspirin other than the direct local effect, these modifying factors must of course be assumed to be independent of aspirin. Current evidence indicates that aspirin is a modifying factor which can increase bleeding from certain types of bleeding lesions (acute mucosal lesions) (Refs. 19 and 32). Langman (Ref. 17) claims that the absence of proof that such modifying factors commonly occur must be considered as evidence that the contribution of aspirin to massive bleeding must be limited. The validity of this conclusion is also of course dependent on the assumption that aspirin acts by only one direct mechanism.

In the opinion of the Panel, there is insufficient evidence to assume that all

gastrointestinal effects of aspirin are limited to one single mechanism. The evidence offered by proponents of this theory (Refs. 1 through 4, and 33) is based on the contention that in order to contribute to massive bleeding aspirin must cause the bleeding erosion by the same mechanism that it causes occult bleeding. An important part of their basic assertion is that this common mechanism requires the involvement of gastric acid since part of the proof involves the reduction of occult bleeding by a highly buffered aspirin preparation. Evidence has been given previously that occult bleeding and massive bleeding are unlikely to be due to the same effects of aspirin and that the direct erosive effects of aspirin and occult bleeding can occur in the absence of gastric acid. Furthermore, the development of erosions associated with massive bleeding can occur in the absence of either acid or aspirin, for example as a result of alcohol or stress (Refs. 24 and 26).

While there is no reason to rule out the possibility that aspirin may initiate acute erosions or increase the bleeding from existing erosions by direct musocal effects, there is no reason to assume that this is the only mechanism possible or that the mechanism requires gastric acid since massive bleeding following aspirin ingestion may occur in patients with achlorhydria (Refs. 25 and 34).

(b) Potentiation of bleeding from existing erosions. Although aspirin at times causes acute mucosal erosions, in many cases reported bleeding took place after only a few aspirin ingestions in patients with gastric conditions in which acute lesions were highly likely to exist, such as chronic gastritis and chronic atrophic gastritis. This is true also, however, in the four studies cited by Langman (Ref. 17) in which aspirin had a greater probability of being involved in bleeding in the presence of a peptic ulcer because mucosal lesions are also associated with peptic ulcer. The typical lesion involved in most acute bleeding cases is described by Katz and Siegel (Ref. 26).

Katz and Siegel (Ref. 26) have discussed the relationship between gastrointestinal hemorrhage and the occurrence of the acute gastric mucosal lesion which is involved in bleeding from acute erosive gastritis (localized or diffuse small erosions a few millimeters in diameter), acute gastric ulcer (single or multiple erosions 10 mm or more in diameter), and hemorrhagic gastritis (which may appear to "weep" blood without recognizable erosions or ulcers). The latter category is not generally detected by gastroscopy but is observed during surgery.

The acute gastric mucosal lesion is characterized histologically by the presence of three features which are: denudation of superficial epithelium; hemorrhage in the capillary-rich area of the neck of the glands; and hemorrhage in the lamina propria which has diffused throughout the gastric gland area. The degree of involvement of each of these categories may not be evident unless multiple biopsies are made. In 93 patients with upper gastrointestinal bleeding, the acute mucosal erosions were present in histological studies in 68.6 percent of patients with gastroscopically observed localized erosions, in 69.7 percent of patients with diffuse gastric erosions, and in 80 percent of patients in whom the cause of upper gastrointestinal hemorrhage was undiagnosed by gastroscopic examination indicating to the authors the possible involvement of antral or duodenal erosions.

The histological acute mucosal lesion is thus the common denominator for a variety of gastric conditions associated with massive gastrointestinal bleeding. The diagnosis actually reported and the incidence in different studies depends upon whether examination was carried out by radiology (x-ray) only, or whether gastroscopic examination was done at all, done on all patients who bled (including x-ray positive cases) or done only in x-ray negative cases. Gastroscopy must be done rapidly as erosions can disappear in a few days after bleeding. Further characterization of the lesion depends upon whether single or multiple biopsies were taken for histological studies (Refs. 24 and 26). Finally, recent studies show that similar types of mucosal lesions are frequently associated with bleeding in the duodenum and jejunum and upper parts of the stomach and esophagus in hiatus hernia and esophageal varices. These lesions are not seen unless special endoscopic procedures (duodenoscopy or esophagoscopy) or surgery are performed.

Several authors have concluded that many cases of x-ray and gastroscopically negative massive bleeding are probably due to acute mucosal lesions (Refs. 25 and 26). The categorization by different authors will also depend on the age group surveyed, the proportion of women and men studied, the proportion of cases involving different inciting agents (aspirin, alcohol, stress) and the precipitating factor (alcohol, stress, aspirin, other drugs).

The acute mucosal lesion is the histological picture seen in hemorrhagic gastritis in which erosions are not seen gastroscopically. This diagnosis is usually not possible gastroscopically but is observed during gastrectomy (Ref. 26). The acute mucosal lesion is seen in 69 percent of localized acute erosive gastritis and 70 percent of diffuse acute erosive gastritis and acute gastric ulcers. The acute mucosal lesion was also observed by Katz and Siegel (Ref. 26) in 80 percent of radiologically and gastroscopically negative cases of overt hemorrhage. It has been shown during surgery that similar erosions can be found concurrently in the gastric and duodenal mucosa and that bleeding may occur from the latter, a possible explanation for some gastroscopically negative cases. A control group had acute lesions in only 6.6 percent of 90 patients which was significantly different from all other groups. The relationships between gastroscopically diagnosed erosions, histologically diagnosed types of gastritis and the frequency of histologically characterized acute mucosal lesions are shown in the following table by Katz and Siegel (Ref. 26):

Relationship between gastroscopically diagnosed erosions, histologically diagnosed gastritis and frequency of histologically characterized acute mucosal lesions

Type of erosion, gastroscopic diagnosis	Number of cases	Cases with acute gastric mucosal lesion (In percent)	Histological diagnosis—type of hemorrhagic gastritis			
			Number chronic gastritis	Chronic superficial gastritis	Chronic atrophic gastritis	Gastric atropy
Localized gastric erosions	35	68.6	7	19	7	2
Diffuse erosive gastritis	33	69.7	8	21	4	0
Undiagnosed (x-ray and gastroscopically negative)	25	80.0	7	13	5	0
Total	93		22	53	16	2

The findings of Katz and Siegel described in the above table are of particular importance showing the high incidence (80 percent) of active mucosal lesions found in the undiagnosed (x-ray and gastroscopically negative) group. Langman in his critical review erroneously concluded that the incidence of aspirin associated bleeding should be small in this group which biased some of his further conclusions.

(1) Acute lesions in peptic ulcer and other x-ray positive conditions. Even when a positive radiological diagnosis of a chronic ulcer is made, further gastroscopic or surgical examination frequently shows that bleeding actually occurs from an acute mucosal lesion (erosion or acute ulcer) and not from the chronic ulcer. A number of studies have been reviewed by Katz and Siegel (Ref. 26) and others showing that the majority of patients with a diagnosis of gastric ulcer are found to be bleeding from coexisting acute gastric mucosal lesions (Ref. 24). Back diffusion of hydrogen ion from gastric acid is generally assumed to be a primary factor in the production of acute gastric erosions, presumably by direct and indirect effects on capillary blood flow through liberation of histamine or other substances from the mast cells in the lamina propria. However, acute mucosal erosions can occur in the stomach with reduced or absent gastric acid (Ref. 26).

The etiology of acute mucosal erosions is apparently the end product of several possible interacting endogenous and exogenous factors which can directly or indirectly affect the mucosal blood supply. Although duodenal ulcer is most often cited as the cause of upper gastrointestinal bleeding, several studies in which early gastroscopy is carried out in all patients have shown that acute gastric erosions are a more frequent site of bleeding than duodenal ulcers (Ref. 35).

It has also been shown that the assumption that alcoholics bleed most often from esophageal varices is false since in one series 43 percent bled from acute gastric mucosal lesions while only 13 percent bled from varices (Ref. 26). Acute erosions were found in 20 of 34 men during acute alcohol intoxication who exhibited abnormal mucosa on histological examination in all 34 cases and acute gastritis in 30 of 34 gastroscopic examinations. Erosions and histology returned to normal after abstinence. It is claimed that the erosions can probably develop in the absence of gastric acid. They also occur in chronic alcoholics in the absence of alcohol ingestion which indicates that alcohol plays a role but is not essential for production of acute mucosal erosions (Ref. 26).

Similarly in hiatus hernia in which the upper portion of the stomach is strangulated, an acute mucosal lesion, similar to those seen lower in the stomach, occurs presumably due to venous congestion from occlusion by the diaphragm. Although aspirin apparently is not the cause of the erosion, bleeding is often precipitated immediately following aspirin ingestion (Ref. 36). Bleeding from acute mucosal erosion in patients with hiatus hernia was involved in 2 percent of all massive bleeding in the series of Katz and Siegel (Ref. 26). Although acute aspirin and alcohol ingestion are frequently involved in bleeding from acute mucosal lesions, it is now clear that acute mucosal erosions can be the end product of a variety of other interacting endogenous and exogenous potential etiological variables which directly or indirectly affect the mucosal circulation.

Histamine produced overt bleeding in one of 17 patients. Histological examination showed minimal denudation of superficial epithelium in only three patients but moderate or severe hemorrhage in the lamina propria in 15 patients and hemorrhage in the neck of all patients. Several studies in animals have indicated the probable role of histamine release from degranulation of mast cells in the lamina propria as a factor in stress ulcers. Other factors including vagal and sympathetic stimulation, epinephrine release, and ACTH release have been shown as possible factors in acute hemorrhagic erosive gastritis associated with a variety of types of physical and emotional stress, infections and hypovolemic shock (Refs. 24 and 26).

In 1961, Kossover and Kaplan (Ref. 32) stated that for more than a decade, controversy has existed regarding the role of salicylates in gastrointestinal bleeding. They stated: "There are those who feel that salicylates could be responsible for the bleeding; those more skeptical who are awaiting additional evidence, and finally the group who ridicules the very idea" and further noted: "Then among those who do believe that this drug can cause bleeding, there is divided opinion between the local gastric irritation theory and the hypothesis that the effect is primarily systemic on blood coagulation." It is interesting that the same controversy still exists even though 15 years ago based upon data available to them, Kossover and Kaplan reached conclusions on the role of aspirin and the mechanisms involved which are essentially the same as the conclusions presented here based on different, more recent experimental evidence.

Based upon information from the literature, from the first report of gastrointestinal bleeding after salicylate medication in 1877 by Balz to the study of Kossover and Kaplan conducted in 1959, the following conclusions were reached (Ref. 32):

(*i*) Stress of different types, including physical and emotional trauma and infections are the primary causes of gastric erosions and may well be the sole cause of gastrointestinal hemorrhage.

(*ii*) The effect of salicylates is at the capillary vascular component possibly by affecting capillary fragility and permeability or affecting clotting mechanisms.

(*iii*) Aspirin may be involved in a reasonable percentage of massive gastrointestinal hemorrhages, in the "cause undetermined" category as well as activation of known gastrointestinal pathology.

Analysis of the data of Grossman (Ref. 19) provides clear and conclusive evidence that aspirin and salicylic acid can both precipitate bleeding from existing lesions and that aspirin has effects which cannot be explained on the basis of the acid-mediated (Davenport) mechanism. Based upon the Davenport mechanism, salicylic acid would be expected to be essentially equivalent to aspirin in producing occult bleeding based on its ability to break the gastric barrier. (See part III. paragraph B.1.a.(2)(ii)(c) above—Acid-mediated erosive gastritis.) There are significant differences, however, between the two drugs in the degree of occult bleeding when given intravenously and orally, and in the duration of increased bleeding after dosing is terminated. In the Grossman study, patients with recent gastrointestinal bleeding who are more susceptible to the effects of salicylates, were given aspirin or salicylic acid orally or intravenously for 3 days followed by a 3-day collection period. These data are summarized below.

Comparison of occult blood loss (milliliter per day) of aspirin and salicylic acid given intravenously and orally to patients with past history of bleeding

	Control before drug	Treatment	Post treatment period (3 d)	Post treatment period 2 (3 d)
Aspirin intravenous 3 g/d×3 d	0.6 ±0.39	1.14±0.89	1.70±0.80	0.81±0.52
Aspirin oral 3 g/d×3 d		2 ±2.8	2.86±2.69	1.06± .066
Aspirin, enteric	.68± .30	1.58± .9	1.42± .21	.52± .3
Salicylic acid, intravenously	.43± .20	.70± .76	.48 .39	
Salicylic acid, oral	.48± .20	.54± .32	.58± .3	.51± .3

Comparison of occult blood loss (milliliter per day) of aspirin and salicylic acid effects in patients with bleeding (primed) lesions

Patient with existing occult bleeding:				
Aspirin:				
Jejunal ulcer	4.0	72.9	209.1	0.66
Duodenal ulcer	4.9	10.1	19.3	4.7
Esophageal varices	6.1	14.3	43.7	21.4
Sodium Salicylate:				
Duodenal	2.9	3.6	24.7	1.6
Esophageal varices	7.1	49.9	9.3	6.2

The effects of aspirin were usually prolonged into the second and third postadministration period of 3 days per period. Sodium salicylate did not exert its effect beyond the first postadministration period even in the "primed" patients with existing erosions. Oral sodium salicylate did however greatly increase blood loss in "primed" patients bleeding from duodenal ulcer and esophageal varices. Oral aspirin greatly increased bleeding in jejunal ulcer, duodenal ulcer and esophageal varices. It is obvious that this effect is not dependent upon the acid-mediated mechanism (Davenport) in the jejunum or esophagus. Thus, part of the action of aspirin appears to be due to local effects of salicylic acid on existing erosions. There is an additional effect which can be exerted from systemic aspirin since it occurs after intravenous administration of aspirin but not salicylic acid. This aspirin effect persists longer than the effect of an equivalent salicylic acid dose. The aspirin effect also increased bleeding longer than salicylic acid in patients with existing bleeding lesions.

The clinical results seen by Grossman et al. (Ref. 19) in patients are virtually identical to the experimental results of Brodie and Hooke (Ref. 37) in rats who showed a difference between aspirin and salicylic acid in the mechanism of inducing bleeding in the fasted rat stomach. Salicylic acid (sodium salt) produced gastric hemorrhage only by the oral route, requiring twice the dose of aspirin to produce this effect (the 50 percent effective dose (ED_{50})). The ED_{50} for salicylic acid and aspirin was 36 mg/kg and 16 mg/kg, respectively. In contrast to salicylic acid which produced gastric lesions only on direct contact, aspirin produced gastric effects also by the intravenous route at the higher dose (36 mg/kg) (Ref. 37).

Both aspirin and salicylic acid potentiate bleeding from existing acute erosions. There is evidence that aspirin has an additional effect that is different from that of salicylic acid. This effect is observed after systemic administration of aspirin but only when potential bleeding from acute erosions exists. It is clear that the potentiating effect of aspirin is not dependent upon gastric acid since

potentiation of bleeding also occurs from duodenal and jejunal ulcers. If the primary effect of aspirin is to enhance bleeding from existing lesions it would be expected that increased occult bleeding would not be observed after intravenous administration of aspirin in normal subjects. This is in fact what has been shown by the data of Leonards and Levy (Ref. 27). Thus, the primary factors in producing occult bleeding in normal subjects appear different than potentiation of bleeding from acute mucosal lesions.

Aspirin-induced occult bleeding in normal subjects can be significantly reduced or eliminated when given as highly buffered aspirin solutions. However, recent studies submitted at the request of this Panel, in patients or animals with existing gastrointestinal lesions, show that increased occult bleeding continues to occur even with highly buffered aspirin preparations. These effects persist even after aspirin is discontinued, similar to the results seen by Grossman et al. (Ref. 19). The role of aspirin in potentiating bleeding from existing erosions is not dependent upon gastric acid because the primary role of hydrogen ion is thought to stimulate histamine release. In existing acute lesions histamine has probably already been stimulated by other factors, the most likely being stress, according to some authors (Refs. 5, 16, 26, and 32).

Increased occult bleeding is produced by aspirin in patients with achlorhydria which is further evidence that some effects of aspirin on abnormal gastric mucosa do not require the presence of gastric acid. This has been shown in several studies in patients with achlorhydria due to atrophic gastritis and pernicious anemia. St. John and McDermott (Ref. 34) have shown, in patients with achlorhydria, that aspirin can induce bleeding in the absence of stomach acid although normal patients gave higher values of blood loss (4.29 ml daily). Achlorhydric patients do show significant blood loss (1.9 ml daily). There are several possible mechanisms by which aspirin can precipitate or potentiate bleeding from existing acute mucosal lesions. The effects of aspirin on platelet function will be seen only when exposed oozing capillaries are involved such as acute gastric or duodenal mucosal ulcer.

Thus, the study by Leonards and Levy (Ref. 27) in normal subjects showing increased bleeding time after intravenous aspirin administration, but no increase in occult bleeding, is what would be expected if the effect of systemic aspirin was to potentiate bleeding from existing acute gastric mucosal lesions rather than to cause lesions. Therefore, the Panel concludes that the use of the Leonards and Levy study in the submission to refute the possibility that effects of aspirin on platelet function cannot contribute to massive bleeding is totally inappropriate.

(2) *Effect of highly buffered aspirin for solution on gastric mucosa.* The arguments that highly buffered aspirin for solution does not directly produce gastric mucosal lesions or occult bleeding in the stomach, in contrast to other aspirin solid dosage forms, are based on the acid-mediated single mechanism theory and a series of contentions (Ref. 1) listed below. These contentions are not consistent with experimental data from animals or occult bleeding studies in man. These erroneous allegations are: "Aspirin which is contained in the dry tablet of [an effervescent aspirin preparation] is entirely converted to the water soluble salt, sodium acetylsalicylic acid"; "A solution of [an effervescent aspirin preparation] does not contain aspirin"; and "Sodium acetylsalicylate possesses chemical and pharmacological properties which distinguish it in fundamental ways from aspirin."

A national news release dated June 6, 1973 cited a subcommittee hearing (Ref. 38) in which it was stated that, "much of the testimony before the subcommittee is founded on a mistaken premise. Many people do not realize the analgesic as taken in (an effervescent aspirin preparation) is not aspirin."

