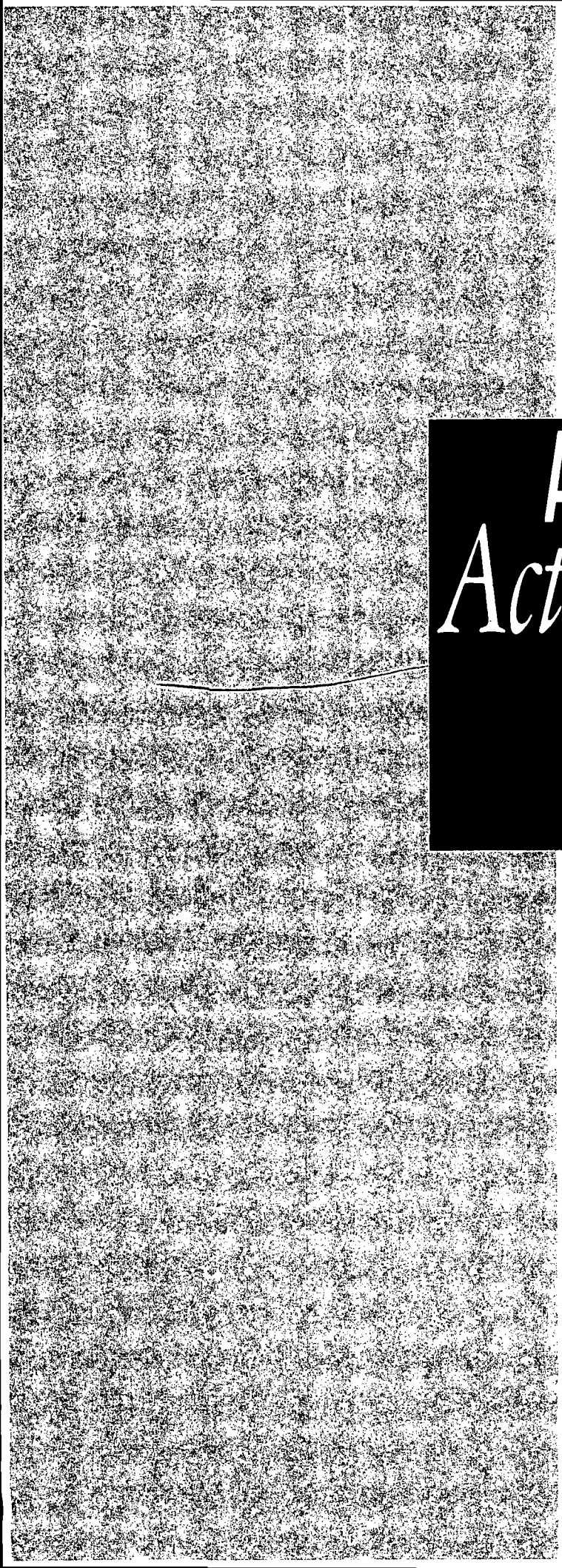

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THE PATIENTS' COALITION

An Independent Coalition of Patients With Serious And Life-Threatening Diseases Working Together For Responsible FDA Reform

PRINCIPLES OF FDA REFORM
The Patient's Perspective

It is the duty of the Federal Government to regulate the safety and efficacy of drugs marketed in the United States. It exercises this duty under the authority of the Food, Drug and Cosmetic Act, as amended, through the Food and Drug Administration whose mission it is to insure that drugs, biological products and medical devices are safe and effective for the treatment of specific health conditions and that evidence relating to that safety and efficacy is accurately represented to the American people. Basing their decisions regarding these products upon an intensive analysis of scientific data, the FDA strives to be a positive force in making safe and effective products available to the citizens of this country, focusing special attention on drugs to benefit those suffering from serious and life-threatening diseases. In addition to ensuring the safety of the American people by the careful oversight of new products, the FDA protects our health by removing unsafe products and drugs from the market.

In fulfilling its role, the FDA promulgates regulations to improve public health, protecting Americans from unsafe, ineffective or impure drugs. The agency also helps to define cost-effective treatment strategies by establishing minimum efficacy standards through the drug regulation and approval process. It is important to remember that most drugs under FDA review are not breakthrough drugs that will have a major impact on public health. These drugs are given "standard" reviews that take more time than the "accelerated" reviews given to drugs for serious and life-threatening diseases. It is the length of time for reviews of the former -- the standard review -- that is the pharmaceutical industry's primary concern. These drugs include anti-hypertensive, anti-inflammatory and anti-depressant drugs.

The FDA should be applauded for its continued efforts to protect the American consumer through oversight of private industry's drug development, the assessment of health risks to Americans, and the acceleration of the drug approval process, with special emphasis on those drugs that may benefit those who suffer from serious and life-threatening illnesses. As stated in the FDA's *Vision For The Year 2000*, the agency will continue to uphold safety and efficacy standards related to products on the market. In addition, FDA's mandate must encourage innovation and progress in medical research. In order to continue to perform its duties and attain these goals, however, the FDA must be given sufficient resources to handle its expanding responsibilities including monitoring the nation's food supply, expediting new drug approval, monitoring existing drugs and manufacturing facilities, and insuring the safety of medical devices, x-ray and mammography facilities, laboratories, food imports, and cosmetics. Most importantly, in regulating many of the core elements of consumers' lives, the FDA must operate at very high ethical standards, free from conflict of interest.

Finally, Industry must improve its performance by designing and implementing high quality research and submitting timely applications with supporting data that will facilitate efficient review and approval. The undersigned organizations ask that Congress join them in recognizing the central importance of the patient's voice in any discussion of potential reform of the FDA . The following principles outline some crucial concerns for patients in these discussions.

Principle 1: The FDA must review drugs for serious and life-threatening diseases differently than drugs for routine and treatable disease.