The Panel strongly disagrees with statements that the aspirin in highly buffered aspirin for solution is physicochemically or pharmacologically different from any other aspirin. This assumption is scientifically unsound and clinically misleading.

All aspirin whether administered as an effervescent buffered solution, tablet, or sodium salt always exists in solution as an equilibrium mixture of both the unionized molecular species (acetylsalicylic acid) and the ionized species (acetylsalicylate). Both species are always present. The relative abundance of each being determined solely by the pH (a measure of acidity) of the solution, and therefore, changes almost instantly whenever the pH of the solution changes. If the pH of the solution is lowered to a pH of 1 to 2 (the usual gastric pH) the ratio of unionized to ionized aspirin is about 1,000-fold. When the pH is raised to pH 6 to 7 (the initial pH after highly buffered aspirin for solution is given) the ratio of unionized to ionized is only 0.001.

Since the ratio of ionized to unionized drug is a function only of pH, it should be clear that regardless of the form administered, when aspirin gets into the cell it will exist almost completely as the ionized acetylsalicylate as the cell has a constant pH between about 5 and 6. The ratio of ionized to unionized aspirin in the gastric cell, the blood, or cells where it exerts therapeutic effects is totally independent of the form of aspirin administered.

Another argument is that the gastric mucosal cell acts as a lipid barrier and hence is impervious to sodium acetylsalicylate which is ionized and therefore not lipid soluble. Therefore, gastric absorption occurs with aspirin (unionized) but not sodium acetylsalicylate (ionized) (Ref. 1). The earlier concept that ionized drug is not absorbed can no longer be considered valid. The data of Davenport clearly shows that ionized species of aspirin is absorbed in the stomach at about one-fifth the rate of unionized species.

Davenport states that at high gastric pH the rate of absorption is by no means negligible. In a surgically prepared dog, the absorption rate of aspirin was found to decrease from 342 μmol/30 min at pH 1 to 65 μmol/30 min at pH 6.5 even though the fraction of aspirin unionized is reduced from 0.997 to 0.001, a 1,000-fold decrease. He suggests that absorption of the ionized species may occur or that there is an acidic microenvironment at the cell surface. Aspirin damages the gastric mucosa only after being absorbed into the cell at sufficient concentration to alter the gastric barrier and result in bleeding. In the normal state the gastric barrier prevents diffusion of hydrogen ions into the cell and to the capillaries.

Morris et al. (Ref. 39) correlated gastric lesions with the absorption of radioactive (^{14}C) sodium acetylsalicylic acid administered to albino rats at a dose of 0.28 μmol/kg of body weight dissolved in 0.15 M citrate buffer. The final pH was 4.6 which is about that usually obtained with highly buffered aspirin for solution preparations. Absorption occurred in the corpus (body) portion of the stomach more rapidly than the rumen (storage) portion. Ninety percent of the drug was absorbed after 1 hour indicating a half-life of about 20 minutes or less. Absorption from the rumen region is very slow. Lesions were produced in the corpus region only by sodium acetylsalicylate and not by sodium salicylate which was absorbed more rapidly than sodium acetylsalicylate.

Anderson (Ref. 40) also found that the addition of buffering did not preclude gastric absorption and gastric erosions when gastric emptying was prevented, concluding that the decreased gastric damage observed with highly buffered solutions is largely due to increased gastric emptying rather than decreased gastric absorption. He showed in guinea pigs that when gastric emptying was prevented (pyloric ligature) the gastric absorption of aspirin from a solution of pH 7.0 was only reduced to about 50 percent of the amount absorbed when the pH was 1 to 3. Most important, lesions were also produced at the high pH (7.0).

Anderson concludes that the critical rate of absorption is of low order in the guinea pig and if a similarly low rate occurs in man the avoidance of gastric erosions would be different with any formulation where the whole dose was immediately available for absorption. The latter statement would, of course, be true for highly buffered aspirin for solution preparations.

The mechanism by which aspirin exerts its effect may simply be a result of accumulation of sufficient acidity in the cell to cause damage by directly interfering with biochemical processes. The accumulation of total salicylate in the cell will be increased when the gastric contents are acidic because of the higher gradient of unionized aspirin outside the cell to the unionized aspirin in the cell (Ref. 41).

Other mechanisms involving delayed gastric acid effects can be postulated. Ethanol, which can damage the hydrogen ion barrier in an alkaline medium, is potentiated by salicylates (Ref. 42). It is not known how long these effects last but they might persist after the buffering capacity of highly buffered aspirin for solution is gone. This might be particularly true for hypersecretors of gastric acid. As is discussed in the next section, the effects of aspirin may persist for several days after dosing has stopped. In prolonged effect cases, the immediate buffering capacity of highly buffered aspirin for solution is obviously of no value if, as the submission contends, that all effects are really mediated by gastric acid.

The many inconsistencies in the data and arguments reviewed do not permit the Panel to accept the argument that the use of highly buffered aspirin for solution will obviate all direct mucosal effects of aspirin.

It has been argued that the presence of the buffer not only decreases aspirin absorption but also reduces excess hydrogen ion which is a necessary component in the production of gastric damage and bleeding. Therefore, the argument continues, "highly buffered acetylsalicylate causes no damage." The Panel finds that although gastric acid undoubtedly contributes to the occult bleeding, the availability of gastric acid is not essential for aspirin to cause gastric erosions or occult bleeding as has been discussed earlier. (See part III. paragraph B.1.a.(2)(ii)(*d*) above—Other mechanisms of aspirin damage.)

The study of Dagle et al. (Ref. 22) in vagotomized rats indicates that microscopic lesions can be produced in the absence of hydrochloric acid. If hydrochloric acid is later added, more severe damage and hemorrhage occurs. Several authors have noted reduced but statistically significant occult bleeding in patients with achlorhydria from a variety of causes including pernicious anemia and atrophic gastritis (Ref. 25 and 34).

(3) *Experimental data submitted to the Panel.* Evidence to support the contentions regarding the mechanism of aspirin effects and each effect of highly buffered aspirin for solution has come from occult bleeding studies in normal subjects or in experimental preparations. The studies of Leonards and Levy were cited to substantiate the following statement: "In all studies where meaningful protocols were employed, it has been consistently found that [an effervescent aspirin preparation] does not cause occult blood loss since in every study the occult blood loss occurring with highly buffered aspirin for solution was not statistically different from that found habitually occurring in the same subjects or were well within the normal limits." (Refs. 11, 12, and 43 through 46).

However, analysis of submitted data show that average occult bleeding loss produced by highly buffered aspirin for solution is less than that produced by regular aspirin but significant compared to controls receiving placebo or no aspirin and significant when multiple doses are given or when patients with peptic ulcer are used (Refs. 11 and 14). The Panel is not concerned with these minor increases in occult bleeding from a clinical point of view. They are significant, however, from the point of view of evaluating mechanistic assumptions. Of additional importance in these studies are certain patterns that can be seen in several different occult bleeding studies which lend support to the involvement of other mechanisms. In particular, the occurrence of unusually greater occult blood loss in a few individuals is consistently seen in several studies. The prolongation of effects for several days after the drug dosing has stopped is also significant (Refs. 11 and 14).

Average increases or decreases in occult bleeding studies represent the response of most of the normal subjects (70 to 80 percent). It is not likely, therefore, to provide useful information on mechanisms related to the atypical massive bleeder. In some studies an occasional subject has shown excessive occult bleeding. These individuals may be two standard deviations higher than others of the group and in some studies these cases have been omitted from statistical evaluation as "outliers." The mean blood loss of the occult bleeding is not predictive of massive bleeding. However, in several studies in animals and humans, there were subjects who constantly showed an excessive pattern of blood loss. It is the opinion of the Panel that these outliers may have some unknown predisposing factors and should be studied further to see if these outliers could provide a possible model for massive bleeding. In the Panel's opinion, it is significant that these outliers occurred most often in subjects who are likely to have acute mucosal lesions, e.g., patients with peptic ulcer, and are therefore subjects with potential or potentially critical bleeding sites. These outliers or "excessive occult bleeders" have occurred with all types of aspirin preparations including highly buffered aspirin for solution (Refs. 3 and 4) and enteric-coated preparations (Ref. 19).

The potential for increased occult bleeding in patients receiving highly buffered aspirin for solution is shown in the Goulston study (Ref. 11). Multiple doses of highly buffered aspirin (effervescent) solution were given to apparently healthy subjects (19 males and 1 female). Ten subjects were given two tablets dissolved in 200 ml water 4 times daily for the first 8 days followed by a control period of 8 days (Group A). The reverse order was given for the second 10 subjects (Group B) resulting in average occult bleeding losses shown below:

	Highly buffered aspirin for solution (milliliter)	Control (milliliter)
Group A	1.7	1.1
Group B	1.5	.5

In the initial submission to the Panel, it was stated that "* * * subjects 8, 11, 12 on some days had fecal blood loss well in excess of the range of the other subjects. Applying statistical analysis ('United States Pharmacopeia,' 16th Ed., p. 873) these aberrant values may be rejected." As a result it was claimed that no statistical difference existed. The notion of omitting the "outliers" which were excessive bleeders therefore atypical, in a study designed to assess bleeding potential following drug treatment is in the Panel's view not only erroneous from a statistical point of view but totally illogical from a clinical point of view. Exclusion of outliers obscures the obvious fact that some patients bleed significantly after receiving highly buffered aspirin effervescent solution. In each of the outliers, cases where significantly increased bleeding occurred, it was only during the highly buffered aspirin for solution drug treatment period. The most dramatic example was the outlier, subject 8, who had no appreciable bleeding in the 8 day control period (average blood loss of 0.4 ml daily; range 0.0 to 0.9 ml daily) but on the 4th, 5th and 6th day of drug treatment experienced daily blood losses of 17.9, 24.9 and 13.5 ml, respectively.

In the opinion of the Panel, the following can be concluded for the population studied in the Goulston study: (1) Highly buffered aspirin for solution given chronically 4 times daily for 8 days slightly increases fecal blood loss. This loss is probably less than would have been produced by aspirin tablets and is not significant clinically.

(2) One subject had a loss of over 50 ml during 3 successive days which is not only clinically significant but suggests that highly buffered aspirin for solution may produce excessive bleeding in an unpredictable abrupt manner similar to that seen in massive (major) gastrointestinal bleeding. Three other subjects had blood losses of 8.0 ml or more in 1 day during drug treatment only.

(3) There is a temporal pattern that appears consistent with other studies. Evidence of increased bleeding occurs only after about 3 to 4 days of multiple dosing but appears to persist for up to 3 days after drug dosing stops. When one compares the bleeding during the control period after drug dosing (1.1 ml daily) with the control period before dosing (0.5 ml daily), there is a statistically significant carryover effect. If one accepts the average blood loss of all controls as 0.79 as given, this value is exceeded in only 3 of 20 subject days in the first 2 days of the second period when the control is given first, but in 15 of 20 days when drug is given in the first period (Ref. 4). When one plots the average and individual values as a function of time, this pattern is quite obvious.

(4) *Review of new studies on occult bleeding in subjects and animal preparations with existing lesions.* The Rider study (Ref. 14) measured average daily fecal blood loss in patients receiving no drug (12 day control period), a placebo (7 days) and a highly buffered aspirin for

solution product (7 days), and a post-treatment period (5 days).

The average data are shown below:

Occult fecal blood loss in patients with active duodenal ulcer

	Average range milliliter per day
Control period (12 d)	0.57 (0.23–1.04)
Placebo period (7 d)	0.71 (0.32–1.22)
Post placebo period (5 d)	[1] 0.67
Highly buffered aspirin for solution period (7 d).	[2] 1.58 (0.57–4.18)
Post highly buffered aspirin for solution period (5 d).	[1] [3] 2.17

[1] Not given.
[2] Significant (p less than .01)
[3] Significance not stated (individual data not given)

The Rider study clearly shows that occult bleeding does increase in patients with active peptic ulcer after administration of the highly buffered aspirin for solution product (mean blood loss 1.58 ml daily) compared to a control period (mean blood loss 0.57 ml daily) and a placebo (mean blood loss 0.71 ml daily).

Perhaps more significant was the finding that the effects of the highly buffered aspirin for solution product persisted for at least 5 days after administration had ceased (mean blood loss 2.7 ml daily compared to mean blood loss of 0.67 ml daily for placebo).

This provides evidence that the increase in bleeding may not involve the direct effects of aspirin. It would be consistent with the long lasting effects (7 days) of aspirin on platelet function which would be expected to be observed only in patients with potential bleeding sites but not in individuals with a normal mucosa. The bleeding lesion may not necessarily be the ulcer but acute gastric erosions which are often associated in patients with peptic ulcer.

Similar results are seen in the recent two studies of Phillip et al. (Ref. 12) in which highly buffered aspirin for solution produced a statistically significant increase in occult bleeding in dogs with chronic ulcer. Excess occult bleeding in some animals (outliers) also occurred in these studies. Further evaluation of these studies was limited because individual data were not available and arbitrary, e.g., "weighting factors" appeared to be applied to the bleeding data in an irregular manner.

(5) *Epidemiological studies on massive bleeding.* Two epidemiologic studies, the Brown and Mitchell study and the Jennings study do not show that there is any difference between the role of regular aspirin and highly buffered aspirin for solution in potentiating massive bleeding. These two studies were critically reviewed by Langman in an industry submission (Ref. 47). The reasons used by Langman in dismissing the highly buffered effervescent aspirin dosage form as a factor in massive bleeding ignore several important points. For example, the fact that highly buffered aspirin preparations are promoted for use in gastric distress was not considered by Langman in his review.

Brown and Mitchell (Ref. 15) showed that a highly buffered aspirin preparation was more frequently used by individuals who bleed from duodenal ulcers whereas plain aspirin was most often used in those who bleed from acute gastritis. Langman concluded from this study that since bleeding from gastritis is more frequently associated with aspirin the types of aspirin dosage forms which have the greatest potential to cause bleeding would be associated in this diagnostic category. This conclusion ignores three important points. First, individuals with duodenal ulcer who frequently also have acute gastritis have a greater incidence of gastric distress than individuals with only acute gastritis, particularly of the atrophic variety. Since at the time of the Brown and Mitchell study (1956), highly buffered aspirin for solution preparations claimed and were promoted for the symptoms of gastric distress, in the Panel's opinion it was more likely that a greater number of individuals with duodenal ulcer ingested this type of preparation. Second, the potentiation of aspirin induced bleeding by alcohol is most often shown for the duodenal ulcer subgroup when subgroups are analyzed, a point noted by Langman in the same paper. Highly buffered effervescent aspirin preparations have been claimed and have been heavily promoted for use for concomitant symptoms of headache and gastritis related to overindulgence with alcohol. Therefore, when alcohol ingestion is a factor, these preparations would more likely be associated with bleeding from duodenal ulcer rather than gastritis. Finally, irrespective of the above, the Panel believes that it is not a matter of whether aspirin tablets cause bleeding more frequently than highly buffered effervescent aspirin but whether or not highly buffered effervescent aspirin can potentiate bleeding, especially since industry contends that this product can be used safely by ulcer patients (Ref. 3).

Langman implies that the epidemiological study of Brown and Mitchell (Ref. 15) in which 83 percent of patients who bled had taken "insoluble" (regular) aspirin and 14 percent of such patients had taken a buffered effervescent preparation, supports only the role of the "insoluble" aspirin product forms in potentiating bleeding. He reached this conclusion by comparing these figures with the 40 percent, the control population, who had taken buffered effervescent prepartions from "time to time". However, this conclusion is entirely unwarranted as the 40 percent figure referred to individuals who might have ingested highly buffered effervescent aspirin as long as several months before the study. It did not refer to aspirin ingestion by the individuals who bled in the last 48 hours just prior to the study. The latter group of individuals would have been the proper control upon which Langman should have based his conclusions.

Because the Panel believes the control group, referred to by Langman in his analysis of the Brown and Mitchell study, was improperly defined, it has estimated what the control group should have been, based upon data in the submissions (Ref. 1). The data (Ref. 2) show that about 38 percent of the total population takes one brand of buffered effervescent aspirin from "time to time". This is consistent with the control group of Brown and Mitchell (Ref. 15). However, calculations from the industry data also show that on any given day less than 5 percent of a random sample would be expected to have consumed the highly buffered effervescent preparations. Using the 5 percent figure rather than the 40 percent as a control upon which to view the Brown and Mitchell study, the Panel concludes that one cannot rule out the possibility that all aspirin preparations regardless of formulation are equally capable of potentiating gastrointestinal bleeding.

Langman (Ref. 47) also reinterpreted the epidemiological data of Jennings (Ref. 15) to show that highly buffered effervescent aspirin products are not implicated in massive gastrointestinal bleeding to the same extent as "insoluble" varieties of aspirin. The Panel does not agree with the assumptions used by Langman in this conclusion.

In the Jennings study, detailed information was provided on the specific types of aspirin used, including highly buffered effervescent aspirin. The distribution of aspirin products in patients with overt gastrointestinal bleeding was as follows: In the radiologically negative group, 42 percent with acute ulceration took ordinary aspirin, 18 percent took soluble varieties, and 7 percent took a buffered effervescent preparation. In contrast, 29 percent of the chronic ulcer patients took ordinary aspirin, 14 percent took soluble varieties, and 21 percent took the highly buffered effervescent preparation. Langman in his review (Ref. 47) states that if the highly buffered effervescent product were the cause of bleeding the incidence of use would be higher in the acute ulceration group which is most often associated with aspirin-induced bleeding. There are several reasons for questioning the validity of this contention. First, patients with chronic ulcer generally have a higher incidence of gastrict distress than patients with acute ulcer. At the time of the study (1965) highly buffered effervescent preparations were specifically and almost exclusively promoted for gastric distress. It would not be surprising therefore that the group with the highest incidence of gastric distress would have the highest incidence of highly buffered effervescent aspirin use. Second, even though aspirin is associated more with acute ulcer (to a higher proportion) than with chronic ulcer, it has nevertheless been associated with bleeding in chronic ulcer patients. In fact, Langman states in his review that in four of five studies, aspirin ingestion was more frequently associated with massive bleeding in duodenal ulcer than in acute gastric lesions.

This argument is found again in this statement by Langman: "Finally Jennings data, which were claimed by the author to suggest synergistic effects of alcohol and aspirin, show that the coincident alcohol and aspirin intake were less common in the acute lesion group than in those with bleeding due to chronic ulcers although the typical aspirin lesion is generally considered to be an acute mucosal erosion."