Drugs for serious and life-threatening diseases require different risk-benefit calculations. They should be reviewed more quickly and considered for marketing at the earliest possible time. Some people with cancer, Alzheimer's Disease, Parkinson's disease, schizophrenia or AIDS, for example, will accept the risks a drug might pose for the benefits it might provide. The FDA should take all steps necessary to ensure that effective new drugs are made available to patients with these conditions as soon in the development process as is practical.

Principle 2: In order to assure the best possible care for patients with serious or life-threatening conditions, pre-approval access to experimental drugs that show reasonable safety and promise of efficacy should be encouraged.

The FDA must balance pre-market access with the need for sound scientific research, which benefits all present and future patients. Under current law, the FDA has pioneered parallel track and expanded access programs, which have helped thousands of people with serious diseases obtain experimental drugs. While the FDA should encourage manufacturers to provide early access to promising therapies, the agency cannot compel the industry to do so. Industry initiative is required for the success of such programs.

Principle 3: Marketing approval is one point on the continuum of drug development. Especially in the context of drugs for serious or life-threatening diseases, which may receive approval based on preliminary efficacy data, post-marketing research is critical.

The data required by the FDA for marketing approval is the foundation upon which present and future doctors and patients decide how, when, and whether to use any drug. The FDA must develop a post-marketing follow-up system bolstered by clearly defined enforcement powers.

Principle 4: While validation and third-party reimbursement of non-FDA approved ("off label") uses of drugs are of critical importance to people with serious or life-threatening diseases, the promotion or validation of such uses must not entail a reduction in efficacy standards.

FDA-required safety and efficacy data that form the basis for initial approval cannot provide a full picture of a drug's usefulness. Additional uses for drugs, discovered through future research, may be appropriate for some patients as determined by medical experts and as prescribed in accepted medical compendia and journals. However, such uses are frequently not reimbursed by third-party payers based on their lack of FDA approval. While the Department of Health and Human Services should accept the responsibility to establish medical practice standards and third-party reimbursement guidelines, it would be a mistake to focus such mechanisms solely in the context of FDA reform. While the FDA should encourage sponsors to submit supplemental approval applications, research to validate "off-label" uses remains the responsibility of industry, government and academia.

Principle 5: The FDA must retain regulatory flexibility.

FDA regulation must remain flexible and must not be obstructive if the agency is to efficiently pursue the goals of ensuring the safety and efficacy of those products under its jurisdiction. Legislative changes to the FDA's authority, therefore, must not restrict the agency's ability to evaluate each drug's unique safety and efficacy profile.

Principle 6: The FDA should ensure that applications for new drugs include data on all populations likely to use such drugs.

The FDA should require data on all relevant populations; currently, drugs are often approved with little or no information on their use for women, racial minorities, older Americans or children.

Principle 7: The FDA must be responsive to the concerns of patient groups, industry, physicians and the American people.

The FDA must develop a consistent approach to drug regulation across all its centers and divisions. To remain responsive, the FDA should solicit non-scientist patient representatives to serve on advisory committees. The unique dynamics of intellectual property rights for drugs, which constitute a critical component of the health care system, must be recognized. In the context of reviewing applications for marketing approvals, the FDA must be allowed to balance its responsibility to protect industry trade secrets against the need for public disclosure.

Principle 8: There must be close communication between the FDA and industry during all stages of clinical drug development.

Drug development and regulation proceeds best and most efficiently when industry and the FDA work together from the early stages of research. Communication should be enhanced between the agency, companies, physicians and the public.

Principle 9: Robust pharmaceutical research is critical to the development of drugs to treat serious or life-threatening diseases. Where appropriate, incentives to encourage industry-, academic- or government-sponsored research should be considered.

Incentives might incorporate a variety of mechanisms, including market exclusivity or regulatory relief for breakthrough drugs.

AIDS Action Council
AIDS Policy Center for Children, Youth and Families
Alpha 1 Antitrypsin Deficiency National Organization
Alzheimer's Association
American Association of University Affiliated Programs
American Cancer Society
American Foundation for AIDS Research
American Laryngeal Papilloma Foundation
American Public Health Association
American Society of Adults with Pseudo Obstruction, Inc.
American Social Health Association
Aplastic Anemia Foundation
The ARC
Arthritis Foundation
Association of Schools of Public Health
Center For Research in Sleep Disorders
Children's Leukemia Foundation of Michigan
Citizen Action
Cooley's Anemia Foundation
Critical Path AIDS Project
Cushing Support & Research Foundation
Cystinosis Foundation, Inc.
Epilepsy Foundation of America
Foundation for Icthiosis and Related Skin Types
Gay Mens Health Crisis
Guillain Barre Syndrome Foundation International
Hemochromatosis Foundation, Inc.
Histiocytosis Association of America
Human Rights Campaign
International Joseph Diseases Foundation, Inc.
International Patient Advocacy Association
International Tremor Foundation
Late Onset Tay-Sachs Foundation
Mobilization Against AIDS
MPS Society
Narcolepsy Network
National AIDS Fund
National Association of Developmental Disabilities Councils
National Association of People With AIDS
National Association of Protection and Advocacy Systems
National Catholic AIDS Network
National Council on the Aging, Inc.
National Episcopal AIDS Coalition
National Foundation for Ectodermal Dysplasias
National Hemophilia Foundation
National Latino/Latina Lesbian and Gay Organization
National Mental Health Association
National Minority AIDS Council
National Osteoporosis Foundation
National Organization for Rare Disorders
National Alliance for the Mentally Ill
National Puerto Rican Coalition
National Tuberous Sclerosis Association
National Sjogren's Syndrome Association
National Women's Health Network
Osteogenesis Imperfecta Foundation
Pediatric AIDS Foundation
Search For A Cure
Sickle Cell Disease Association
Society for the Advancement of Women's Health Research
Society for Progressive Supranuclear Palsy
Sturge-Weber Foundation
The TMJ Association, Ltd.
Tourette Syndrome Association, Inc.
Treatment Action Group
United Leukodystrophy Foundation
United Patients' Association for Pulmonary Hypertension
United Parkinson Foundation
Wilson's Disease Association

THE PATIENTS' COALITION

An Independent Coalition of Patients With Serious And Life-Threatening Diseases Working Together For Responsible FDA Reform

June 7, 1996

The Honorable
United States Senate
Washington, DC 20510

Dear Senator:

We, the undersigned patient, health and consumer organizations believe that **The FDA Performance and Accountability Act (S. 1477)** poses a serious threat to the health of all Americans and we urge you to oppose this bill.

This bill, despite Senator Kassebaum's sincere efforts to bring positive reforms to the FDA, will not improve either the effectiveness or the efficiency of the FDA. Rather, the provisions in this bill would harm all Americans by undermining crucial public health protections and casting the regulation of drugs, medical devices and foods into dangerous and untested territory. The bill would lower safety and efficacy standards for new drugs. It would privatize some of FDA's central regulatory responsibilities, contracting out functions ranging from the review of clinical research data to inspections of manufacturing facilities. Under the system outlined in the bill, medical device manufacturers, for example, would select and pay the private companies that review and inspect their products, creating a system of regulation built upon inherent conflict-of-interest -- a system driven by financial incentives to approve new products rather than objective, public health standards. The bill also micromanages the agency's process -- including rigid timelines and easy appeals of any agency decision -- that will require significant resources, create additional layers of bureaucracy, and potentially prolong the time to approval for new products. S. 1477 is the wrong type of FDA reform.

We believe that the FDA does need to be responsive to the legitimate needs of both the regulated industry and the public on whose behalf regulation is performed. Patients need fast and efficient drug approvals. FDA must be well-managed, adequately funded, and free from conflicts-of-interest. Responsible FDA reform preserves crucial public health protections, ensuring drugs and medical devices sold in the United States are proven safe and effective through objective scientific research. Responsible reform increases FDA's flexibility so that technological and scientific advances can be quickly incorporated into our nation's drug, medical device, and food regulatory system.

S. 1477 is neither responsive nor responsible FDA reform. We urge you to stand with all American consumers and patients by opposing S. 1477.

Sincerely,

AIDS Action Council
AIDS National Interfaith Network
AIDS Policy Center
Alpha 1 National Association
American Association on Mental Retardation
American Foundation for AIDS Research
(continued)

American Public Health Association
Americans for Democratic Action
Aplastic Anemia Foundation, MD/DC/VA Chapter
Association of Nurses in AIDS Care
Bazelon Center for Mental Health Law
Center for Medical Consumers
Center for Women Policy Studies
Cities Advocating Emergency AIDS Relief
Citizen Action
Committee for Children
Consumers Union
Freeman-Sheldon Parent Support Group
Funders Concerned About AIDS
Grass Roots the Organic Way
Guillain-Barre Syndrome Foundation International
Hemochromatosis Foundation, Inc.
Human Rights Campaign
Institute for Agriculture and Trade Policy
International Joseph Diseases Foundation
Jewish Labor Committee
Mothers' Voices
Narcolepsy Network
National Association of People With AIDS
National Association of Protection and Advocacy Systems
National Association of Social Workers
National Coalition Against the Misuse of Pesticides
National Episcopal AIDS Coalition
National Hispanic Council on Aging
National Latino/Latina Lesbian and Gay Organization
National Minority AIDS Council
National Native American AIDS Prevention Center
National Organization for Rare Disorders
National Puerto Rican Coalition
National Therapeutic Recreation Society
National Women's Health Network
National Women's Law Center
National Task Force for AIDS Prevention
Neighbor to Neighbor
NETWORK: A National Catholic Social Justice Lobby
New York Coalition for Alternatives to Pesticides
Older Women's League
Public Citizen
Rachel Carson Council
Research Institute for Independent Living
Safe Alternatives for our Forest Environment (S.A.F.E.)
Service Employees International Union
Society for Progressive Supranuclear Palsy, Inc.
The Sturge-Weber Foundation
Treatment Action Group
United Church of Christ, Office for Church in Society
United Parkinson Foundation
Wilson's Disease Association

MAJOR PROBLEMS WITH S.1477 AS REPORTED FROM THE LABOR COMMITTEE

Despite constructive elements, S.1477 in its current form fails the basic test of good regulatory reform, because it will put the health of the American people at risk. Unfortunately, even though many improvements have been made to S.1477 since it was introduced late last year, provisions remain that would seriously undermine both FDA and the laws it enforces and expose American consumers to unsafe and ineffective drugs, devices, biologics, and food. If such provisions remain in the bill, FDA will not have the tools to prevent public health tragedies like DES (diethyl stilbestrol), the Dalkon Shield, the Shiley heart valve, the Cutter polio vaccine, and contaminated blood. Over the long run, these provisions of the bill could destroy FDA as an effective regulatory body.

Although our concerns are spelled out in depth below, major provisions of S.1477 that are unacceptable include:

• Prohibiting FDA from requiring prior review and approval of critical manufacturing changes -- changes that, for example, could turn a vaccine designed to prevent polio into one that causes it;

• Turning central regulatory decisions over to private industry, creating an inherent conflict of interest and draining FDA of the resources and expertise it needs to remain an effective guardian of public health;

• Establishing unrealistic timeframes for product review, but failing to provide adequate resources for FDA to achieve these goals and still carry out the thorough, careful review the public deserves;

• Creating new bureaucratic burdens that will make it more difficult for the agency to promptly review new products;

• Requiring FDA to give priority to products approved abroad, even if they are less important than products proposed for first-time approval in the United States. This not only will slow review of the highest priority products, but it will encourage U.S. companies to take their research abroad; and

• Weakening FDA's authority to require appropriate consumer labeling for drugs and foods, thus denying consumers the reliable information that they need to protect themselves against adverse drug reactions and to make nutritional choices based on accurate information.