The data of Jennings (Ref. 16), showing a higher incidence of aspirin and alcohol associated with hemorrhage in patients with chronic ulcer including duodenal ulcer, are consistent with other recent studies.

Therefore, the Panel concludes that arguments of Langman cannot be used to dismiss this study as reasonable evidence that highly buffered effervescent aspirin is as likely to be associated with gastric bleeding as any other form of aspirin.

(5) *Benefit to risk considerations.* Several benefit to risk considerations were involved in the Panel's recommendation not to allow highly buffered aspirin for solution to be indicated for use in individuals with a history of symptoms of gastrointestinal bleeding, ulcer or symptoms of gastric distress with or without concurrent headache. The Panel's conclusions regarding the mechanisms involved in aspirin-induced major gastrointestinal bleeding were a significant factor in this decision, particularly the fact that the "primed" bleeding lesion may be caused by factors other than direct gastric erosion induced by aspirin. It was concluded that bleeding can be precipitated by aspirin from existing acute mucosal lesions which occur in a variety of different conditions, e.g., atrophic gastritis which is associated with a variety of causes, hypertrophic gastritis associated with alcohol, and acute erosions related to stress.

The Panel is concerned that the same conditions, alcohol and stress, which frequently "prime" the gastrointestinal tract for massive bleeding, are also those which most frequently produce the symptoms of concomitant headache and gastric distress. Highly buffered aspirin solution has been claimed for use to relieve the concurrent conditions.

A further concern of the Panel is that if an antacid (highly buffered)-aspirin combination product is promoted for use in gastric distress, even if the concurrent claim of a headache is allowed, the public will regard these products as safer than unbuffered (plain) or slightly buffered aspirin but also somewhat different. The Panel feels that this is misleading.

The Panel is concerned that in cases where concurrent gastritis and headache occur, individuals will usually take some analgesic, probably containing aspirin, and that they may assume that the availability of highly buffered aspirin for solution would at least provide the safest aspirin product that could be taken. However, if as the new information suggests, the primary role of aspirin is not the initiation of the bleeding lesion but the promotion of bleeding from existing lesions by systemic effects, then the dosage form is irrelevant and highly buffered aspirin for solution offers no advantage over unbuffered (plain) aspirin. In fact, the Panel finds that the use of highly buffered aspirin for solution may increase the risk because it delivers more pure aspirin to the systemic circulation than regular aspirin products (Ref. 48).

Even if a claim was allowed only for use for concurrent symptoms of gastric distress and headache, in the opinion of the Panel based on marketing history (Ref. 2), such products would be more likely to be used in instances involving gastric symptoms only. When one considers that massive gastric hemorrhage related to aspirin involves a 10 percent mortality rate this is much too severe a risk relative to the minimal, if any, benefit derived (Ref. 49).

The Panel concludes that is is unproven, and unlikely that highly buffered aspirin for solution is less apt to produce major gastrointestinal hemorrhage than regular aspirin. Neither is there evidence to show that it would be safer to use this product rather than regular aspirin for concurrent symptoms of headache and gastric distress. Current evidence suggests that alcohol gastritis and stress are the two most likely causes of concomitant symptoms of headache and gastric distress. Alcohol and stress are also the two major factors which may produce acute mucosal lesions and thus increase the risk of bleeding from the use of any aspirin product.

The Panel does not believe that current evidence warrants an exemption from the labeling recommendation for any form of aspirin for persons with gastric distress which states: "*Caution:* Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

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d. *Labeling claims for marketed products containing analgesics combined with antacid or buffering ingredients*—(1) *Introduction.* The Panel has examined the claims relating to the performance of marketing aspirin products that contain antacid or buffering ingredients. These products have been termed buffered or highly buffered aspirin. The Panel has been particularly concerned with the labeling claims of such products that imply an advantage over plain aspirin products. These advantages have been, in various ways, stated to be due to a more rapid dissolution resulting in faster absorption into the bloodstream, and consequently preventing the adverse local reactions to the stomach that may be caused by plain (unbuffered) aspirin products. The statements that have most frequently been used on the labeling of buffered and highly buffered aspirin products suggest these advantages in terms or phrases such as "Faster to the bloodstream" or "Gentle to the stomach".

The Panel concludes that these claims give the consumer the impression that buffered and highly buffered aspirin products have a therapeutic advantage over plain aspirin products, and may mislead those consumers who can be adversely affected by buffered aspirin as well as by plain aspirin. Until such statements can be adequately documented, the Panel recommends that claims be limited and restricted on the label to discourage unproven claims of therapeutic advantage.

Therefore, for the reasons discussed below, the Panel recommends that such labeling be restricted to the principal display panel of the product and be limited to the following Category III statements: "Faster to the bloodstream than plain aspirin" and "Provides ingredients that may prevent the stomach distress that plain aspirin occasionally causes but should not be taken by certain individuals with stomach disorders as cautioned elsewhere on the label". The Panel also concluded that any other statement(s) that suggests or represents a product as having a more rapid absorption or as preventing any side effects to the stomach because of the antacid or buffering ingredients in the product be classified as Category II.

(2) *Effect of rate of absorption into the bloodstream.* The Panel has reviewed data, opinions and recommendations from both sides of the controversy regarding claims that buffered aspirin has therapeutic advantages over plain aspirin due to a more rapid rate of drug absorption into the bloodstream.

The problem is complex largely due to inadequacies in the available data and the lack of understanding of the relationship between salicylate blood levels and onset of analgesic effects. There is clear experimental evidence based upon well-designed blood level studies which substantiate the claim that buffered aspirin is more rapidly absorbed than plain aspirin (Refs. 1 through 3). Comparisons of the most commonly used plain and buffered aspirin show that salicylate blood levels are twice as high in the first 10 to 20 minutes for the buffered aspirin product compared to regular aspirin. It can be shown that the differences in plasma levels in the first 20 minutes correlate quite well with the amount of drug absorbed (Ref. 4).

The basic problem is that there are no well-controlled clinical studies that unequivocally prove or disprove that these differences in absorption will result in clinically important differences in the onset, intensity or incidence of relief of pain or fever.

In the absence of this definitive information on the clinical significance of the increased rate of absorption, there is a secondary question that was debated by members of the Panel and consultants. This second question pertained to divergent opinions regarding the validity and value to the public of statements regarding differences in drug absorption with no mention of therapeutic effect. One argument is that since the information regarding absorption is true and these differences likely relate to real therapeutic advantages, the information should be available to the public for their assessment. The opposite view, held equally strong, is that such information will usually be confusing or misleading to the public. Any statement regarding more rapid absorption will always be interpreted by the public as implying some therapeutic advantage. Else, why would it be made?

The Panel does not believe that questions regarding the public's interpretation of presently undefined promotional statements can be objectively resolved by any practical methods presently available to the Panel. One suggestion was that the Panel should carefully formulate an accurate statement. However, regarding the relative rates of aspirin absorption which would be accurate and informative, the problem of public interpretations of labeling claims relates not only to the current controversy but to the interpretation also of future statements based on new studies. Similar problems have and will occur with statements regarding prolonged blood levels produced with some dosage forms and the inference that prolonged duration of effect will occur.

The Panel views the problem of evaluating claims relating to differences in blood levels of drug products as involving several interrelated steps. First is the assessment of current scientific information and the sensitivity of available methodology to determine the validity of the claims. Category III should be used to classify claims which cannot be fully evaluated with present data but have some reasonable basis and can probably be evaluated by further testing, perhaps, involving more sensitive methodology. Second is to establish a policy that allows the maximum amount of information to be given to the public provided that information is well defined and can be put in perspective by the general public. Third is to define the specific information that should be supplied by additional scientific studies not only to validate the clinical significance of differences in blood level data but also to accurately communicate them to the public.

While current studies have failed to show a direct one-to-one correlation between plasma levels of an analgesic drug and pharmacologic response, there is some evidence that a complex nonlinear relationship between these two variables undoubtedly does exist and involves nonlinear complex functions and time lags. These reasons include the fact that

a nonlinear dose-response function has been shown by different methods and that a graded time course of pharmacologic activity has also been shown (See part III. paragraph B.1.a.(1) above—Effectiveness.) There are known relationships between dose and plasma concentration (also nonlinear). It follows logically and mathematically that some expression does exist and recent advances in computer assisted pharmacokinetic modeling, analytical methodology and analgesic testing will probably allow elucidation of this function in the future. When an insensitive test does not show clear differences between two products it can only be said that present insensitive methods cannot determine a difference between the two. In the absence of other evidence, no means of validating claims are available.

There is some other evidence to indicate potential clinical differences due to rates of absorption. First, from a theoretical point of view, it can be shown by mathematical analysis that because the rate of elimination of aspirin is much more rapid than most other drugs (50 percent is eliminated in 15 to 20 minutes), changes in rates of absorption within normal ranges can result in twofold changes in the peak plasma concentration (Ref. 1). Experimental data on the blood levels of aspirin by Leonards (Ref. 5) have shown that the peak blood level and relative amount of aspirin absorbed as assessed by the areas under the blood level-time curves is twice as great for an effervescent preparation as for a simple aspirin tablet. Even greater peak blood levels were observed when the sodium salt of aspirin was administered.

Some possible approaches to define the conditions required in a study to move claims from Category III to Category I are in the literature. Feinblatt et al. (Ref. 6) compared the salicylate levels attained with buffered aspirin products with an unspecified plain aspirin tablet. The initial plasma levels and, therefore, the rates of absorption of the buffered products were from 1½ to 2½ times greater than plain aspirin preparations.

One of the buffered products was tested against the plain aspirin in two crossover studies comparing time of onset for relief of pain in patients with recurring headaches and pain of rheumatoid arthritis for arthritis pain. Unfortunately, the data were given only as the mean and range of the time of initial onset of relief. It is claimed that the buffered aspirin preparation had a more rapid onset in both headache and arthritis pain relief. The data were not evaluated statistically and individual data were not provided. Therefore, the apparent increased onset of pain relief with buffered aspirin cannot be further evaluated.

However, because two preparations were evaluated with two types of pain, the data can be analyzed to see if they are consistent with the possibility that the rate of absorption could affect the onset. Preliminary pharmacokinetic analysis by the Panel indicates that with certain assumptions the data are consistent with a low threshold for pain relief requiring only 1 to 3 mg/100 ml to initiate pain relief. Because of the great variability in absorption rates even in the same individual, it is readily seen that differences in onset of pain relief on the order of a 10 minute difference between two products would be very difficult to show statistically because of the large number of subjects that would be required.

The Panel recognizes that the differences in a few minutes in the onset of pain relief may be considered by some to be meaningless and of little practical value. The Panel believes that this subjective evaluation of effectiveness is best left to the consumer provided that sufficient facts are given to make an informed decision. Claims such as "faster acting" may be scientifically accurate but misleading for example, if the difference is 1 or 2 minutes in a small percentage of the target population. The Panel recommends, therefore, that claims implying a greater or faster onset of therapeutic effect or claims relating to blood level data showing differences in the rate of absorption may be moved from Category III to Category I if the claimed differences of analgesic effect can be quantitated to provide information on the quantitative estimates or the average differences in the time of onset of analgesic that can be expected. Scientifically valid studies must provide some estimate of the degree and incidence of effect that can be expected by the average user for comparative claims. Claims such as safer to the stomach, faster to the blood stream, are of limited or negative value to the consumer unless sufficient information is given to put them in a proper perspective.

The Panel suggests once the clinical studies are available to adequately demonstrate quantitative differences in the action of different aspirin products that such information be included in labeling. Reference to blood level data or other indirect data inferring a therapeutic advantage should be accompanied by clear concise statements regarding the quantitative information on the significance and degree of the difference. The specific information that should be conveyed is the average difference in magnitude of effect that has been proven and what percent of the usual target population will be involved.

In the Panel's view, value judgments on comparable claims are best left to the consumer provided all the pertinent facts are available. In the absence of available information on the relative degree of effect or incidence of effect in the target population, comparative statements are of limited value and even potentially misleading. Indeed, the Panel notes that statements such as "safe to the stomach" may be taken as a comparative judgment involving properties not possessed by other agents.

(3) *Validation of Category III labeling.* The Panel notes that clinical or blood level studies showing an increased rate of absorption for one buffered product are not necessarily valid for other buffered products, or even different production lots of the same product. There is also ample evidence that some buffered products have formulations, such that, they are more slowly absorbed than regular aspirin. (See part VI. paragraph B.1.b. above—Products containing aspirin combined with buffering ingredients (correctives).) For these reasons, the term buffered aspirin has limited value as a general labeling term in identifying or assuring particular performance characteristics. The Panel, therefore, considered the need for in vivo and in vitro standards to define the therapeutically significant characteristics of the dosage form.

The Panel does not believe this to be a high priority until the claims for buffered aspirin have been validated and, accordingly, justify a special designation. It does not seem justified to expend considerable time and money to define the in vivo blood level characteristics at this point. Methodology for in vivo stomach acid neutralization properties that relate to absorption and stomach safety claims should also probably have a lower priority at this point in time. There will be other needs, however, for in vitro dissolution and in vitro neutralization standards as a more expedient means to routinely evaluate products and lots.

In addition to serving as a means of simulating in vivo performance of the dosage form, in vitro procedures may be needed as components of a quality control program not only for buffered aspirin but all standard regular aspirin tablets. Therefore, although methodology of development is now beyond the scope of the Panel, preliminary planning with the FDA was initiated to consider possible recommendations to suggest a starting point for methodology development, which is discussed elsewhere in this document. (See part VI. paragraph C.1. below—Aspirin standard testing procedures.) This methodology must be thoroughly evaluated before it can be used to screen products which may have poor biological performance. With less extensive modification, it may be useful for quality control programs. The Panel recommends that, if possible, the development of suitable in vitro methodology for aspirin and buffered aspirin be continued by the appropriate FDA staff in collaboration with all interested parties, e.g., industry, academia and the *United States Pharmacopeia*.

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2. *Benzoic acid-containing ingredients.* The Panel has classified the following active ingredients as ineffective antirheumatic adjuvants:

Aminobenzoic acid (para-aminobenzoic acid (PABA))
Sodium para-aminobenzoate

Further, para-aminobenzoic acid or sodium aminobenzoate may not be included in combinations for safety reasons discussed below.

a. *Effectiveness.* The Panel concludes that para-aminobenzoic acid (PABA) is ineffective for use as an OTC antirheumatic adjuvant and classifies it as Category II. The Panel further concludes that the combination of para-aminobenzoic acid (PABA) or sodium aminobenzoate with any ingredient(s) discussed above in the antirheumatic section of this document are also classified as Category II. (See part V. above—ANTI-RHEUMATIC AGENTS.) There is no evidence that para-aminobenzoic acid or sodium aminobenzoate contribute to the antirheumatic action of known antirheumatic agents.

In 1947, Rosenblum and Fraser studied the efficacy of para-aminobenzoic acid in nine patients with rheumatic fever and found depression of fever and relief of joint pain in seven patients after 2 days of administration of 1 to 3 g every 2 to 3 hours (Ref. 1). In 1951, Hollander and Harris studied 27 patients with active rheumatoid arthritis. The effect of the drug on relief of pain and stiffness was studied after administration of 4 g of PABA daily for at least 1 week. No patient experienced relief of pain and stiffness whereas relief was noted in patients given 4 g of sodium salicylate for at least 1 week (Ref. 2).

Para-aminobenzoic acid (PABA) in the form of sodium aminobenzoate is a sulfonamide antagonist which competitively counteracts bacteriostasis induced by sulfonamides. Certain microorganisms require PABA for incorporation into folic acid. It is capable of altering the course of experimental and clinical rickettsial disease. In large doses, PABA can increase the blood level of salicylate by competing for glycine and thereby slowing the rate of conversion of salicylate to salicyluric acid, as shown by studies of Salassa et al., who demonstrated that PABA in doses of 24 g daily along with a single dose of 3 g of sodium salicylate produced a sustained, elevated plasma salicylate level (Ref. 3). This observation was confirmed by Hoagland (Ref. 4).

Carski compared the blood salicylate levels after the administration of a single dose of 650 mg sodium salicylate with the blood salicylate level after a single dose of 650 mg sodium salicylate plus 650 mg PABA and found no difference in blood salicylate level (Ref. 5). Similarly, there was no difference in blood salicylate levels after 1 week of the same doses administered 4 times daily.

Hollander and Harris showed that 4 g each of sodium salicylate and PABA raised the plasma salicylate level more than did 4 g of sodium salicylate alone (Ref. 2). However, analgesic effectiveness could not be related to the level of salicylate achieved.

The studies on the antirheumatic effectiveness of PABA do not provide objective evidence of effectiveness.

Analgesic effectiveness in relief of arthritis pain is claimed by Barden and Cuneo (Ref. 6), Cass et al. (Ref. 7), Smith (Ref. 8) and Hebert and Renzi (Ref. 9). Only clinical impressions of effectiveness are given.

Ford and Blanchard compared the functional capacity of arthritis patients before and after the treatment with physical therapy and the combination (sodium salicylate plus PABA) (Ref. 10). Some patients were also given the combination plus 2.5 mg cortisone. No conclusions regarding either the antirheumatic or analgesic effectiveness of the combination can be reached from this study because the design of the study did not separate the effect of hospitalization and physical therapy from the effect of the drug combination.

The enteric-coated combination of aspirin and PABA may be excreted intact as described by Smith in three patients (Ref. 8).

Studies of the blood salicylate levels of aspirin alone and with PABA reveal no significant differences when taken in a dose of 900 mg aspirin every 6 hours for 12 doses as compared to 900 mg aspirin plus 900 mg PABA every 6 hours for 12 doses (Ref. 11). The combination was found to produce a greater number of mild gastrointestinal side effects.

Taylor (Ref. 12) studied the antirheumatic effectiveness of the combination in osteoarthritis patients by observing activity status and early morning pain. No details are provided regarding the definition of these parameters and therefore no conclusions can be reached.

(b) *Safety.* PABA has been shown to be goiterogenic in large doses (Ref. 13).