S.1477 unacceptably weakens essential FDA oversight of drug and biologic manufacturing. Section 604 eliminates FDA's ability to require pre-approval of any manufacturing changes for drugs and biologics, including blood and vaccines, even if the change has a substantial potential to harm public health. Instead, section 604 would require certain kinds of validation or testing and reporting to FDA, depending on the kind of product involved. However, history teaches that manufacturing changes can make a product unsafe or less effective and that validation or testing against finished product specifications may not detect problems and protect the public. For example, changing the solvent used to kill viruses like HIV or hepatitis in blood products can result in products that transmit life-threatening diseases. A change in the filters or virus lines used to produce vaccines can turn a protective vaccine into a deadly one. A change in the filters used to produce the Cutter polio vaccine resulted in more than 200 cases of paralytic polio in 1955, before FDA required more rigorous standards. Even with the tight controls now in place, there have been 26 cases in just the last two years -- including cases involving vaccines -- where only FDA intervention prevented thousands of patients from being exposed to dangerous products.

Because of the strict requirements now in place, every American patient who has an operation or receives a transfusion has confidence that the blood they will receive is safe, uncontaminated by HIV, hepatitis, or other diseases. Likewise, every parent whose child is vaccinated assumes that the vaccine will prevent illness, not cause it. If Section 604 becomes law, this confidence may no longer be justified. Not only may Americans be injured, but so will our pharmaceutical and biotechnology industries, which benefit from the justified confidence that Americans now have in the quality of products like blood and vaccines.

S.1477 turns critical functions of FDA over to private industry and drains the agency of the resources and expertise necessary to protect the public in a number of ways. Section 709, which was described as a pilot to test third party review when offered in committee, actually allows device companies to have any medical device reviewed by third parties that they select and with whom they negotiate the price. The conflict of interest that occurs when a manufacturer that wants a product approved both chooses and pays the reviewer who will determine whether the product is safe and effective is obvious and unacceptable.

As written, section 709 requires FDA to accredit third parties to review every kind of device. Once third parties are accredited, manufacturers are free to choose product review by these third parties, rather than FDA, even for products that involve totally new technologies, that are the most complex, or that are critical to the public health, including pacemakers, breast implants, heart valves, and blood screening kits. Section 709 does purport to give FDA final say over the decisions of private reviewers, but the time-frames for FDA action are so short and the erosion of FDA's expertise as the result of turning over its responsibilities to third-party reviewers would be so extensive, that it is hard to see how FDA's review would be much more than a rubber stamp.

FDA is currently conducting a true pilot program to test the effectiveness of third party review on low risk devices with tight FDA oversight, clear provisions relating to conflicts of interest, and clear FDA authority for final approval. To mandate that FDA fully implement an unproven concept for all devices is unacceptable.

In addition to requiring third party review for all medical devices, the bill strips FDA of its functions and turns them over to private industry in other ways. Under section 404, if FDA fails to meet timeframes for review (established by the legislation) for 95% of the products within a particular product class, FDA is required to contract out review of all products in that class to private organizations in the following fiscal year, at the request of the product sponsor. Contracting out would be required even if doing so would increase review costs or even if quality could not be assured. In many product classes, failure to review just one drug or device within the statutory time frame could trigger mandatory contracting out. Over time, FDA would be drained of the resources it needs to continue as an effective regulatory body.

Section 403 requires FDA to contract out review of food additive petitions and premarket notifications for class I and class II devices. In addition, section 403 could be interpreted as creating a presumption in favor of contracting out aspects of review of all products.

The immediate effect of these provisions will be to turn the job of approving new products over to private businesses, even though there is no evidence that private review will provide the public with the same level of protection as FDA review and even though the case for private review is based on an outdated description of agency performance. Not only will these businesses lack the expertise that FDA has built up over decades of experience, but in many cases the conflict of interest could be such that it will be impossible for the public to have any confidence in their decisions.

The long-term effect of these provisions can only be fully understood in light of the fact that S.1477 creates new, unreasonable timeframes, not only for product reviews, but for numerous other agency actions, and imposes a series of new bureaucratic requirements on the agency. These additional requirements are established without providing any new resources for the agency. For example, the bill shortens the period of review for non-priority drugs and biologics that was negotiated by FDA, Congress, and the industry as part of the Prescription Drug User Fee Act (PDUFA) in 1992, to six months (from a year) and thus requires FDA to treat priority and non-priority, "me-too" products the same. Similarly, S.1477 cuts in half -- from 180 days to 90 days -- the time FDA has to review indirect food additives and new animal drugs, including those used in food-producing animals, even though the safety of these substances is critical to the millions of Americans who consume them on a daily basis.

Without additional resources, FDA will be unable to meet these targets. As it strives to come closer to these goals without enough funds or personnel it may be forced to perform less thorough reviews. Further, as noted above, if FDA does not meet the timeframes, FDA must, at the request of the applicant, pay a third party to review a product -- further bleeding the agency of the resources it needs to meet the deadlines. It is hard to see how this catch-22 benefits the American consumer.

By hamstringing the agency with a host of new bureaucratic requirements, S.1477 makes it even more unlikely that FDA will be able to conduct timely, thorough review of products. The bill imposes at least eighteen separate requirements to publish and implement new policies, regulations, or procedures. It establishes thirty-one new statutory deadlines, and elaborate statutory meeting requirements. While some of these requirements will contribute to greater collaboration, predictability, and efficiency, others will only tie the agency up and slow down more important work. Taken as a whole, these additional bureaucratic requirements will divert resources from essential activities to administrative work. To cite one particularly egregious example, the bill burdens scientific advisory committees with the responsibility of considering any appeal of a scientific issue raised by a company. Under Section 108, appeals can be made at any time -- even if the agency decision is not final and even if the company has not gone through the agency's own internal appeal procedures.