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3. *Caffeine (citrated caffein).* The Panel concludes that caffeine (citrated caffeine) when used alone in an adult oral dosage of 65 mg not to exceed 600 mg in 24 hours is safe but ineffective as an OTC analgesic, antipyretic and/or antirheumatic ingredient and is classified as Category II. However, there are insufficient data available to classify the adjuvant effect of caffeine (citrated caffeine) when used in combination with Category I analgesic, antipyretic and/or antirheumatic agents as an effective analgesic, antipyretic and/or antirheumatic adjuvant and it is therefore classified in combination as Category III.

The Panel notes that the Advisory Review Panel on OTC Sedative, Tranquilizer and Sleep-Aid Drug Products, in their report published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292) concluded that caffeine is safe and effective for use as an OTC stimulant when used in the recommended oral dosage of 100 to 200 mg not more often than every 3 to 4 hours. The current *United States Pharmacopeia XIX* also categorizes caffeine as a stimulant whereas a former edition of another official compendium, *National Formulary XIII*, categorizes caffeine in combination with aspirin and phenacetin (widely known as APC compound) as an analgesic mixture. This combination is no longer found in current official compendia. However, caffeine is still widely used in analgesic-antipyretic preparations. In fact, several of the submissions submitted to the Panel for review contained combination products which include caffeine in varying amounts averaging from 15 to 65 mg per dosage unit. Unfortunately, the information and data submitted, fail to demonstrate conclusively that caffeine in combination is effective as an analgesic, antipyretic and/or antirheumatic ingredient. The Panel finds there is little evidence to show that this ingredient even contributes to these pharmacologic effects in the clinical situation.

The pharmacologic rationale for the long accepted use of caffeine in APC compound and in other similar products is not clearly understood. The Panel recognizes the known pharmacologic actions of the drug in stimulating the central nervous system, acting on the kidney to produce diuresis, and in stimulating cardiac and relaxing smooth muscle. Perhaps, it is this latter effect which accounts for its popularity. Caffeine has been claimed to be useful in treating certain migraine headaches due to constriction of cerebral blood vessels and has been shown to be important in the treatment of caffeine withdrawal headache. The latter is discussed below. The Panel, therefore, finds that an important historical use for these preparations containing caffeine has been for the treatment of certain types of headache. There is also some evidence that caffeine may contribtue to the effectiveness of analgesics, and therefore, the Panel has categorized this possible contributory effect as a potential adjuvant action of caffeine.

a. *Effectiveness*—(1) *Caffeine as an analgesic adjuvant.* As noted above, the Panel finds that there is some inconclusive evidence to suggest that caffeine may exert additional analgesia when used in combination with other analgesics. Therefore, the Panel concludes that although caffeine combined with any Category I analgesic is safe, there are insufficient data to demonstrate any additional contribution of caffeine to the action of the Category I analgesic ingredient.

Although there is weak evidence to suggest that the combination is more effective than the analgesic ingredient alone, more clinical studies need to be done to show that caffeine contributes to the claimed effect(s) and to study the interaction of these combinations in terms of their analgesic and antipyretic effects. As will be discussed below, there is only one well-controlled clinical study to determine whether aspirin plus caffeine is more effective than aspirin alone and the results of this study are equivocal (Ref. 1). Several other clinical studies provide some support for this hypothesis, and there are also supporting animal data, and data related to sensory changes to suggest that caffeine enhances the analgesic properties of mild analgesics (Refs. 2 and 3).

The reasons for the lack of clinical studies of the potentiating effect of caffeine on other mild analgesics are many and include the difficulty of carrying out controlled clinical assays with mild analgesics. Another possibility is that clinical analgesiometry is sufficiently imprecise in patients so that a biologically significant effect might not be measurable. A third possibility is that the assay is not sensitive to measure changes in pain intensity for the particular type of pain studied. Although the efficacy of mild analgesics has been studied in experimental pain and in patients with post partum pain, the effects of caffeine would probably be more apparent if, under closely controlled conditions, patients with headache other than migraine headache were the study population. Still another possibility is that mixtures of caffeine and mild analgesics may contribute therapeutic benefits beyond those of pain relief, such as mood changes, which are not measured by typical clinical pain relief studies.

One of the earliest reports by Moyer et al. (Ref. 4) compared the effects of aminophylline (theophylline with ethylenediamine) and caffeine on cerebral hemodynamics and cerebral spinal fluid pressure in patients with headache clinically identified as hypertensive headache. The study demonstrated that aminophylline is more effective but that both aminophylline and caffeine cause prompt relief of headache which results from the hypertensive state. There was immediate relief of headaches following aminophylline in seven of nine patients. After caffeine, relief from headache was obtained in five of nine patients.

There have been other studies which have shown that caffeine may exert a beneficial effect on pain relief through an effect on the blood vessels. It has been known for many years and shown by the work of Leake et al. (Ref. 5) that the production of experimental headache by nitrites was accompanied by dilatation of the meningeal blood vessels.

Likewise, Pickering in 1933 (Ref. 6) studied headache produced by intravenous injections of small amounts of histamine. These studies were enlarged by Clark et al. in 1934 (Ref. 7), and by Schumacher et al. in 1940 (Ref. 8) who demonstrated that this experimental headache was accompanied by increased amplitude of pulsation of the cerebral blood vessels. Thus, there is good evidence to support the theory that some headaches are related to cerebral vascular distension.

A plausible explanation for the biochemical mechanism by which caffeine is effective in treating this vascular smooth muscle spasm has to do with the biologic role of adenosine-3',5'-monophosphate (cyclic AMP) (Ref. 9). Caffeine (an inhibitor of a phosphodiesterase) can cause cyclic AMP to be increased and act as a second messenger to increase vascular tone. This mechanism would explain, then, the common effect of catecholamines and amphetamines and caffeine on the small blood vessels and thereby serve as the pharmacologic mechanism by which caffeine could be effective in treating headache associated with constriction of cerebral blood vessels.

In studies of other types of headache, Dreisbach and Pfeiffer (Ref. 10) showed that caffeine could be important in the treatment of caffeine withdrawal headache. The authors recognized that many people ascribe an occasional headache to lack of morning coffee and the "let-down" which may result if this stimulant is withdrawn from habituated individuals. This study of caffeine withdrawal headaches was one of the earliest experiments and in their double-blind study in 22 young volunteers, they produced headache by the abrupt withdrawal of caffeine after the administration of up to 0.78 g caffeine daily usually in the morning over a period of 7 to 8 days. It was uniformly noted that headache following caffeine withdrawal was quite different from the migraine syndrome in the five subjects who also suffered from migraine, although the caffeine withdrawal headache was accompanied by nausea in four of the migraine subjects, and vomiting in one of them. The investigators found that in 55 percent of 38 trials in 22 subjects, headache as extreme and severe as the subject had ever experienced was produced by the sudden withdrawal of caffeine. This headache responded to treatment by caffeine or aspirin. The authors concluded that this study also provides a plausible explanation for the hitherto empirical addition of caffeine to many headache remedies.

The psychotropic effect of caffeine has been studied in detail by Goldstein et al. (Ref. 11). In the study, the effects of caffeine in coffee were compared in two groups of subjects (abstainers and users of coffee). The study was well controlled and well analyzed, and the authors concluded that caffeine had no demonstrable effect upon objectively measured performance, although it made some subjects feel more awake and physically active. There was a strong positive association between the subjects' sensitivity to mood elevating effects of caffeine, and a sensitivity to the wakefulness caused by caffeine. The central nervous system stimulant effects of caffeine have been discussed in detail in the OTC Sedative, Tranquilizer and Sleep-Aid Panel report published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292).

The Panel finds these studies tend to demonstrate that the habitual use of caffeine for central nervous system effects may lead to withdrawal headache. Hence, the likelihood of headache associated with the use of analgesic agents in combination with caffeine may be increased without proven compensatory analgesic benefit when the product is taken continuously for central nervous system effects or for caffeine withdrawal headache.

It is of interest to note that in some recent, controlled clinical studies comparing aspirin alone, aspirin in combination with phenacetin, salicylamide and caffeine, or aspirin, phenacetin and caffeine, the combinations produced a mean pain relief score higher than those for aspirin alone (Refs. 1 and 12). Although the difference was not statistically significant in the study of DeKornfeld et al. (Ref. 12), it seemed to suggest that caffeine was contributing to the pain relief observed. However, this study was not designed to test the hypothesis that caffeine augments the effect of the analgesic(s), and the higher scores could have been due to higher total equivalent dosage of analgesic or indeed, as the authors interpreted, due to chance.

In a study presented by Houde (Ref. 1), the effect of caffeine is statistically significant. Houde found that a com-

bination of 210 mg aspirin, 150 mg acetaminophen and 30 mg caffeine gave somewhat better pain relief than either aspirin or acetaminophen alone. Houde concluded, "while our data does not permit a conclusive statement, there is at least some evidence in it to show that caffeine contributes something to the efficacy of these drugs." This is the only well-controlled clinical study the Panel was able to find to suggest that caffeine may contribute to the analgesic efficacy of analgesics.

More recently Booy studied pain relief in patients following tooth extraction (Ref. 13). His data indicate that on the first day 500 mg acetaminophen plus 50 mg caffeine produced more pain relief than 500 mg acetaminophen alone. This difference was not apparent on the second day.

In a study by Lim et al., (Ref. 14) in which experimental pain was induced in man by bradykinin intraperitoneally, they observe that the addition of caffeine to the combination of aspirin and acetaminophen produced more pain relief. Their method was sensitive enough to distinguish between two dose levels of aspirin, as well as the two dose levels of the combination of 32.5 mg caffeine, 325 mg aspirin, 162.5 mg acetaminophen, and double these doses. These analgesic data are cautiously interpreted and the authors suggest that more work needs to be done on the potentiating effect of caffeine.

Williams (Ref. 15) studied experimental pain in rats and found that caffeine alone was capable of raising experimental pain reaction thresholds and thereby exerted analgesic effects. However, when combined with aspirin, there was no potentiation, but the effect appeared additive. In addition, the possibility of inhibition was in evidence. Recently Vinegar et al. (Ref. 16) showed in the rat not only the analgesic potentiating effect of caffeine on aspirin but also potentiation of the anti-inflammatory effect of aspirin.

(2) *Caffeine as an antipyretic adjuvant.* Caffeine may cause a slight hyperthermia probably through its central stimulating action since it increases wakefulness and muscle tone. Carbon dioxide tension is reduced and the sensitivity of the respiratory center to carbon dioxide is increased (Ref. 17).

A recent preliminary report of the interference of caffeine with the antipyretic action of aspirin in rabbits, when pyrogens were used to induce fever, has been published (Ref. 18). The study involved comparisons of temperature response in rabbits following administration of aspirin, aspirin combined with caffeine, caffeine and placebo (saline). The investigators found that in the absence of pyrogens and fever, the drugs were without significant effect. Rabbits receiving pyrogens plus caffeine developed a significantly greater fever than those receiving pyrogens alone. In addition, as expected, aspirin markedly reduced pyrogen induced fever but aspirin combined with caffeine had no antipyretic action. The investigators postulated that caffeine may raise levels of 3',5'-cyclic AMP, a substance reported to raise body temperature by inhibiting 3',5'-cyclic AMP phosphodiesterase. They concluded by recommending that these experiments be repeated in man and if similar responses are found that caffeine and mixtures containing caffeine not be used during fever.

The Panel believes that if combinations are to claim antipyretic efficacy the inclusion of caffeine must be shown not to interfere with the fever-reducing effect of the antipyretic in man. Therefore, combinations employing caffeine are placed in Category III for this indication. To test for such interference, a study should be done in humans to demonstrate an effect of the single entity and no interference with this effect when 65 mg caffeine is given concomitantly. Thus, following the guidelines under clinical testing the study would contain placebo, a dose of the single entity both alone and in combination with caffeine in a 2x2 factorial design. (See part VI. paragraph C.2. below—Combination products containing caffeine as an analgesic, antipyretic and/or antirheumatic adjuvant.)

b. *Safety.* The Panel concludes that caffeine when used as an adjuvant is safe at a single adult dosage of 65 mg not to exceed 600 mg in 24 hours.

The behavioral effects of caffeine were reviewed in detail by Weiss and Laties in 1962 (Ref. 19), who reported that there was a wide range of behavior with the exception of intellectual tasks that could be enhanced by caffeine. They were unable to find any evidence of physical dependence to continued use of caffeine, although abrupt cessation of the drug has been reported to cause headache. It is the consensus of many workers that caffeine probably does more than restore performance degraded by muscular fatigue, sleep deprivation, and boredom.

More recently, the toxicity of caffeine has been reviewed by Peters (Ref. 20). Most of the work regarding caffeine toxicity has been done in animals. The LD_{50} for mice has been determined to be 101 mg/kg and for rats 105 mg/kg. The minimal lethal intravenous dose for cats is 80 to 100 mg/kg. It is believed that human subjects may be more sensitive to the lethal effects of caffeine, but extrapolating from the animal data, it appears that the therapeutic doses used in combination with analgesics are safe. Although toxicity is extremely low and fatalities extremely rare, they are not unheard of (Refs. 21 and 22). In his excellent review, Peters (Ref. 20) pointed out that it has been shown for humans that the absorption of caffeine after oral administration is faster than after intramuscular administration, where the peak plasma level occurs after 30 minutes to 1 hour. Thus, orally administered caffeine is very quickly taken up and has a half-life of 3 to 3½ hours in the body.

The stimulant effects and toxicity of caffeine have also been reviewed extensively by the OTC Sedative, Tranquilizer and Sleep-Aid Panel in the report published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). They discussed, in addition, the mutagenic effects in detail. This Panel agrees with their conclusions regarding the safety of caffeine.

Chronic toxicity has not been observed in humans, but some resistance to the drug does develop. In animals, the dose that killed 50 percent of young adult female rats in 100 days, or one-tenth of their life span, was estimated to be 150 mg/kg daily. The maximal dose that was estimated to produce no death in 100 days was 110 mg/kg daily. The figure of 110 mg/kg daily extrapolated to man corresponds to drinking 60 to 100 cups of coffee daily. Thus, caffeine consumption by man, in the most readily available form, is not likely to cause death in young healthy persons.

Related to chronic toxicity is the factor of tolerance to caffeine. Tolerance appears to develop within 2 to 3 days after the daily dosage. Tolerance to the hypertensive effects of caffeine has also been demonstrated to develop in cats. Thus, in man it is likely that some tolerance to caffeine develops with daily use. In the rat, sensitivity to the toxic dose of caffeine increases with age. There is little information available on the biochemical effects of caffeine on blood glucose level or the sugar tolerance curve. In high doses, caffeine produces a sharp rise in the free fatty acids level of blood, an action similar to the effect of stress. Caffeine increases lipolysis by direct action on the adipose tissue (Ref. 23). These actions, like other pharmacologic actions of caffeine, resemble those of the catecholamines.

Ingestion of caffeine in some patients resembles the effects of catecholamines on the heart, too, in that it induces a rise in cardiac index, oxygen consumption, mean arterial pressure and ventricular filling pressure (Ref. 24). In some individuals the use of coffee causes an increase in premature ventricular contractions and recently Jick et al. (Ref. 25) reported a positive association between coffee consumption and acute myocardial infarction but no association between tea consumption and acute myocardial infarction. However, a later report from the Framingham Study provided no support for the hypothesis that coffee intake is either qualitatively or quantitatively related to the initial development of manifestations of atherosclerotic disease (Ref. 26).

Also, caffeine has been reported to cause increased acid secretion in the stomach and possibly contribute to gastric bleeding (Ref. 27). In vitro it inhibits platelet aggregation (Refs. 28 and 29) and its use in patients with gastritis is not recommended.

Habituation to the use of caffeine is well documented. The Panel concurs with the OTC Sedative, Tranquilizer and Sleep-Aid Panel that this is not a serious problem and does not believe that a warning regarding habituation is necessary. At the same time it is concerned that inclusion of caffeine in OTC analgesic preparations may lead to their continued use and abuse. While this could be

a factor in analgesic abuse the Panel finds insufficient evidence to justify a warning at the present time and the potential benefits outweigh this risk.

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4. *Antihistamine-containing ingredients.* The Panel has classified the following as ingredients for potential use as direct acting adjuvants:

Methapyrilene fumarate
Pheniramine maleate
Phenyltoloxamine
Pyrilamine maleate

The Panel received data only on phenyltoloxamine (Refs. 1 through 5) for use as an adjuvant. However, it is the opinion of the Panel that such potential activity is shared by antihistamines in general. Therefore, the Panel has included for consideration other antihistamines submitted to the Panel for review i.e., methapyrilene fumarate, pheniramine maleate and pyrilamine maleate.

a. *Methapyrilene fumarate.* The Panel concludes that methapyrilene fumarate when used alone in the currently marketed OTC adult oral dosage of 25 mg not to exceed 100 mg in 24 hours is safe but ineffective as an OTC analgesic, antipyretic and/or antirheumatic ingredient and is classified as Category II. However, there are insufficient data available to classify the adjuvant effect of methapyrilene fumarate when used in combination with Category I analgesic, antipyretic and/or antirheumatic agents as an effective analgesic, antipyretic and/or antirheumatic adjuvant and it is therefore classified in combination as Category III.

The Panel notes that the Advisory Review Panel on OTC Sedative, Tranquilizer and Sleep-Aid Products, in their report published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292) concluded that the available data were insufficient to make a final determination as to the safety and effectiveness of methapyrilene fumarate for use as a nighttime sleep-aid or daytime sedative. The Panel recommended a proposed dosage of 25 to a maximum 100 mg single dose at bedtime as a nighttime sleep-aid and a maximum 25 mg single dose up to 4 times daily for the drug as a daytime sedative.

b. *Pheniramine maleate.* The Panel concludes that pheniramine maleate when used alone in the currently marketed OTC adult oral dosage of 12.5 mg not to exceed 50 mg in 24 hours is safe but ineffective as an OTC analgesic, antipyretic and/or antirheumatic ingredient and is classified as Category II. However, there are insufficient data available to classify the adjuvant effect of pheniramine maleate when used in combination with Category I analgesic, antipyretic and/or antirheumatic agents as an effective analgesic, antipyretic and/or antirheumatic adjuvant and it is therefore classified in combination as Category III.

The Panel notes that the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products, in their report published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38312) concluded that pheniramine maleate is safe and effective as an OTC antihistamine. The Panel recommended an adult oral dosage of 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.

c. *Phenyltoloxamine dihydrogen citrate.* The Panel concludes that phenyltoloxamine dihydrogen citrate when used alone in the currently marketed OTC adult oral dosage of 30 mg not to exceed 240 mg in 24 hours is safe but ineffective as an OTC analgesic, antipyretic and/or antirheumatic ingredient and is classified as Category II. However, there are insufficient data available to classify the adjuvant effect of phenyltoloxamine dihydrogen citrate when used in combination with Category I analgesic, antipyretic and/or antirheumatic agents as an effective analgesic, antipyretic and/or antirheumatic adjuvant and it is therefore classified in combination as Category III.

The Panel notes that the Advisory Review Panel on OTC Sedative, Tranquilizer and Sleep-Aid Products, in their report published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292) concluded that the available data were insufficient to make a final determination as to the safety and effectiveness of phenyltoloxamine dihydrogen citrate for use as a nighttime sleep-aid or daytime sedative. The Panel recommended a proposed dosage of 100 to a maximum 200 mg single dose at bedtime as a nighttime sleep-aid and a maximum 100 mg single dose up to 4 times daily for the drug as a daytime sedative.

Phenyltoloxamine belongs to the ethanolamine group of antihistamines. It is currently marketed in OTC combination products for the treatment of asthma, allergic conditions and for headache and other pain. The drug has been shown to be effective in relieving vasomotor rhinitis, hay fever, pruritus, eczema, urticaria, asthma and certain other allergic drug reactions. Animal studies have shown that the drug is one of the least toxic antihistamines. However, it may cause drowsiness, dizziness, insomnia, nervousness and epigastric distress in some people.

The Panel is unaware of any OTC marketing of phenyltoloxamine alone as an analgesic, antipyretic and/or antirheumatic. However, the Panel did receive submissions of the use of phenyltoloxamine in combination with acetaminophen only, with acetaminophen, phenacetin, phenylpropanolamine, and with acetaminophen and caffeine. Labeling for these marketed products include phrases such as "for enhanced relief of pain", "relief of mild to moderate pain and discomfort due to simple headaches; for temporary relief of such pain associated with muscle and joint soreness, neuralgia, sinusitis, minor menstrual cramps, the common cold or grippe, toothache, and minor aches and pains of rheumatism and arthritis" and "produces mild sedation and tranquilization".

The results of two clinical studies were submitted to the Panel to support the analgesic adjuvant effects of phenyltoloxamine in combination with acetaminophen. One study was designed to determine the analgesic-calmative effects of a currently marketed combination product containing acetaminophen and phenyltoloxamine in the treatment of simple nervous tension accompanied by headache and the second study was designed to determine the effectiveness of the combination product in relief of musculoskeletal pain associated with anxiety.

In the single-dose, double-blind crossover study on simple nervous tension accompanied by headache, both acetaminophen and phenyltoloxamine were found to be effective (Ref. 1). There were 200 females and 6 males in the study. Subjects were instructed to take two tablets on the day they developed nervous tension with headaches. Each subject completed four, single-dose trials and received each drug alone, the combination and placebo with a minimum of 48 hours between. The interaction of phenyltoloxamine and acetaminophen was not significant.

The Panel carefully reviewed this study and the additional data submitted (Refs. 1 and 5). The Panel finds that problems in the 2x2 factorial analysis prevent a firm conclusion from being reached since it cannot be determined if the combination is significantly more effective than acetaminophen alone in the treatment of headache.

In the other double-blind study on relief of musculoskeletal pain associated with anxiety, both acetaminophen and phenyltoloxamine were reported to be effective (Ref. 2). Patients with acute episodes of mild to moderate traumatic or nonrheumatic musculoskeletal pain associated with anxiety were included. There were 73 females and 87 males in the study such that the 160 subjects were divided into four medication groups of 40 subjects. Each patient received two tablets 3 times daily for 3 days.

Both were found to be effective, 325 mg acetaminophen in relieving pain and 60 mg phenyltoloxamine in relieving anxiety. It was reported that after a single dose, and after one day of dosing, the combination, i.e., 325 mg acetaminophen and 60 mg phenyltoloxamine, was equivalent to the combined effects of the two drugs in relieving pain and anxiety. After 2 days of dosing, the analgesic effect of the combination was significantly greater than the effect of acetaminophen alone (p is less than 0.01).

The Panel carefully evaluated this study and the additional data submitted (Refs. 2 and 5) and found that while the data suggested the combination of acetaminophen and phenyltoloxamine produced more pain relief than acetaminophen alone, this was statistically significant only at 2 days. Therefore, the Panel finds these data insufficient to classify phenyltoloxamine as an adjuvant in combination with acetaminophen in Category I.

The Panel concludes, based upon all the data submitted, that the statistical analysis does not support the conclusion that the combination is effective in the treatment of tension headache or for the relief of musculoskeletal pain associated with anxiety. The Panel has classified such claims as Category II. (See part III. paragraph B.2. above—Category II Labeling.) The Panel further concludes that the available data are insufficient to support the conclusion that the combination is more effective than acetaminophen alone. The Panel has classified the potential adjuvant effect of phenyltoloxamine in combination as Category III.

d. *Pyrilamine maleate.* The Panel concludes that pyrilamine maleate when used alone in the currently marketed OTC adult oral dosage of 12.5 mg not to exceed 50 mg in 24 hours is safe but ineffective as an OTC analgesic, antipyretic and/or antirheumatic ingredient and is classified as Category II. However, there are insufficient data available to classify the adjuvant effect of pyrilamine maleate when used in combination with Category I analgesic, antipyretic and/or antirheumatic agents as an effective analgesic, antipyretic and/or antirheumatic adjuvant and it is therefore classified in combination as Category III.

The Panel notes that the Advisory Review Panel on OTC Sedative, Tranquilizer and Sleep-Aid Products, in their report published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292) concluded that the available data was insufficient to make a final determination as to the safety and effectiveness of pyrilamine maleate for use as a nighttime sleep-aid or daytime sedative. The Panel recommended a proposed dosage of 25 to a maximum 50 mg single dose at bedtime as a nighttime sleep-aid and a maximum 25 mg single dose up to 4 times daily for the drug as a daytime sedative.

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5. *Salicylamide.* The Panel concludes that there are insufficient data to determine that salicylamide is either safe or effective when used in combination as an OTC adjuvant in the currently marketed dosage of 97.2 to 400 mg. The Panel finds that salicylamide when used alone at a higher dosage (1,000 mg every 4 hours while symptoms persist not to exceed 6,000 mg in 24 hours for not more than 10 days) may be effective but has not been demonstrated to be safe for OTC use. However, the Panel recommends that salicylamide not be made available for OTC use at the higher dosage range until suitable studies have been completed to show both safety and effectiveness. (See part III. paragraph B.3.c. above—Salicylamide and part IV. paragraph B.3.c. above—Salicylamide.)

The Panel concludes that there is some evidence that salicylamide may effectively contribute to the analgesic effectiveness of combination products in doses (200 mg) considerably below those required when salicylamide is used as a single analgesic agent.

Current evidence, although still incomplete, suggests that salicylamide may be acting either as an adjuvant to directly enhance the pharmacologic activity of other agents, e.g., increased hypnotic activity of acetaminophen, or possibly indirectly by increasing the amount of the aspirin absorbed possibly by competition or inhibition of metabolizing systems in the intestine or liver. This mechanism provides one possible explanation for the "aspirin sparing" claim submitted for one analgesic combination (Ref. 1).

Salicylamide has been demonstrated to inhibit salicylate metabolism competing with aspirin for the glucuronidation pathway. It has also been shown that it competitively inhibits the metabolism of acetaminophen in the glucuronidate and sulfate formation (Refs. 2 and 3).

The mechanisms involved, doses required and effects of formulation variables are not well defined. Claims for adjunctive effects of salicylamide should be evaluated for each product.

Studies on the systemic availability of salicylamide in man at doses of 300 to 600 mg indicate that very little free drug reaches the systemic circulation. In most clinical studies, these doses of salicylamide have provided little or no effect over that obtained with placebo. Doses of 1 to

2 g and higher are usually required to show analgesic effects.

Based on the knowledge of single doses of salicylamide alone, it would seem unlikely that the small oral doses of 300 to 600 mg found in most combination products would result in effective plasma levels of salicylamide. There is accumulating evidence, however, that combinations of salicylamide with salicylates and acetaminophen may result in higher blood levels of all three agents than when they are given alone. Levy and co-workers have shown that a mutual inhibition of metabolism occurs in man with a combination of salicylamide and sodium salicylate (Ref. 2) and also a combination of salicylamide and acetaminophen (Ref. 3). This was not the case, however, with the combination of acetaminophen and salicylic acid (Ref. 4).

When 2.32 g sodium salicylate was given to healthy adults 2 hours before the administration of 600 mg salicylamide, there was a mutual inhibition of glucuronide formation by both drugs and a suggestion of a salicylate-induced inhibition of salicylamide sulfate formation (Ref. 2). Such inhibitory action would be expected to result in higher blood levels of the free unmetabolized drugs with a concomitant increased pharmacologic action.

A similar competitive inhibition in the metabolism of acetaminophen and salicylamide occurred when the drugs were administered to healthy subjects. When 1 or 2 g salicylamide was given 1.5 hours after the administration of 1 g acetaminophen, a decrease in the formation of acetaminophen sulfate, acetaminophen glucuronide and salicylamide sulfate was observed as evidenced by the decreased excretion rates of these metabolites in the urine. The inhibition of sulfate formation was counteracted by L-cysteine, a source of sulfate, administered concomitantly with salicylamide (Ref. 3). On the other hand, when sodium salicylate was given after acetaminophen administration, there was no apparent mutual inhibition of the formation of the metabolic conjugates (glucuronides and sulfates) of acetaminophen or the formation of the metabolites of sodium salicylate (Ref. 4). This is in contrast to the mutual metabolic inhibition that occurred when acetaminophen was administered with salicylamide (Ref. 3).

The results of the metabolic studies using combinations of salicylamide and acetaminophen, salicylamide and sodium salicylate, and acetaminophen and sodium salicylate, indicate that salicylamide is the major determinant in the metabolic inhibitory interactions between acetaminophen and salicylamide and between sodium salicylate and salicylamide. The pronounced competitive inhibitory effect of salicylamide on glucuronide and sulfate formation is most likely due to its very rapid metabolism. Available data indicate that the formation of salicylamide glucuronide and sulfate proceeds about 10 times more rapidly than the formation of acetaminophen glucuronide and sulfate at body levels of 1 g of these drugs (Ref. 4).

Barr et al. (Ref. 5) have shown that salicylic acid can competitively inhibit salicylamide glucuronide formation and noncompetitively inhibit salicylamide sulfate formation in a rabbit in vitro intestinal preparation resulting in a 40 percent increase in free salicylamide transfer across the everted intestine.

The extent to which combinations of these analgesics may interact in man at intestinal metabolism sites to increase systemic plasma levels of the active forms of the analgesics has not been measured directly. Considering the metabolic interactions, however, these combinations might be expected to have greater than additive effects. Synergistic pharmacologic effects of combinations of salicylamide with acetaminophen or with phenacetin have been demonstrated in animals and man (Refs. 3, 6, and 7).

Berger (Ref. 6) in 1954 reported that salicylamide had a hypnotic effect that was enhanced by phenacetin which has no sedative effect of its own.

The findings of Berger are corroborated by the studies in mice by White et al. (Ref. 7) who in 1956 found sedative effects of several combinations at doses which had no effect when given separately, including salicylamide-phenacetin, salicylamide-acetaminophen and salicylamide-acetanilide. These workers also found that with a mixture of 240 mg acetaminophen and 600 mg salicylamide, 76 of 108 patients noted a sedative effect and some patients commented on the analgesic effect of the mixture. The same dose given 4 times daily to 15 subjects resulted in daytime sedation in 14 patients and in 7 patients receiving a placebo. No other adverse reactions were noted.

The effectiveness of two dose levels of a combination of acetaminophen-salicylamide (487.5 mg plus 487.5 mg, and 325 mg plus 325 mg) in the treatment of headaches was compared to a dose of 648 mg aspirin and to placebo in university students, employing a double-blind Latin-square design (Ref. 8). In a total of 94 subjects with 229 headaches, relief was obtained in 46 percent by placebo, 78 percent by aspirin and 76 and 69 percent, respectively, by the high and low doses of the acetaminphen-salicylamide combination. The effectiveness of all drug treatments was significantly different from the placebo efficacy, but not different from each other.

It is reasonable to conclude that in considering the dose of each individual ingredient in a combination product that includes salicylamide, reliance cannot be placed upon using the same dose of the ingredients that is contained in single ingredient products. The inhibitory action on the metabolism of the ingredients in the combination, by the presence of salicylamide, might be expected to increase the amounts of the free unmetabolized drugs to levels that would not otherwise occur if each ingredient were administered alone at the same dose. Such increased levels might result in overdosage and toxic effects. It is possible that competition for metabolism either at intestinal or hepatic sites during absorption will provide a "sparing" effect.

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C. DATA REQUIRED FOR EVALUATION

1. *Aspirin standard testing procedures.* The studies cited above have shown that buffered aspirin products vary among themselves with respect to dissolution rate, rate of absorption and effect on gastric tolerance. (See part II, paragraph J, above—Effects of Product Formulation on Drug Absorption and Pharmacologic Effectiveness.) Variations in these characteristics, are also found in plain aspirin products. Although buffered aspirin products generally have faster dissolution rates, are better tolerated and are absorbed faster than plain aspirin products, all buffered aspirin products cannot be equated to have the same ability to be absorbed and therefore to produce comparable blood levels in a specified time. On the other hand, while plain (unbuffered) aspirin products generally dissolve and are absorbed at a slower rate, and are less well tolerated, some plain aspirin products are comparable to buffered aspirin products in their ability to be rapidly dissolved and rapidly absorbed. The similarities and/or dissimilarities between plain aspirin products and buffered aspirin products may be accounted for on the basis of formulating procedures of the manufacturers and/or the dissolution methodology employed by different investigators. To avoid any discrepancies in dissolution methodology and to eliminate products that are, without question, improperly formulated for the safe use of aspirin, the Panel proposes to set standards for plain and buffered aspirin products. The Panel has proposed a tentative testing procedure for future development and implementation.

a. *Buffered aspirin acid neutralizing testing procedure.* The Panel concludes that aspirin tablets may be labeled as

"buffered aspirin" providing each dosage unit containing the equivalent of 325 mg (5 gr) of aspirin contains at least 1.9 mEq of acid neutralizing capacity as determined by the following procedure:

(1) *Apparatus and reagents.* (i) pH meter, equipped with glass and saturated calomel electrodes.

(ii) Magnetic stirrer.

(iii) Magnetic stirring bars (about 40 mm long and 10 mm in diameter).

(iv) 50 ml buret.

(v) Buret stand.

(vi) 100 ml beakers.

(vii) 250 ml beakers.

(viii) 10 ml, 20 ml and 30 ml pipets calibrated to deliver.

(ix) Tablet comminuting device.

(x) A number 20 and 100 U.S. standard mesh sieve.

(xi) Tablet disintegration apparatus.

(xii) 0.1 N, 0.5 N and 1.0 N hydrochloric acid.

(xiii) 0.5 N sodium hydroxide.

(xiv) Standard pH 4.0 buffer solution (0.05 M potassium hydrogen phthalate).

(xv) 95 percent ethanol.

(xvi) Purified water U.S.P.

(2) *Reagent standardization.* Standardize the sodium hydroxide (NaOH) and hydrochloric acid (HCl) solutions according to the procedures in the *United States Pharmacopeia XVIII* (NaOH page 1036 and HCl page 1034) or the Official Methods of Analysis of the Association of Official Analytical Chemists, 11th Ed., 1970, (NaOH page 876 and HCl page 873).

(3) *Temperature standardization.* All tests shall be conducted at 25° C±3° or 37° C±3°.

(4) *Acid neutralizing capacity test*—(i) *pH meter.* Standardize the pH meter at pH 4.0 with the standardizing buffer and check for proper operation at pH 1 with 0.1 N HCl.

(ii) *Dosage form testing*—(a) *Tablet sample.* Place an accurately weighed amount of a tablet composite equivalent to the minimum labeled dosage into a 250 ml beaker. (The composite shall be prepared by determining the average weight of not less than 20 tablets and then comminuting the tablets sufficiently to pass through a number 20 U.S. standard mesh sieve and held by a number 100 U.S. standard mesh sieve. Mix the sieved material to obtain a uniform sample.) If wetting is desired, add not more than 5 ml of 95 percent ethanol and mix to wet the sample thoroughly (ethanol may affect the acid neutralizing capacity). Add water to a volume of 70 ml and mix on magnetic stirrer at 300±30 r.p.m. for about 1 minute. Capsules should be tested in the same manner using the sieved capsule powder as the sample. Analyze the sample according to the procedure set forth in section (5) below.

(b) *Effervescent sample.* Place an amount equivalent to the minimum labeled dosage into a 250 ml beaker. Add 10 ml water and swirl the beaker gently while allowing the reaction to subside. Add another 10 ml of water and swirl the beaker gently. Wash down the walls of the beaker with 50 ml of water and mix on a magnetic stirrer at 300±30 r.p.m. for about 1 minute. Analyze the sample according to the procedure set forth in § 331.26.

(5) *Acid neutralizing capacity test procedure.* (i) Pipette 30.0 ml of 1.0 N HCl into the sample solution while stirring on the magnetic stirrer at 300±30 r.p.m.

(ii) Stir for exactly 15 minutes after addition of acid.

(iii) Begin titrating immediately and in a period not to exceed an additional 5 minutes titrate the excess 1.0 N HCl with 0.5 N NaOH to a stable pH of 3.5.

(iv) Check the sample solution 10 to 15 seconds after obtaining pH 3.5 to make sure the pH is stable.

(v) Calculate the number of mEq of acid neutralized by the sample as follows:

Total mEq = (30.0 ml) (normality of HCl) − (ml of NaOH) (N of NaOH).

Use appropriate factors, i.e., density, average tablet weight, etc., to calculate the total mEq of acid neutralized per minimum labeled dosage.