Currently, advisory committees are invaluable to FDA when it needs advice from the most distinguished outside experts on important decisions. Advisory committees only meet two to four times a year -- typically for two days. The distinguished physicians and scientists serving on committees are essentially donating time from very busy schedules. A review of the advisory committee system by the Institute of Medicine concluded that one of the major problems FDA faced was attracting the best people to serve and prioritizing the issues that the experts needed to consider, given the limited time they had available. The provisions of this bill make it likely that so many additional, unnecessary matters will come to advisory committees that FDA will be able neither to attract top experts to serve, nor to assure that they consider the most important and pressing questions.

Turning over important FDA functions to the private sector and bleeding the agency of resources threatens public health in other ways. At the same time as FDA is forced to comply with numerous new bureaucratic requirements, it will lose the independent, committed, expert public servants on whose work public safety depends. FDA will no longer have expertise (now developed through the review of product applications and conducting facility inspections) to be an effective post-approval guardian. Yet post-market surveillance has repeatedly protected Americans from harm. Among the problem drugs that FDA post-market surveillance efforts has identified are Oraflex, Selacryn, Zomax, Merital, and Omniflox. Device surveillance has resulted in critical

corrections to such devices as pacemakers, infant ventilators, and patient restraints and the withdrawal from the market of Orcolon, an eye gel that caused cases of blindness. Surveillance was responsible for identifying potentially fatal allergic reactions to sulfites, which are a common preservative in food, and putting in place a warning. FDA surveillance picked up counterfeit infant formula that would have injured infants if consumed and an illegal pesticide in some of the nation's most popular breakfast cereals.

S.1477 also requires FDA to give priority to products approved in Europe even if the product is not a priority product under S.1477. Under section 404, the agency is mandated to review certain products approved in Europe within six months and make a final decision within 30 days at the request of the manufacturer once the six months has elapsed. No comparable treatment is provided for drugs which are submitted for approval for the first time in the United States. Thus, FDA is forced to give priority to products approved in Europe at the expense of potentially more important products submitted for the first time in the U.S. Not only does this potentially undermine public health, it encourages companies to do their research in Europe rather than the United States in order to secure a priority here. This requirement for priority to European-approved products is particularly inappropriate since, as described below, the U.S. now approves drugs more quickly, on average, than European countries, and FDA's safety record is far superior to foreign drug approval authorities.

Section 607 suspends FDA's authority to implement requirements for pharmacists to provide consumer labeling for prescription drugs and limits its ability to oversee any voluntary program, if within 120 days of enactment, industry proposes its own program. However, the provisions contain little in the way of standards for this voluntary program and do not provide for any review to determine if the voluntary plan is adequate. Authority (but only to propose a rule) is only reinstated if HHS finds that the industry is not complying with its vaguely described voluntary program. It is also unclear what effect this provision could have on FDA's legal authority to require manufacturers to provide consumer labeling. At a time when hospitalizations from improper use of prescription drugs by senior citizens now cost Medicare $20 billion a year, it seems foolish to hamstring FDA and count on voluntary efforts that have been promised but not delivered since 1980.

Section 903 allows food manufacturers to make health claims without FDA review based on statements by other government agencies. While it is certainly reasonable to ask FDA to take into account the findings of other science-based agencies that have expertise in health and nutrition, section 903 goes too far. It appears to allow a manufacturer to rely on any statement, no matter how informal, that has ever been made by one of these government bodies. Taking away the preapproval requirements would also shift the burden from the manufacturer to prove that the claim is a valid one before it can go on a food label to FDA, which would have to go to court, to remove the claim from the marketplace. Given that FDA's food program is already under-funded and that S.1477 imposes new resource-intensive requirements on FDA's product approval programs, it seems extremely unlikely that FDA will be in a position to police food labels with any vigor. Right now, under the Nutrition Labeling and Education Act (NLEA) FDA approval is required of all

health claims, and the process has worked well.[1] Since the NLEA became effective, the FDA has approved a variety of legitimate health claims that help consumers maintain proper dietary practices. These claims now appear on the labels of food industry including: Campbell Soup, Pillsbury, Kellogg, and Quaker Oats. Furthermore, the FDA is considering additional health claims for sugar-free foods, dairy products, and cereal grains such as oats. There is no reason to take a step back towards the outrageous claims that prompted enactment of the NLEA in the first place.

In addition to these major issues, there are a number of other important problems with S.1477 that should be addressed before the bill is considered by the full Senate. For example, the bill purports to codify the current expanded access regulations of FDA allowing patients to receive unapproved drugs on a humanitarian basis if no other treatment is available. While this program is a laudable one, the legislation leaves out key parts of the regulation allowing the Secretary to suspend expanded access if new information indicates that the drug may be doing more harm than good or for other reasons.

The primary justification for the radical reforms included in S.1477 is that FDA is too slow to approve products, thereby denying patients needed treatment already available in foreign countries. Although there may have been some basis for this concern a decade ago, it is not valid today. FDA cut average time to drug approval by 40% between 1987 and 1992. According to the General Accounting Office, in 1994, the U.S. was reviewing drugs as fast as, or faster than Great Britain and other foreign countries. Since PDUFA was negotiated by FDA, Congress, and industry and passed in 1992, review times have dropped even farther. In fact, drug user fees have proved an overwhelming success. According to FDA, median time to approval dropped farther in 1995. Moreover, under PDUFA, by FY 97, FDA was to be conducting a complete review of 90% of applications for priority drugs within six months and other drugs within twelve months. By FY 95, FDA had already surpassed the 1997 goal -- by conducting a complete review of 96% of applications within these time limits.