(6) *Test modifications.* The formulation and/or mode of administration of certain products may require modification of this in vitro test. Any proposed modification and the data to support it shall be submitted to the Food and Drug Administration for approval prior to use.

b. *Aspirin (plain and buffered) tablet dissolution testing procedure.* Each dosage unit containing the equivalent of 325 mg (5 gr) of aspirin shall be suitable for labeling as an "aspirin" or if applicable "buffered aspirin" product if the quantity of aspirin dissolved within "x" minutes is not less than 162.5 mg (2.5 gr) (50 percent of labeled amount) and the quantity of aspirin dissolved in "x" minutes is not less than 292.5 mg (4.5 gr) (90 percent of labeled amount) as determined by the following procedure:

(1) *Laboratory technique.* Throughout this procedure use scrupulously clean glassware, which previously has been rinsed with dilute hydrochloric acid, distilled or deionized water, then with alcohol, and carefully dried. Take precautions to prevent contamination from airborne, fluorescent particles and from metal and rubber surfaces.

(2) *Dissolution test apparatus.* The apparatus consists of a suitable water bath, a 500 ml round bottom glass vessel (Kimble Glass No. 33710-S1, or equivalent), a motor, and a stirring blade (Sargent S-76637, Size B, 3-in length; Hanson 65-700-300; or equivalent) on a stirring shaft (Sargent S-76636, 14, 5-in length; Hanson 65-700-001; or equivalent). The water bath may be of any convenient size that permits keeping the water temperature uniformly at 37° C ±0.5° C throughout the test. The water bath must not transmit perceptible vibration to the vessel. The vessel is cylindrical, with a spherical bottom. It is 16 cm high and is 10 cm in inside diameter. Its sides are flanged near the top. The vessel is positioned so that the stirring shaft from the motor is centered on the vessel's cylindrical axis. The motor is fitted with a speed-regulating device that allows the motor speed to be held at 50 rpm±2 rpm. The motor is suspended above the vessel in such a way that it may be raised or lowered to position the stirring blade. The stirring shaft is 10 mm in diameter and about 37 cm in length. It must run true on the motor axis without perceptible wobble. The stirring blade is 4 mm thick and forms a section of a circle whose diameter is 83 mm and which is subtended by parallel chords of 42 and 77 mm. The blade is positioned horizontally, with the 42 mm edge down, so that the lower edge of the blade is 2.5 cm±0.2 cm above the lowest inner surface of the vessel.

(3) *Dissolution medium.* Use a reagent containing 2.0 g sodium chloride, 3.2 g papain, 5.0 g mucin and 10 ml 0.1 N hydrochloric acid (HCl) combined and diluted with distilled water per each 1,000 ml solution.

(4) *Procedure.* Place 500 ml of dissolution medium in the vessel, immerse it in the constant-temperature bath set at 37° C.±0.5° C. and allow the dissolution medium to assume the temperature of the bath. Position the shaft so that there is a distance of 2.5 cm±2 cm between the midpoint of the bottom of the blade and the bottom of the vessel. With the stirrer operating at a speed of 50 rpm ±2 rpm, place 1 tablet containing the equivalent of 325 mg (5 gr) buffered aspirin into the flask. After 5, 10, 20 and 30 minutes, accurately timed, withdraw 10 ml, using a glass syringe connected to a glass sampling tube, of solution from a point midway between the stirring shaft and the wall of the vessel, and approximately midway in depth. Filter the solution promptly after withdrawal, using a suitable membrane filter of not greater than 0.8 micron porosity. This is the test solution. Repeat the dissolution procedure on 5 additional tablets containing the equivalent of 325 mg (5 gr) buffered aspirin per tablet.

(5) *Measurement of acetylsalicylic acid and salicylic acid.* Dilute the test solution with an equal volume of 0.1 N HCl. The absorbance of the diluted test solution is measured in a spectrophotometer at a wavelength of 275 millimicrons for acetylsalicylic acid and at a wavelength of 302 millimicrons for salicylic acid. The values are corrected for blank absorbance using the reagent dissolution medium. The amounts of acetylsalicylic acid and salicylic acid in the test solution at the time of sampling are determined by comparing their absorbancies with standard curves prepared for the two acids from known solutions. The solutions from which the standard curves are prepared should contain a known amount of acid dissolved in reagent dissolution medium and their absorbancies should be read immediately after preparation. The amounts of the acids in the test solution at the time of sampling are expressed in mg. The decreasing volume of the test solution after repeated samplings as well as the amounts of acetylsalicylic acid and salicylic acid removed in each sample should be considered in deter-

mining the total amounts of acetylsalicylic acid and salicylic acid in solution at the time of each sampling. The amounts of acetylsalicylic acid and salicycylic acid should be converted to express the total amount of acetylsalicyclic acid, in mg, (Ref. 1) resulting from the dissolution of a dosage unit (tablet) containing 325 mg (5 gr) buffered aspirin in (x) minutes.

2. *Combination products containing an analgesic, antipyretic and/or antirheumatic adjuvant*—a. *General principles.* (1) Combinations must demonstrate at least as much analgesic effectiveness as 650 mg (10 gr) dose of aspirin.

(2) Combinations must be at least as safe as the recommended 650 mg (10 gr) single dose of aspirin or the recommended maximum 24 hour dose of 3,900 mg of aspirin.

(3) Each component must make a statistically significant contribution to the total effect. For instance in the case of caffeine, this could be determined by factorially designed studies which might include aspirin 650 mg, aspirin 650 mg plus caffeine 60 mg, caffeine 60 mg, and placebo. The analysis must show caffeine in combination to have a significant effect to justify its continued inclusion in combinations.

b. *Determination of effectiveness.* To establish Category I status for a Category III compound requires at least two studies by independent investigators which conform to the guidelines included above for compounds for which safety is unquestioned. (See part III, paragraph C, above—Data Required for Evaluation.)

c. *Combinations containing adjuvants.* Combinations containing adjuvants which have been shown to affect the metabolic pathways of other ingredients must be shown on repeated dosage schedules not to inhibit or interfere with the metabolism in such a way that toxic levels of any ingredients are achieved. For example, for a combination containing salicylamide and aspirin, it must be shown with repeated dosing that the blood salicylate level does not exceed 20 mg percent.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes that Subchapter D be amended by adding new Part 343 to read as follows:

PART 343—INTERNAL ANALGESIC, ANTIPYRETIC AND ANTIRHEUMATIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
343.1 Scope.
343.3 Definitions.

Subpart B—Active Ingredients

343.10 Analgesics.
343.12 Antipyretics.
343.14 Antirheumatics.
343.20 Permitted combinations of active ingredients.

Subpart C—[Reserved]

Subpart D—Labeling

343.50 Labeling of analgesic and antipyretic products.
343.80 Professional labeling.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 343.1 Scope.

An over-the-counter internal analgesic, antipyretic, or antirheumatic product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 343.3 Definitions.

(a) *Acetaminophen analgesic equivalence value.* The analgesic effectiveness for a product containing acetaminophen when compared to the standard acetaminophen 325 mg (5 gr) dosage unit.

(b) *Acetaminophen (pediatric dosage unit).* A single dosage unit containing 80 mg (1.23 gr) acetaminophen for children under 12 years.

(c) *Acetaminophen (standard dosage unit).* A single dosage unit containing 325 mg (5 gr) acetaminophen.

(d) *Adjuvant.* An agent which, in the amount used, has no significant analgesic effect itself but contributes to the therapeutic effect of the active agent either directly or indirectly.

(1) *Direct acting.* An adjuvant which enhances the pharmacologic response directly by synergistic or additive effects at the site of action.

(2) *Indirect acting.* An adjuvant which does not have effects at the site of action, but indirectly increases the activity of the active agent(s) of the preparation by modifying the disposition (absorption, metabolism, excretion or distribution) of the active agent.

(e) *Age (dosage) usage.* Infant or baby (under 2 years), child (2 years to under 12 years), and adult (12 years and over).

(f) *Analgesic drug.* An agent useful to alleviate the symptoms of pain.

(g) *Antipyretic drug.* An agent used to reduce fever.

(h) *Antirheumatic drug.* An agent which reduces joint or muscle tenderness or swelling.

(i) *Aspirin analgesic equivalence value.* The analgesic effectiveness for a product containing aspirin or aspirin salts, e.g., aluminum aspirin or calcium carbaspirin when compared to the standard aspirin 325 mg (5 gr) dosage unit.

(j) *Aspirin (buffered).* A solid dosage form containing 325 mg (5 gr) aspirin with sufficient buffering capacity with antacid active ingredient(s) identified in § 331.11 of this chapter such that the finished product contains at least 1.9 mEq of acid neutralizing capacity per 325 mg of aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of this chapter and provided that product is identified as buffered aspirin with labeling only as an analgesic and/or antipyretic.

(k) *Aspirin (highly buffered) for solution.* A solid dosage form to be dissolved in water prior to oral administration as a solution. The product shall contain 325 mg (5 gr) aspirin and sufficient buffering capacity with antacid active ingredient(s) identified in § 331.11 of this chapter such that the finished product contains at least 20 mEq of acid neutralizing capacity per 325 mg of aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of this chapter and provided the product is identified as highly buffered aspirin with labeling only as an analgesic and/or antipyretic.

(l) *Aspirin (pediatric dosage unit).* A single dosage unit containing 80 mg (1.23 gr) aspirin for children under 12 years.

(m) *Aspirin (standard dosage unit).* A single dosage unit containing 325 mg (5 gr) aspirin.

(n) *Corrective.* An agent in the drug delivery system intended to reduce some undesirable effect of the therapeutically active agent.

(o) *Sodium salicylate analgesic equivalence value.* The analgesic effectiveness for a product containing sodium salicylate or other salicylates, e.g., choline salicylate, magnesium salicylate, or salsalate when compared to the standard sodium salicylate 325 mg dosage unit.

(p) *Sodium salicylate (standard dosage unit).* A single dosage unit containing 325 mg sodium salicylate.

Subpart B—Active Ingredients

§ 343.10 Analgesics.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Aspirin.*—(1) *For products containing 325 mg (5 gr) per dosage unit.*—(i) *Standard schedule.* Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg (7.5 gr) every 4 hours while symptoms persist not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while symptoms persist not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while symptoms persist not to exceed 1,625 mg (25 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg

(3.75 gr) every 4 hours while symptoms persist not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while symptoms persist not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *Nonstandard schedule.* Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) *For products containing 80 mg (1.23 gr) per dosage unit.* Children 11 to under 12 years oral dosage is 480 mg (7. 38 gr) every 4 hours while symptoms persist not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while symptoms persist not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while symptoms persist not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while symptoms persist not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 160 mg (2. 46 gr) every 4 hours while symptoms persist not to exceed 800 mg (12.3 gr) in 24 hours for not more than 10 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(3) *For products containing more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) per dosage unit.* Adult oral dosage is more than 325 mg (5 gr) but not more than 842 mg (12.96 gr) initially, followed by more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) every 3 hours while symptoms persist not to exceed 3,789 mg (58.32 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *For products containing more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) per dosage unit.* Adult oral dosage is more than 421 mg (6.48 gr) but not more than 970 mg (14.92 gr) initially, followed by more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) every 4 hours or 842 mg (12.96 gr) but not more than 970 mg (14.92 gr) every 6 hours while symptoms persist not to exceed 3,880 mg (59.68 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(5) *For products containing more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) per dosage unit.* Adult oral dosage is more than 485 mg (7.46 gr) but not more than 1,000 mg (15.38 gr) initially, followed by more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) every 3 hours or 970 mg (14.92 gr) but not more than 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(6) *For products containing more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) per dosage unit.* Adult oral dosage is more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Acetaminophen*—(1) *For products containing 325 mg (5 gr) per dosage unit*—(i) *Standard schedule.* Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg (7.5 gr) every 4 hours while symptoms persist not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while symptoms persist not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while symptoms persist not to exceed 1,625 mg (25 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg (3.75 gr) every 4 hours while symptoms persist not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while symptoms persist not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *Nonstandard schedule.* Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) *For products containing 80 mg (1.23 gr) per dosage unit.* Children 11 to under 12 years oral dosage is 480 mg (7.38 gr) every 4 hours while symptoms persist not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while symptoms persist not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while symptoms persist not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while symptoms persist not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 160 mg (2.46 gr) every 4 hours while symptoms persist not to exceed 800 mg (12.3 gr) in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(3) *For products containing 500 mg (7.69 gr) per dosage unit.* Adult oral dosage is 500 mg (7.69 gr) to 1,000 mg (15.38 gr) initially, followed by 500 mg (7.69 gr) every 3 hours or 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Calcium carbaspirin.* Adult oral dosage is 414 to 828 mg every 4 hours while symptoms persist not to exceed 4,968 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 621 mg every 4 hours while symptoms persist not to exceed 3,105 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 517.5 mg every 4 hours while symptoms persist not to exceed 2,587.5 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 414 mg every 4 hours while symptoms persist not to exceed 2,070 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 310.5 mg every 4 hours while symptoms persist not to exceed 1,552.5 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 207 mg every 4 hours while symptoms persist not to exceed 1,035 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Choline salicylate.* Adult oral dosage is 435 to 870 mg every 4 hours while symptoms persist not to exceed 5,220 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 652.5 mg every 4 hours while symptoms persist not to exceed 3,262.5 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 543.8 mg every 4 hours while symptoms persist not to exceed 2,719 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 435 mg every 4 hours while symptoms persist not to exceed 2,175 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 326.5 mg every 4 hours while symptoms persist not to exceed 1,632.5 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 217.5 mg every 4 hours while symptoms persist not to exceed 1,087.5 mg in 24 hours for not more than 5 days. Children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(e) *Magnesium salicylate.* Adult oral dosage is 325 to 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while symptoms persist not to exceed

2,437.5 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while symptoms persist not to exceed 2,031.5 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while symptoms persist not to exceed 1,625 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while symptoms persist not to exceed 1,219 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while symptoms persist not to exceed 812.5 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(f) *Sodium salicylate.* (1) *For products containing 325 mg per dosage unit.*—(i) *Standard schedule.* Adult oral dosage is 325 to 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while symptoms persist not to exceed 2,437.5 mg in 24 hours for not more than 5 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while symptoms persist not to exceed 2,031.5 mg in 24 hours for not more than 5 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while symptoms persist not to exceed 1,625 mg in 24 hours for not more than 5 days. Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while symptoms persist not to exceed 1,219 mg in 24 hours for not more than 5 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while symptoms persist not to exceed 812.5 mg in 24 hours for not more than 5 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *Nonstandard schedule.* Adult oral dosage is 325 mg to 975 mg initially, followed by 650 mg every 4 hours while symptoms persist not to exceed 3,900 in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) *For products containing more than 325 mg but not more than 421 mg per dosage unit.* Adult oral dosage is more than 325 mg but not more than 842 mg initially, followed by more than 325 mg but not more than 421 mg every 3 hours while symptoms persist not to exceed 3,789 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(3) *For products containing more than 421 mg but not more than 485 mg per dosage unit.* Adult oral dosage is more than 421 mg but not more than 970 mg initially, followed by more than 421 mg but not more than 485 mg every 4 hours or 842 mg but not more than 970 mg every 6 hours while symptoms persist not to exceed 3,880 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *For products containing more than 485 mg but not more than 500 mg per dosage unit.* Adult oral dosage is more than 485 mg but not more than 1,000 mg initially, followed by more than 485 mg but not more than 500 mg every 3 hours or 970 mg but not more than 1,000 mg every 6 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(5) *For products containing more than 500 mg but not more than 650 mg per dosage unit.* Adult oral dosage is more than 500 mg but not more than 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 343.12 Antipyretics.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Aspirin.*—(1) *For products containing 325 mg (5 gr) per dosage unit.*—(i) *Standard schedule.* Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while fever persists not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 487.5 mg (7.5 gr) every 4 hours while fever persists not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while fever persists not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while fever persists not to exceed 1,625 mg (25 gr) in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 243.8 mg (3.75 gr) every 4 hours while fever persists not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while fever persists not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *Nonstandard schedule.* Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) *For products containing 80 mg (1.23 gr) per dosage unit.* Children 11 to under 12 years oral dosage is 480 mg (7.38 gr) every 4 hours while fever persists not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while fever persists not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while fever persists not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while fever persists not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 3 days. Children 2 to 4 years oral dosage is 160 mg (2.46 gr) every 4 hours while fever persists not to exceed 800 mg (12.3 gr) in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(3) *For products containing more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) per dosage unit.* Adult oral dosage is more than 325 mg (5 gr) but not more than 842 mg (12.96 gr) initially, followed by more than 325 mg (5 gr) but not more than 421 mg (6.48 gr) every 3 hours while symptoms persist not to exceed 3,789 mg (58.32 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *For products containing more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) per dosage unit.* Adult oral dosage is more than 421 mg (6.48 gr) but not more than 970 mg (14.92 gr) initially, followed by more than 421 mg (6.48 gr) but not more than 485 mg (7.46 gr) every 4 hours or 842 mg (12.96 gr) but not more than 970 mg (14.92 gr) every 6 hours while symptoms persist not to exceed 3,880 mg (59.68 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(5) *For products containing more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) per dosage unit.* Adult oral dosage is more than 485 mg (7.46 gr) but not more than 1,000 mg (15.38 gr) initially, followed by more than 485 mg (7.46 gr) but not more than 500 mg (7.69 gr) every 3 hours or 970 mg (14.92 gr) but not more than 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(6) *For products containing more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) per dosage unit.* Adult oral dosage is more than 500 mg (7.69 gr) but not more than 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Acetaminophen.* (1) *For products containing 325 mg (5 gr) per dosage unit.*—(i) *Standard schedule.* Adult oral dosage is 325 mg (5 gr) to 650 mg (10 gr) every 4 hours while fever persists not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. Children 11 to un-

der 12 years oral dosage is 487.5 mg (7.5 gr) every 4 hours while fever persists not to exceed 2,437.5 mg (37.5 gr) in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 406.3 mg (6.25 gr) every 4 hours while fever persists not to exceed 2,031.5 mg (31.25 gr) in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 325 mg (5 gr) every 4 hours while fever persists not to exceed 1,625 mg (25 gr) in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 243.8 mg (3.75 gr) every 4 hours while fever persists not to exceed 1,219 mg (18.75 gr) in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 162.5 mg (2.5 gr) every 4 hours while fever persists not to exceed 812.5 mg (12.5 gr) in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *Nonstandard schedule.* Adult oral dosage is 325 mg (5 gr) to 975 mg (15 gr) initially, followed by 650 mg (10 gr) every 4 hours while symptoms persist not to exceed 3,900 mg (60 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) *For products containing 80 mg (1.23 gr) per dosage unit.* Children 11 to under 12 years oral dosage is 480 mg (7.38 gr) every 4 hours while fever persists not to exceed 2,400 mg (36.9 gr) in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 400 mg (6.15 gr) every 4 hours while fever persists not to exceed 2,000 mg (30.75 gr) in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 320 mg (4.92 gr) every 4 hours while fever persists not to exceed 1,600 mg (24.6 gr) in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 240 mg (3.69 gr) every 4 hours while fever persists not to exceed 1,200 mg (18.45 gr) in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 160 mg (2.46 gr) every 4 hours while fever persists not to exceed 800 mg (12.3 gr) in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(3) *For products containing 500 mg (7.69 gr) per dosage unit.* Adult oral dosage is 500 mg (7.69 gr) to 1,000 mg (15.38 gr) initially, followed by 500 mg (7.69 gr) every 3 hours or 1,000 mg (15.38 gr) every 6 hours while symptoms persist not to exceed 4,000 mg (61.52 gr) in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Calcium carbaspirin.* Adult oral dosage is 414 to 828 mg every 4 hours while fever persists not to exceed 4,968 mg in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 621 mg every 4 hours while fever persists not to exceed 3,105 mg in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 517.5 mg every 4 hours while fever persists not to exceed 2,587.5 mg in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 414 mg every 4 hours while fever persists not to exceed 2,070 mg in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 310.5 mg every 4 hours while fever persists not to exceed 1,552.5 mg in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 207 mg every 4 hours while fever persists not to exceed 1,035 mg in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physican.