Nor is there any "treatment" lag with other countries when it comes to drugs. Of 40 new drugs that offer significant therapeutic advances over existing products and that were approved in the United States, Great Britain, Germany, or Japan between 1990 and 1994, all were approved in the U.S. and more than half were approved in this country first. Every new AIDS drug was approved in the United States first, and FDA recently announced steps to bring promising new cancer drugs to the market even more rapidly. Unlike foreign approval authorities, FDA has successfully combined speed with safety. Between 1970 and 1992, a total of 56 drugs were introduced in France, Germany, Great Britain, and the United States that subsequently had to be withdrawn because they were unsafe. Only 9 of these 56 drugs had been approved in this country, compared to 31 in France, 30 in Germany, and 23 in Great Britain.

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[1] Some claim that the fact that CDC began recommending in 1992 that women of child bearing age consume adequate amounts of folic acid in order to reduce the risk of certain birth defects and that FDA did not approve the claim until March 1996, shows that the system is not working. However, when the FDA began considering to allow health claims for foods containing folic acid, it noted that over consumption of this nutrient could mask the symptoms of anemia in persons with a vitamin B-12 deficiency, thus permitting irreversible neurological damage in certain individuals to progress unknowingly. This factor was not considered fully by the CDC. FDA authorized health claims for folic acid only after determining steps that could be taken to avoid this situation from occurring. Had food companies been permitted to make health claims for folic acid based on the CDC findings alone, serious public health consequences could have resulted.

The agency's successes with devices also demonstrates how committed FDA is to trying to achieve the balance between speed and consumer protection. During the late 1980's and early 1990's, FDA was under a series of investigations by Congress as a result of various problematic medical devices (e.g., heart valves, pacemaker leads, infant apnea monitors), *see, e.g.*, S. Rep. No. 513, 101st Cong., 2d Sess. (1990); H.R. Rep. No. 808, 101st Cong., 2d Sess. (1990). It was then required to implement the provisions of the Safe Medical Devices Act of 1990. As a result, FDA review time for medical devices slowed down considerably. In the last Congress, a significant amount of work was done by Congress, FDA, and the medical device industry to put together a device user fee package to give FDA the additional resources needed to improve device review times. Unfortunately, chances for user fee legislation fell apart when part of the industry refused to support the proposal.

Nevertheless, even without the additional resources that user fees would have provided, FDA has successfully decreased median review times for premarket notifications, the premarket submission used for 97% of all devices, to 91 days, only one day shy of the 90 days in regulation, while the average review time is 138 days. At the end of FY 95 only 9 premarket notifications were active and overdue (past 90 days), as compared with 460 at the end of FY 94 and 1,894 at the end of FY 93.

In addition to speeding up review times, FDA has exempted a significant number (about 75%) of class I devices from the premarket notification process. This frees up agency resources to review more important products and relieves manufacturers of those devices of a regulatory burden. FDA has also devoted significant resources to working with manufacturers, so that investigational device exemption (IDE) can be approved on their first submission and investigations can begin quickly. This has required frequent meetings and communication between FDA and industry to identify and resolve questions regarding the IDE. According to FDA's annual report, in FY 95, FDA approved 57% of IDEs the first time through, up from 35% in FY 94 and 27% in FY 93. In order to accomplish this, FDA states it held more than 200 pre-submission meetings with companies and reviewed more than 100 pre-IDE submissions.

FDA is by no means perfect, but it is still renowned as one of the most effective consumer protection agencies in the world. Under the leadership of Dr. David Kessler, FDA has already accomplished many reforms that have brought Americans improved, high-quality medical care, and its record of excellence in protecting the health of the American public is unmatched. While some provisions in S.1477 would help FDA move forward, unless the major concerns described above are addressed, too much remains that would undermine FDA's ability to ensure public health and safety.

ISSUES OF CONCERN TO PATIENTS IN THE DEBATE OVER FDA REFORM

The Patients' Coalition is a group of independent organizations representing Americans with a wide variety of serious and life-threatening diseases. An efficient and effective Food and Drug Administration (FDA) is of paramount importance to us because we desperately need access to safe and effective treatments to help ameliorate and one day cure the diseases that afflict us. Many of us have long worked for changes in FDA regulations and improved management and operations at the agency in order to get speedy access to promising new drugs, biologics, and medical devices.

We are concerned, however, by many of the FDA reform proposals now being considered by or recommended to Congress. It is our view that many of these proposals are not in the best interests of patients. Many proposals seek to legislate a reduction in the efficacy standard for approval of new drugs and diminish significantly the safety and efficacy requirements for approval of new uses of approved drugs. Other provisions undermine the FDA's authority to make decisions that are in the best interests of the American public.

We believe that a strong, independent and responsive regulatory agency is necessary to ensure that American pharmaceuticals continue to be safe and effective, and that more, not less, clinical research is performed to help physicians understand how best to use these new products to the benefit of their patients. The AIDS epidemic has taught us that early access to drugs provides little advantage without adequate information about their value or appropriate use.

Many proposed "FDA reforms" place the short-term business interests of industry above the health of American patients. The Patients' Coalition believes that FDA reform should provide needed incentives for the industry to finance and conduct more research.

We have identified the following issues related to regulation of drugs and biologics and of concern to patients, health care providers, industry and the agency itself, and offer suggestions for effecting desired changes without undermining the ability of the FDA to achieve its critical mission of protecting and promoting the public health through responsible regulation of drugs and devices in the United States.

1. MAINTAINING THE EFFICACY STANDARD

Issue: Should the efficacy standard for approval of new drugs be amended in the law?

Proposal: The current statutory standard, requiring substantial evidence of efficacy from adequate and well-controlled clinical investigations (i.e., more than one), should not be changed unless specific authority is believed necessary to allow FDA to approve a new product based on only one controlled trial (with "confirmatory evidence") in those exceptional circumstances when a single study is very persuasive in demonstrating the efficacy of a new product based on well accepted clinical endpoints in a serious or life-threatening disease.

Comment: The current requirement is the only scientifically defensible approach to planning the trials needed to establish he efficacy of new products or indications. As described in detail in the existing regulations, well-controlled trials need not always be large or data intensive. Adequacy of the clinical research database and regulatory flexibility in its interpretation are key characteristics for the optimal development and approval of any new drug for a defined indication.

If sponsors regularly plan and perform only one study in support of a new drug application, because the law states that only one trial is required, agency reviewers will have to *disapprove* more applications than they would if at least two adequate and well-controlled studies were routinely performed. In fact, there is a reasonable likelihood that a *single* controlled study of a new drug for a given indication will be inappropriately designed, underpowered, or otherwise inadequate to demonstrate substantial evidence of efficacy.

Replication of experimental results is a basic tenet of good science, especially when the safety and well being of millions of potential recipients of a new drug depend on informed regulatory judgments. Borderline significant results from a single study cannot be confirmed or refuted with any confidence in the absence of a second controlled study. In addition, the second study may broaden the initial approvable indication and increases the scientific credibility of the results. The unbiased evaluation of clinical trial results intended to assess the safety and efficacy of new drugs is a scientific discipline that requires adequate data, in most cases from more than one controlled study.

If the indication being sought is a serious or life-threatening condition without satisfactory treatments and the new product appears to offer substantial therapeutic advantage, the FDA can and has granted approval based on one controlled study (with "confirmatory evidence"). Most new drugs, however,

offer, at best, incremental improvement in the treatment of the condition (e.g. improved convenience in dosing schedule) and should be thoroughly tested for safety and efficacy before being marketed. Caution on the part of the FDA is appropriate in the evaluation of "routine" drugs, for the safety of patients is more important than getting a new agent on the market. For serious and life-threatening conditions, more risk-taking based on fewer data is appropriate, and the FDA has demonstrated its flexibility in approving such drugs on an expedited basis, best exemplified in AIDS.

2. EFFICIENT AND TIMELY REVIEW

Issue: Should detailed deadlines be prescribed by law for the review of drugs, biologics, and medical devices? Are default approvals and mandatory external reviews appropriate mechanisms to enforce statutory deadlines?

Proposal: At this time, there is no compelling reason to alter the basic approval process. Arbitrary statutory deadlines -- especially when they are unrealistically short -- within which the FDA must make vital safety and efficacy decisions should be avoided, although performance goals should be set and carefully monitored. A recent GAO report found that important reductions in the average review time for new drug applications occurred during the five year period prior to the passage of the User Fee Act of 1992, under which increased resources are provided to the agency and aggressive but realistic performance standards have been set. Review times for drugs and biologics, to which the User Fee Act applies, have been reduced further since 1992, and additional improvements are expected.

Proposals to approve products in the U.S. by default (i.e., when the product is already approved for the indication in the United Kingdom/European Union) and the mandatory contracting of reviews to outside groups with acceptance of their recommendations if statutory time lines are not met are inappropriate. Transfer of responsibility to approve new drugs from the U.S. government to other nations or to non-government groups if arbitrary deadlines are not met undermines the authority of the FDA and its ability to carry out its mission of protecting and promoting the health of the American public.

Comment: Arbitrary deadlines could lead to hasty rejection of valuable drugs or premature approval of dangerous ones without compensating benefit. Without additional resources dedicated exclusively to the FDA's approval process, statutory deadlines are ineffective in shortening review times. In addition, it should be remembered that there is an irreducible minimum time needed to review adequately each new drug application, which is not uniform for all products and

intended uses. In particular, given limited resources, the review time for "priority" drugs is and should be substantially shorter than for more "routine" products and indications.

3. STRENGTHENING CONFLICT OF INTEREST PROTECTIONS

Issue: Are existing laws governing conflicts of interest adequate, and are they being enforced appropriately?

Proposal: The clear absence of conflict of interest on the part of all non-FDA employees involved in a paid or official capacity in the evaluation and approval of new products for specific uses is critical to unbiased regulatory decisions on which the public depends. The intent of the conflict of interest laws are clear, but current interpretation and enforcement has not proved adequate to prevent conflicts of interest among those non-FDA employees who are involved with the scientific evaluation of a drug or medical device in a paid or official capacity.

Enforcement of current law should be revised to ensure the following:

1) Members of FDA advisory committees should be required to disclose publicly their financial interests. Individuals, whatever their expertise, who receive financial or other valuable compensation from a company whose profitability would be affected by the outcome of a regulatory decision should not be involved in making or influencing that decision.

2) Outside contractors and consultants to the FDA who evaluate the safety and efficacy of drugs should meet the same conflict of interest standards as full-time FDA employees.

3) Waivers of conflict of interest laws, now widely given, should be severely limited.

Comment: One of the most important reasons that FDA decisions are highly regarded and respected is their objectivity, which is grounded in the absence of conflicts of interest. FDA employees are not allowed to own stock in any company that sells a product regulated anywhere in the FDA. Nor are FDA scientists allowed authorship on scientific publications of clinical trial results that may form part of the basis for an FDA decision in which they are involved, even though they may have contributed substantially to the intellectual basis for the trial.

It is very important to the public health to maintain and uphold these strict standards designed to prevent conflicts of interest, not only for FDA employees, but also for their consultants and advisors, so far as is possible. If full financial and intellectual (academic) freedom from conflict of interest is not practical (for example, for certain advisory committee members), then full public disclosure should be mandatory. Advisory committee recommendations must be interpreted by the FDA and others with such real or potential conflicts of interest in mind, and should not be regarded as *de facto* regulatory decisions, as so often occurs today.