(d) *Choline salicylate.* Adult oral dosage is 435 to 870 mg every 4 hours while fever persists not to exceed 5,220 mg in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 652.5 mg every 4 hours while fever persists not to exceed 3,262.5 mg in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 543.8 mg every 4 hours while fever persists not to exceed 2,719 mg in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 435 mg every 4 hours while fever persists not to exceed 2,175 mg in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 326.5 mg every 4 hours while fever persists not to exceed 1,632.5 mg in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 217.5 mg every 4 hours while fever persists not to exceed 1,087.5 mg in 24 hours for not more than 3 days. Children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(e) *Magnesium salicylate.* Adult oral dosage is 325 to 650 mg every 4 hours while fever persists not to exceed 3,900 mg in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while fever persists not to exceed 2,437.5 mg in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while fever persists not to exceed 2,031.5 mg in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while fever persists not to exceed 1,625 mg in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while fever persists not to exceed 1,219 mg in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while fever persists not to exceed 812.5 mg in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(f) *Sodium salicylate.*—(1) *For products containing 325 mg per dosage unit.*—(i) *Standard schedule.* Adult oral dosage is 325 to 650 mg every 4 hours while fever persists not to exceed 3,900 mg in 24 hours for not more than 3 days. Children 11 to under 12 years oral dosage is 487.5 mg every 4 hours while fever persists not to exceed 2,437.5 mg in 24 hours for not more than 3 days. Children 9 to under 11 years oral dosage is 406.3 mg every 4 hours while fever persists not to exceed 2,031.5 mg in 24 hours for not more than 3 days. Children 6 to under 9 years oral dosage is 325 mg every 4 hours while fever persists not to exceed 1,625 mg in 24 hours for not more than 3 days. Children 4 to under 6 years oral dosage is 243.8 mg every 4 hours while fever persists not to exceed 1,219 mg in 24 hours for not more than 3 days. Children 2 to under 4 years oral dosage is 162.5 mg every 4 hours while fever persists not to exceed 812.5 mg in 24 hours for not more than 3 days. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *Nonstandard schedule.* Adult oral dosage is 325 mg to 975 mg initially, followed by 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) *For products containing more than 325 mg but not more than 421 mg per dosage unit.* Adult oral dosage is more than 325 mg but not more than 842 mg initially, followed by more than 325 mg but not more than 421 mg every 3 hours while symptoms persist not to exceed 3,789 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(3) *For products containing more than 421 mg but not more than 485 mg per dosage unit.* Adult oral dosage is more than 421 mg but not more than 970 mg initially, followed by more than 421 mg but not more than 485 mg every 4 hours or 842 mg but not more than 970 mg every 6 hours while symptoms persist not to exceed 3,880 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *For products containing more than 485 mg but not more than 500 mg per dosage unit.* Adult oral dosage is more than 485 mg but not more than 1,000 mg initially, followed by more than 485 mg but not more than 500 mg every 3 hours or 970 mg but not more than 1,000 mg every 6 hours while symptoms persist not to exceed 4,000 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(5) *For products containing more than 500 mg but not more than 650 mg per dosage unit.* Adult oral dosage is more than 500 mg but not more than 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours for not more than 3 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 343.14 Antirheumatics.

The active ingredients of the product consist of the following:

(a) *Aspirin.* There is no recommended dosage except under the advice and supervision of a physician.

(b) *Calcium carbaspirin.* There is no recommended dosage except under the advice and supervision of a physician.

(c) *Choline salicylate.* There is no recommended dosage except under the advice and supervision of a physician.

(d) *Magnesium salicylate.* There is no recommended dosage except under the advice and supervision of a physician.

(e) *Sodium salicylate.* There is no recommended dosage except under the advice and supervision of a physician.

§ 343.20 Permitted combinations of active ingredients.

(a) *Active ingredients.* The active ingredients of the combination product consist of any two of the following at the dosage limit established for each ingredient:

(1) Aspirin 325 mg (5 gr) per dosage unit.

(2) Acetaminophen 325 mg (5 gr) per dosage unit.

(3) Calcium carbaspirin 414 mg per dosage unit.

(4) Choline salicylate 435 mg per dosage unit.

(5) Magnesium salicylate 325 mg per dosage unit.

(6) Sodium salicylate 325 mg per dosage unit.

(b) *For analgesic combination products.* Adult oral dosage is 1 dosage unit every 4 hours while symptoms persist not to exceed 6 dosage units in 24 hours for not more than 10 days. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *For antipyretic combination products.* Adult oral dosage is 1 dosage unit every 4 hours while fever persists not to exceed 6 dosage units in 24 hours for not more than 3 days.

(d) *For combination products containing nonanalgesic and/or nonantipyretic active ingredients.* (1) Any single active ingredient identified in § 343.10 or § 343.12 or any combination of active ingredients identified in § 343.20(a) may be combined with generally recognized as safe and effective antitussive active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(2) Any single active ingredient identified in § 343.10 or § 343.12 or any combination of active ingredients identified in § 343.20(a) may be combined with generally recognized as safe and effective expectorant active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for expectorant action to help loosen phlegm (sputum) and bronchial secretions".

(3) Any single active ingredient identified in § 343.10 or § 343.12 or any combination of active ingredients identified in § 343.20(a) may be combined with generally recognized as safe and effective nasal decongestant active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and for the temporary relief of nasal congestion due to the common cold (cold)".

(4) Any single active ingredient identified in § 343.10 or § 343.12 or any combination of active ingredients identified in § 343.20(a) may be combined with generally recognized as safe and effective antihistamine active ingredient(s) provided the product is labeled for the concurrent symptoms involved, e.g., "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever, and to alleviate, decrease, or temporarily relieve running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(5) Any single active ingredient identified in § 343.10(b), or § 343.12(b) may be combined with antacid active ingredient(s) which meet the requirements of § 331.10 of this chapter provided the product is labeled for the concurrent indications identified in § 343.50(a) and § 331.30(a) of this chapter.

(6) Aspirin identified in § 343.10(a) or § 343.12(a) may be combined with antacid active ingredient(s) identified in § 331.11 of this chapter such that the finished product contains at least 20 mEq of acid neutralizing capacity per 325 mg (5 gr) aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of this chapter and provided the product is identified as highly buffered aspirin with labeling only as identified in § 343.50(a).

(7) Aspirin identified in § 343.10(a) or § 343.12(a) may be combined with antacid active ingredient(s) identified in § 331.11 of this chapter such that the finished product contains at least 1.9 mEq of acid neutralizing capacity per 325 mg (5 gr) aspirin and results in a pH of 3.5 or greater at the level of the initial 10-minute period as measured by the method established in § 331.25 of this chapter and provided the product is identified as buffered aspirin with labeling only as identified in § 343.50(a).

Subpart C—[Reserved]

Subpart D—Labeling

§ 343.50 Labeling of analgesic and antipyretic products.

(a) *Indications.* The labeling shall identify the product pursuant to the appropriate definition(s) established in § 343.3 and shall contain the following:

(1) For products containing analgesic ingredients identified in § 343.10 or § 343.20 if applicable under the heading "Indications," the labeling shall state "For the temporary relief of occasional minor aches, pains and headache."

(2) For products containing antipyretic ingredients identified in § 343.12 or § 343.20 if applicable under the heading "Indications," the labeling shall state "For the reduction of fever."

(3) For products containing analgesic-antipyretic ingredients identified in §§ 343.10 and 343.12 or § 343.20 if applicable under the heading "Indications," the labeling shall state "For the temporary relief of occasional minor aches, pains and headache, and for the reduction of fever."

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions identified under §§ 343.10 and 343.12, followed by "or as directed by a physician."

(c) *Warnings.* The labeling of the product contains the appropriate warnings under the heading "Warnings" which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable as follows:

(1) For products containing any analgesic ingredient identified in § 343.10:

(i) "Adults: Do not take this product for more than 10 days. If symptoms persist, or new ones occur, consult your physician".

(ii) "Children under 12 years: Do not take this product for more than 5 days. If symptoms persist, or new ones occur, consult your physician".

(2) For products containing any antipyretic ingredient identified in § 343.12: "If fever persists for more than 3 days (72 hours), or recurs, consult your physician".

(3) For products containing any analgesic or any antipyretic ingredient identified in §§ 343.10 and 343.12 other than acetaminophen identified in §§ 343.10(b) and 343.12(c):

(i) "Take this product for the treatment of arthritis only under the advice and supervision of a physician".

(ii) "Stop taking this product if ringing in the ears or other symptoms occur".

(iii) For products intended for oral administration as a solid dosage form, e.g., tablets: (*a*) "Adults: Drink a full glass of water with each dose".

(*b*) "Children under 12 years: Drink water with each dose".

(iv) *"Caution:* Do not take this product if you have stomach distress, ulcers or bleeding problems except under the advice and supervision of a physician".

(v) *"Caution:* Do not take this product if you are presently taking a prescription drug for anticoagulation (thinning the blood), diabetes, gout or arthritis except under the advice and supervision of a physician".

(4) For products containing any analgesic or any antipyretic ingredient identified in § 343.10 (a) and (c) or § 343.12 (a) and (c) or § 343.20 if applicable:

(i) "This product contains aspirin. Do not take this product if you are allergic to aspirin or if you have asthma except under the advice and supervision of a physician".

(ii) "Do not take this product during the last 3 months of pregnancy except under the advice and supervision of a physician".

(iii) For oral product formulations to be chewed before swallowing: "Do not take this product for at least 7 days after tonsillectomy or oral surgery except under the advice and supervision of a physician".

(5) For products containing acetaminophen identified in § 343.10(b), § 343.12 (b) or § 343.20 if applicable:

(i) "Do not exceed recommended dosage because severe liver damage may occur".

(ii) "Do not take this product for the treatment of arthritis except under the advice and supervision of a physician".

(6) For products containing any analgesic or any antipyretic ingredient identified in § 343.10 (d), (e), (f), § 343.12 (d), (e), (f), or § 343.20 if applicable: "Do not take this product if you are allergic to salicylates except under the advice and supervision of a physician".

(7) For products containing magnesium salicylate identified in § 343.10 (e), § 343.12(e) or § 343.20 if applicable in an amount more than 50 mEq of magnesium in the recommended daily dosage: "Do not take this product if you have kidney disease except under the advice and supervision of a physician".

(8) For products containing sodium identified in § 343.10(f), § 343.12(f) or § 343.20 if applicable:

(i) For products containing 0.2 mEq (5 mg) or higher of sodium per dosage unit: The labeling of the product contains the sodium content per dosage unit (e.g., tablet, teaspoonful) if it is 0.2 mEq (5 mg) or higher.

(ii) For products containing more than 5 mEq (125 mg) sodium in the maximum recommended daily dosage: "Do not take this product if you are on a sodium restricted diet except under the advice and supervision of a physician".

(d) *Statement on dosage unit.* (1) For products containing the standard aspirin dosage unit identified in § 343.10(a)(1) or § 343.12(a)(1) shall be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) aspirin per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(2) For products containing aspirin in an amount different than the standard aspirin dosage unit identified in § 343.10 (a) (3), (4), (5), (6) or § 343.12(a) (3), (4), (5), (6) shall be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg (X gr) aspirin per dosage unit compared to the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount "X" of aspirin for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(3) For products containing the standard acetaminophen dosage unit identified in § 343.10(b)(1) or § 343.12(b)(1) shall be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(4) For products containing 500 mg (7.69 gr) acetaminophen identified in § 343.10(b)(3) or § 343.12(b)(3) shall be clearly labeled on the principal display panel: "Contains nonstandard strength of 500 mg (7.69 gr) acetaminophen per dosage unit compared to the established standard of 325 mg (5 gr) acetaminophen per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(5) For products containing the standard sodium salicylate dosage unit identified in § 343.10(f)(1) or § 343.12 (f)(1) shall be clearly labeled on the principal display panel: "Contains the standard strength of 325 mg sodium salicylate per dosage unit". The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(6) For products containing sodium salicylate in an amount different than the standard sodium salicylate dosage unit identified in § 343.10(f) (2), (3), (4), (5) or § 343.12(f) (2), (3), (4), (5) shall be clearly labeled on the principal display panel: "Contains nonstandard strength of X mg sodium salicylate per dosage unit compared to the established standard of 325 mg sodium salicylate per dosage unit". The actual amount "X" of sodium salicylate for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(e) *Statement on analgesic equivalence value.* (1) For products containing calcium carbaspirin identified in § 343.10 (c) or § 343.12(c) shall be clearly labeled on the principal display panel: "Equivalent to X mg (X gr) per dosage unit of the established standard of 325 mg (5 gr) aspirin per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(2) For products containing choline salicylate identified in § 343.10(d) or § 343.12(d) shall be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

(3) For products containing magnesium salicylate identified in § 343.10(e) or § 343.12(e) shall be clearly labeled on the principal display panel: "Equivalent to X mg per dosage unit of the established standard of 325 mg sodium salicylate per dosage unit". The actual amount of "X" of equivalent analgesic effectiveness for the specific product shall be used. The term "dosage unit" may be replaced by the applicable dosage form such as tablet or capsule.

§ 343.80 Professional labeling.

The labeling of a product provided to health professionals (but not to the general public) containing active ingredients identified in § 343.14 may contain any of the following indications: "For rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis (degenerative joint disease), ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and fibrositis."

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before October 6, 1977. Such comments should be addressed to the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before November 7, 1977. Received comments may be seen in the above office between the hours of 9 a. m. and 4 p. m. Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A-107.

Dated: June 7, 1977.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

[FR Doc.77-19108 Filed 7-7-77;8:45 am]

federal register

FRIDAY, JULY 8, 1977

PART VIII



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

■

MEDICARE

Limitations on Provider Costs

Effective July 1, 1977

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Health Care Financing Administration

SCHEDULE OF LIMITS ON HOSPITAL INPATIENT GENERAL ROUTINE SERVICE COSTS UNDER THE HEALTH INSURANCE PROGRAM

Cost-Reporting Periods Beginning on or After July 1, 1977, and Before October 1, 1977

A revised Schedule of Limits on Hospital Inpatient General Routine Service Costs in the Medicare program, applicable for cost reporting periods beginning on or after July 1, 1977, and before October 1, 1977, is set forth by the Administrator, Health Care Financing Administration, with the approval of the Secretary of Health, Education, and Welfare. Section 1861(v)(1) of the Social Security Act permits the Secretary to set prospective limits on costs to be recognized as reasonable based on estimates of the cost necessary in the efficient delivery of needed health services. The revised Schedule of Limits replaces the Schedule currently in effect which was published in the FEDERAL REGISTER (41 FR 26992) on June 30, 1976. The schedule applies to the total of the cost of hospital inpatient general routine service costs. These limits do not apply to the cost of special care units or ancillary services.

The Secretary of Health, Education, and Welfare is strongly committed to a national policy of containing the rapidly escalating health care costs. Therefore, the Secretary hereby serves notice of his intention to publish in the near future for comment a proposed new schedule of limits which, when published in final form, will become effective for cost reporting periods beginnnig on or after October 1, 1977. The Secretary also serves notice that either this or the subsequent schedule of limits may be required to be revised to conform with any Federal cost containment legislation enacted subsequent to the effective date of this schedule.

The initial classification system, which is described in the FEDERAL REGISTER (39 FR 20168) published June 6, 1974, was developed to provide for comparison of hospitals of similar size and in similar economic environments. Several refinements of the initial classification system were made effective July 1, 1975, and are described in the FEDERAL REGISTER (40 FR 23622) published May 30, 1975.

An additional refinement was made in the revised schedule of limits effective July 1, 1976. The refinement was the result of changes in the size of units of economic environment, and is described in the FEDERAL REGISTER (41 FR 26992) published June 30, 1976.

A refinement is made in the revised schedule of limits effective July 1, 1977. This limited refinement arose from the definition of metropolitan environments in the New England area. Under the Office of Management and Budget (OMB) definition, which has been used to distinguish between metropolitan and nonmetropolitan areas, Standard Metropolitan Statistical Areas (SMSA's) and Standard Consolidated Statistical Areas (SCSA's) in New England are based on cities and towns rather than on counties, as is the case in the rest of the United States. Because towns and cities are used to delineate SMSA's and SCSA's in New England, a county may be part of more than one SMSA or only a part of a county may be in an SMSA. However, income data supplied by the Department of Commerce, Bureau of Economic Analysis (BEA), which are used to group various areas according to economic environment, are available only on a county basis. In order to use the available data, BEA has slightly changed SMSA definitions in New England so that the SMSA's follow county lines.

Therefore, under the classification system presently in force, a hospital located in the part of the county not included by OMB in the SMSA/SCSA would be subject to a nonmetropolitan limit even though the per capita income of the hospital's location had been used for SMSA/SCSA classification grouping purposes. This situation is limited to New England and is inconsistent with the classification grouping for the rest of the United States where the OMB and BEA definitions of SMSA's consistently follow county lines.

In order to rectify this inconsistency, a change is made in the description of metropolitan environment used in the classification system. The change would alter the requirements for metropolitan status and would deem an entire county to be within an SMSA/SCSA if any part of such county was included by OMB in the SMSA/SCSA. Where a county contains the major city of an SMSA and is considered by OMB to be part of two or more SMSA's, the entire county would be deemed to be part of the SMSA whose major city it encompasses. Where a county is considered by OMB to be part of two or more SMSA's and does not contain the major city of any SMSA, the county would be included in the SMSA having the highest per capita income. An SMSA's major city is defined as the city from which the SMSA takes its name. Where the application of this provision results in a provider being placed in a group with a limit lower than the limit to which it would have been subject without the change, the higher limit may be applied in the cost reporting period to which this schedule applies.

An additional refinement is made in the revised schedule of limits effective July 1, 1977, for nonmetropolitan areas. In nonmetropolitan areas, which are frequently single industry areas, per capita income levels are extremely sensitive to changes in economic conditions from one year to the next. This is especially true where the primary source of income is from agriculture. In these cases, hospital costs usually reflect the trend of the area's economy rather than year to year fluctuations. In order to provide more equitable treatment to nonmetropolitan areas, a change has been made that would base the classification of State nonmetropolitan areas on a 5-year per capita average income instead of a one year base period. In these areas the longer base would be more reflective of the economic environment than a single year's income.

The same change was considered for the metropolitan (SMSA/SCSA) areas. However, these areas do not exhibit the same volatility of per capita income from one year to the next as do the non-SMSA areas. This may be attributed to diversity in economic activity in the SMSA areas plus the additional benefits, such as supplemental unemployment compensation, which are available to the mostly unionized workers in these areas. Therefore, no change is being made in the classification system for SMSA/SCSA areas.

The revised Schedule of Limits retains the provision to protect metropolitan area providers, for the period in which this schedule is in effect from the effects of lower limits that might result from circumstances that result in a lower per capita income for the provider's area. Thus, if a metropolitan area's per capita income in a year, or a change in SMSA/SCSA designation during the year, places the area in a group lower than in the previous year, the limit to be applied for that year will be the higher of the current period group or the immediately preceding year group. This provision will lessen the effect of unusual short-term fluctuations in area per capita income on reimbursement to individual providers.

For the period in which this schedule is in effect the same provision will be applied to nonmetropolitan providers which have been placed in a lower group as a result of the new classification methodology. SMSA and non-SMSA areas that are affected by this provision are indicated in the list of groups by an asterisk preceding the area name.

Example: Hospital A, Bed Size: 150. Per capita income in the provider's SMSA during the period on which the classification is based was reduced because of the effects of a natural disaster. Provider A had been classified in Group II effective July 1, 1976, and is now classified in Group III beginning July 1, 1977. The limit to be applied to Provider A beginning July 1, 1977, is the higher of the Group II limit or the Group III limit.

All SMSA's and SCSA's have been divided into the following five groups based on per capita income. Counties, rather than SMSA/SCSA areas, are listed for New England States.

SMSA/SCSA Group I

Alaska

Anchorage

California

Los Angeles-Long Beach-Anaheim (SCSA)

Los Angeles-Long Beach
Anaheim-Santa Ana-Garden Grove
Oxnard-Simi Valley-Ventura
Riverside-San Bernardino-Ontario

Salinas-Seaside-Monterey

San Francisco-Oakland-San Jose (SCSA)

San Francisco-Oakland
San Jose
Vallejo-Fairfield-Napa

Colorado

Denver-Boulder

Connecticut

Fairfield County
Hartford County
Litchfield County
Middlesex County
Tolland County

District of Columbia

Washington, DC, DC-MD-VA

Florida

Miami-Fort Lauderdale (SCSA)

Fort Lauderdale-Hollywood
Miami

Sarasota
West Palm Beach-Boca Raton

Illinois

Chicago-Gary, IL-IN (SCSA)

Chicago, IL
Gary-Hammond-East Chicago, IN

Peoria
Springfield

Iowa

Davenport-Rock Island-Moline, IA-IL

Michigan

Detroit-Ann Arbor (SCSA)

Detroit
Ann Arbor

Minnesota

Minneapolis-St. Paul, MN-WI

Nevada

Reno

New Jersey

SEE NEW YORK SCSA

New York

New York-Newark-Jersey City, NY-NJ-CT (SCSA)

New York, NY-NJ
Newark, NJ
Jersey City, NJ
Patterson-Clifton-Passaic, NJ
Nassau-Suffolk, NY
Long Branch-Asbury Park, NJ
New Brunswick-Perth Amboy-Sayerville, NJ

Rochester

Ohio

Cleveland-Akron-Lorain, (SCSA)

Cleveland
Akron
Lorain-Elyria

Virginia

Richmond

Washington

Richland-Kennewick

Wisconsin

Milwaukee-Racine (SCSA)

Milwaukee
Racine

Kenosha

SMSA/SCSA Group II

Arizona

Phoenix

California

Bakersfield
Santa Barbara-Santa Maria-Lompoc
San Diego
Stockton

Connecticut

New Haven County
New London County

Delaware

SEE PHILADELPHIA SCSA

Georgia

Atlanta

Hawaii

*Honolulu

Idaho

Boise City

Illinois

Bloomington-Normal
Decatur
Kankakee
*Rockford

Indiana

Fort Wayne
Indianapolis

Iowa

Cedar Rapids
Des Moines
Waterloo-Cedar Falls

Kansas

Topeka
Wichita

Kentucky

Louisville, KY-IN

Maryland

Baltimore

Massachusetts

Berkshire County
*Essex County
*Middlesex County
*Norfolk County
*Plymouth County
*Suffolk County
Worcester County

Michigan

*Flint
Grand Rapids
Jackson
Kalamazoo-Portage
Saginaw

Missouri

Kansas City, MO-KS
St. Louis, MO-IL

Nebraska

Lincoln

New Hampshire

Rockingham County

New Jersey

SEE PHILADELPHIA SCSA

Nevada

*Las Vegas

New York

*Albany-Schenectady-Troy
Buffalo
Poughkeepsie

North Carolina

Greensboro-Winston-Salem-High Point

North Dakota

*Fargo-Moorehead, ND-MN

Ohio

Dayton
Lima
Toledo, OH-MI
Youngstown-Warren

Oregon

Portland, OR-WA

Pennsylvania

Philadelphia-Wilmington-Trenton, PA-DE-MD-NJ (SCSA)

Philadelphia, PA-NJ
Trenton, NJ
Wilmington, DE-NJ-MD

Allentown-Bethlehem-Easton, PA-NJ
Harrisburg
Lancaster
Pittsburgh
Reading

Rhode Island

Washington County

Texas

Houston-Galveston (SCSA)

Houston
Galveston-Texas City

Dallas-Fort Worth
Midland

Washington

Seattle-Tacoma, (SCSA)

Seattle-Everett
Tacoma

Wisconsin

Madison

SMSA/SCSA Group III

Alabama

Birmingham

12

Arizona

Tucson

Arkansas

Little Rock-North Little Rock

California

Fresno
Modesto
Sacramento
Santa Cruz
Santa Rosa

Colorado

Greeley

Florida

Jacksonville
Orlando
Tampa-St. Petersburg

Illinois

Champaign-Urbana-Rantoul

Indiana

*Anderson
Evansville, IN-KY
*South Bend

Iowa

Dubuque
Sioux City, IA-NE

Kentucky

Lexington-Fayette

Louisiana

New Orleans

Maine

Cumberland County
York County

13

Massachusetts

Hampden County
Hampshire County

Michigan

*Battle Creek
Bay City
*Lansing-East Lansing

Minnesota

*Rochester

Mississippi

Jackson

Montana

Billings

Nebraska

Omaha, NE-IA

New Hampshire

Hillsborough County
Merrimack County

New Jersey

Atlantic City
Vineland-Millville-Bridgeton

New York

Binghamton, NY-PA
Elmira
Syracuse

North Carolina

Charlotte-Gastonia
Raleigh-Durham

Ohio

Cincinnati-Hamilton, OH-KY-IN (SCSA)

Cincinnati, OH-KY-IN
Hamilton-Middletown, OH

Canton
Columbus
Mansfield
Springfield

Steubenville-Weirton, OH-WV

Oklahoma

Tulsa

Oregon

Salem

Pennsylvania

Erie
York

Rhode Island

Bristol County
Kent County
Newport County
Providence County

South Dakota

Sioux Falls

Tennessee

Memphis, TN-AR-MS
Nashville-Davidson

Texas

Amarillo
Beaumont-Port Arthur-Orange
Wichita Falls

Virginia

Newport News-Hampton
Norfolk-Virginia Beach-Portsmouth, VA-NC
Petersburg-Colonial Heights-Hopewell
Roanoke

Washington

Spokane
Yakima

West Virginia

Charleston

Wisconsin

Appleton-Oshkosh

SMSA/SCSA Group IV

Alabama

Montgomery

Colorado

Colorado Springs
Fort Collins
Pueblo

Florida

Daytona Beach
Fort Meyers
Gainesville
Lakeland-Winter Haven
Melbourne-Titusville-Cocoa
Tallahassee

Georgia

Augusta, GA-SC
Columbus, GA-ALA
Macon
Savannah

Indiana

*Lafayette-West Lafayette
Muncie

Kentucky

Owensboro

Louisiana

Baton Rouge
Shreveport

Massachusetts

Bristol County

Michigan

Muskegon-Norton Shores-Muskegon Heights

Minnesota

Duluth-Superior, MN-WI

Missouri

*St. Joseph

Montana

*Great Falls

New Mexico

Albuquerque

New York

Utica-Rome

North Carolina

Ashville
Burlington

Oklahoma

Oklahoma City

Oregon

Eugene-Springfield

Pennsylvania

Johnstown
Wilkes Barre-Scranton-Harleton (Northeast PA)
Williamsport

South Carolina

Columbia
Greenville-Spartanburg

Tennessee

Chattanooga, TN-GA
Clarksville-Hopkinsville, TN-KY
Knoxville

Texas

Abilene
Austin
Killeen -Temple
Longview
Lubbock
Odessa
San Angelo
San Antonio
Sherman-Denison
Tyler
Waco

Utah

Salt Lake City-Ogden

Virginia

Lynchburg

West Virginia

Parkersburg-Marietta, WV-OH
Wheeling, WV-OH

Wisconsin

Green Bay
La Crosse

SMSA/SCSA Group V

Alabama

Anniston
Florence
Gadsden
Huntsville
Mobile
Tuscaloosa

Arkansas

Fayetteville-Springdale
Fort Smith, AR-OK
Pine Bluff

Florida

Pensacola

Georgia

Albany

Indiana

Bloomington
*Terre Haute

Louisiana

Alexandria
Lafayette
Lake Charles
Monroe

Maine

Androscoggin County

Minnesota

St. Cloud

Missouri

Columbia
*Springfield

Mississippi

Biloxi-Gulfport
Pascagoula-Moss Point

North Carolina

Fayetteville
Wilmington

Oklahoma

Lawton

Pennsylvania

Altoona

Puerto Rico

Caguas
Mayaguez
Ponce
San Juan

South Carolina

Charleston-North Charleston

Tennessee

Johnson City-Kingsport-Bristol, TN-VA

Texas

Brownsville-Harlingen-San Benito
Bryan-College Station
Corpus Christi
El Paso
Laredo
McAllen-Pharr-Edinburg
Texarkana, TX-AR

Utah

Provo-Orem

West Virginia

Huntington-Ashland, WV-KY-OH

Wisconsin

Eau Claire

*Hospitals in areas (SCSA or SMSA) identified by an asterisk will receive the higher of the limit published herein for the group in which the hospital is actually classified or the limit published herein for the group in which the hospital was classified in the immediately preceding cost reporting period.

Non-SMSA areas will be classified according to the per capita income of all non-SMSA counties within a State. The following are the five income groupings, (with States classified according to a 5-year per capita income average) to be used for hospitals located in non-Standard Metropolitan Statistical Areas in those States.

Non-SMSA

Group I

Alaska	Massachusetts	New Jersey
Iowa	Nebraska	Washington
Kansas	Nevada	Wyoming

Group II

California	Hawaii	Maryland
Connecticut	*Illinois	*North Dakota
Delaware	Indiana	

Group III

Colorado	*Minnesota	Oregon
Florida	Montana	Pennsylvania
Idaho	New Hampshire	*South Dakota
Michigan	New York	Vermont
	Ohio	Wisconsin

Group IV

Arizona	*Missouri	*Oklahoma
Maine	North Carolina	Texas

Group V

Alabama	Mississippi	Utah
*Arkansas	New Mexico	*Virginia
Georgia	Puerto Rico	Virgin Islands
Kentucky	South Carolina	West Virginia
Louisiana	Tennessee	

*Hospitals in States identified by an asterisk will receive the higher of the limit published herein for the group in which the hospital is actually classified or the limit published herein for the group in which the hospital was classified in the immediately preceding cost reporting period.

With respect to the Standard Consolidated Statistital Area/Standard Metropolitan Statistical Area groupings, the groupings were developed by combining those SCSA/SMSA's which reflect a similar economic environment as expressed by per capita income data. The SCSA/SMSA's were arrayed in order of the size of their per capita income and groupings were established. The same procedure was followed for grouping the non-SCSA/SMSA areas to arrive at State groups.

The following bed-size categories are used to classify hospitals:

Standard Metropolitan Statistical Areas

Groups I and II	Groups III, IV, and V
Less than 100	Less than 100
100-404	100-404
405-684	405 and above
685 and above	

Non-Standard Metropolitan Statistical Areas

Less than 100
100-169
170 and above

The limits were developed in the following manner:

1. Inpatient general routine service cost data for each participating hospital were obtained from the fiscal intermediaries.

2. The data for hospitals in each class were arrayed in descending order of inpatient general routine service cost.

3. The 80th percentile and the median were computed for each class.

4. For each class, an amount equal to 10 percent of the median was added to the 80th percentile amount.

5. This sum was adjusted to reflect the 14.0 percent annual rate of estimated cost increases in per diem routine service costs following the date of data collection.

6. The amounts calculated in step 5 are rounded to the next highest dollar which establishes the limit for each class, subject to adjustment for hospitals reporting on other than a reporting period beginning July 1, 1977.

Under the authority of section 1861(v) of the Social Security Act, the following cost limitations apply to the total of the hospital inpatient general routine service costs (excluding costs incurred for special care units and ancillary services), adjusted upward as provided for below. The limits are applicable to cost reporting periods beginning on or after July 1, 1977, and will remain in effect until the effective date of a revised schedule.

The limits are applicable to any hospital with a cost reporting period beginning on or after July 1, 1977. Where a hospital

has a cost reporting period beginning after July 1, 1977, the published limit will be adjusted upward by a factor of 1.17 percent for each elapsed month between July 1, 1977, and the month in which the hospital's reporting period begins. The result of this calculation is not rounded and is to be given in dollars and cents.

SCHEDULE OF LIMITS ON HOSPITAL INPATIENT GENERAL ROUTINE SERVICE COSTS FOR HOSPITALS WITH COST-REPORTING PERIODS BEGINNING ON OR AFTER JULY 1, 1977 (A)

HOSPITALS LOCATED WITHIN SMSA'S (METROPOLITAN) BED SIZE

SMSA group	Less than 100	100 to 404	405 to 684	685 and above
I[1]	$ 139	$ 144	$ 160	$ 211
II	121	123	126	151
III	109	110	109	109
IV	100	105	108	108
V	89	87	109	109

[1]Limits apply to all SMSA's except Anchorage, Alaska, and Honolulu, Hawaii, where cost-of-living adjustment (25 percent Anchorage, Alaska; 17.5 percent Honolulu, Hawaii) was made. The limits for these areas are as follows:

	Less than 100	100 to 404	405 to 684	685 and above
Anchorage	$ 174	$ 180	$ 200	$ 264
Honolulu	164	170	188	248

HOSPITALS LOCATED OUTSIDE SMSA'S (NONMETROPOLITAN) BED SIZE

State group	Less than 100	100 to 169	170 and above
I[2]	$ 103	$ 114	$ 112
II[3]	119	114	107
III	100	105	103
IV	92	89	91
V	84	83	84

[2]Limits apply to all Group I States except Alaska where cost of living adjustment (25%) was made - limits for Alaska are:

Less than 100	100 to 169	170 and above
$ 129	$ 143	$ 140

[3]Applies to all Group II States except Hawaii where cost of living adjustment (12.5%) was made - limits for Hawaii are:

Less than 100	100 to 169	170 and above
$ 134	$ 129	$ 121

(A) The schedule of limits and adjustment factor are only for a 12-month cost reporting period. For providers with other than 12-month cost reporting periods, intermediaries must contact the Health Care Financing Administration for adjustment factor.

The Department finds that there is good cause for dispensing with a notice and comment period for this Notice of Limits because of the need to inform hospitals whose cost reporting year begin July 1 of the limits which will be applicable to them for this year. Continued uncertainty on the part of such hospitals as to the limits to which they will be subject for this cost reporting year would not serve the public interest.

(Secs. 1102, 1861(v)(1), 1866(a), and 1871, Social Security Act; 49 Stat. 647, as amended; 79 Stat. 313, as amended; 79 Stat. 327, as amended; 79 Stat. 331 (42 U.S.C. 1302, 1395x (v), 1395cc(a), and 1395hh).)

(Catalog of Federal Domestic Assistance Program No. 13.800, Health Insurance for the Aged—Hospital Insurance.)

NOTE: The Health Care Financing Administration has determined that this document does not contain a major proposal requiring preparation of an Economic Impact Statement under Executive Order 11821 and OMB Circular A-107.

Dated: June 30, 1977.

DAVID N. WEINMAN,
Acting Administrator, Health Care Financing Administration.

Approved: June 30, 1977.

JOSEPH A. CALIFANO, JR.,
Secretary of Health, Education, and Welfare.

[FR Doc.77-19360 Filed 7-1-77;5:01 pm]