4. IMPROVING ACCOUNTABILITY AND INDEPENDENT OVERSIGHT OF FDA

Issue: How can constructive oversight of the FDA, and, more broadly, of the safety of prescription drugs, biologics, and medical devices, be achieved?

Proposal: A non-partisan oversight agency, modeled on the highly successful National Transportation Safety Board, could be very useful in providing independent, non-political oversight of agency policies and industry performance. This Board, established by Congress, should have the following powers:

1) To investigate significant safety problems and other concerns or controversies with the potential to compromise the public health that involve drugs, medical devices, or biological products;

2) To inquire into allegations of FDA mismanagement, including delays in approval, arbitrary or unreasonable decisions, or retaliatory or punitive actions;

3) To collect and publish information about the overall performance of system, including statistics about deaths and injuries attributable to drugs, approval times, drug withdrawals, relabelling and product recalls;.

4) To make recommendations to FDA, the medical profession and the public for ways to achieve safer and more effective use of drugs, medical devices and biological products.

Comment: Both concerned consumers and regulated industry have complained that there is no independent, systematic oversight of the FDA except through Congress, which has many obligations and limited expertise in this complex area. When major controversies occur -- such as the safety of silicon gel breast implants, excess mortality due to antiarrhythmic drugs, or complaints about undue delays in

approving medical devices or access to drugs to treat life-threatening diseases -- there is no outside body to review FDA's policies or hear credible complaints and recommend redress.

Furthermore, no independent body regularly collects vital information about how the whole system is functioning. Are approval times increasing or growing shorter? For some classes of drugs but not others? Are adverse effects rising, signaling a problem with the system, or with a particular family of drugs? Is the marketing of valuable new drugs or devices being delayed?

To win the confidence of groups with all perspectives, the Board should be politically non-partisan and insulated from all special interest groups, including industry. In addition, to be credible, both Board members and staff must have relevant experience and expertise in the complex issues that the FDA must address.

5. PROMOTION AND MARKETING OF DRUGS FOR UNAPPROVED USES

Issue: Should drug companies be allowed to disseminate proactively (promote) information regarding unapproved uses of marketed drugs?

Proposal: The current ban on promotion of drugs for unapproved uses should be continued because it helps to protect the public from the consequences of taking medicines for untested uses, where the likelihood of toxicity without compensating benefit is high. Although physicians should continue to have the flexibility to prescribe approved drugs to meet the specific needs of their patients, promotion (including unsolicited dissemination of selected published trial results) for such uses on the part of manufacturers, who clearly stand to gain from increased sales, should not be allowed.

If there are substantial data supporting a new use, an independent group, such as a professional medical association or a voluntary health organization, should take responsibility for disseminating this information to practitioners and patients. Ideally, an independent and respected not-for-profit group without conflicts of interest would review published trial results on a routine basis, and then compile and disseminate them to physicians and other interested parties. If such organizations do not have the resources to take on this task, then more thought should be given to how the pharmaceutical industry can best support -- through neutral third parties -- the unbiased dissemination of new information about unapproved uses. Perhaps a small part of the marketing budgets of the big pharmaceutical companies could be directed toward financing such an effort.

Comment: There is inherent bias in the selection of material that a company, which manufactures and sells the drug, would voluntarily provide to physicians or other health care providers. "Full disclosure" of potential or real conflict of interest on the part of those disseminating information does not protect the practicing physician or patient consumer from the biased effects of such promotion/dissemination.

It is unrealistic to assume that most physicians receiving unsolicited information on new uses from manufacturers would review in detail the articles, question the results, and put them in the appropriate context. If practicing physicians are typically too busy to initiate requests for information, read the medical literature, and/or attend meetings to learn of new uses from less biased sources, they are unlikely to take the time (and many don't have the background or training) to evaluate carefully unsolicited information. Increased dissemination of information to physicians and patients is clearly desirable, but the need for independent "packaging" of these complex and changing databases must be recognized.

The benefits and safety of a drug for each potential use can only be established with confidence from the results of controlled clinical trials, which are reviewed by an independent group with no financial stake in the outcome of their assessment. If manufacturers are permitted to promote their products for unapproved uses, an important incentive for companies to conduct badly needed research on the safety and efficacy of new uses would be significantly diminished. We must find better ways to increase incentives and decrease disincentives for sponsors to perform the studies and submit the data to FDA to get the new uses approved and "on label."

6. IMPROVING THE SUPPLEMENTARY APPROVAL PROCESS FOR NEW USES OF APPROVED DRUGS

Issue: Why don't sponsors submit more efficacy supplements to FDA to get new uses approved and "on-label," thereby reducing problems with reimbursement and dissemination of information regarding unapproved uses?

Proposal: Insufficient attention is directed towards the development and approval of new uses of approved drugs largely because the primary focus of the pharmaceutical industry and Congress, and therefore the FDA, has traditionally been on the development and review of *new* chemical entities (NCE's) in preference to investigating new uses for approved drugs. The patent life of new products following FDA approval is the life blood of the pharmaceutical industry, so a

premium is placed on the rapid development, approval, and marketing of new, recently patented products.

Regulatory disincentives for manufacturers to submit supplementary NDAs containing data to support the safety and efficacy of approved drugs for new uses include longer average review periods at the FDA (review of supplemental indications are of lower priority than review of original NDAs for most indications) and extensive data requirements similar to those required to support initial approval. These disincentives should be minimized by shortening review times and developing more flexible data requirements for approval of many new indications, while maintaining the basic requirement for demonstration of safety and efficacy.

One way to ensure adequate prioritization of FDA review of supplemental indications, which consist primarily of clinical data, would be to assign FDA reviewers to a separate center or unit where review of supplemental NDAs was the priority. Separating the review of supplemental NDAs from direct competition with the review of original applications, coupled with clear performance expectations, should reduce review time at the FDA and create the opportunity for somewhat different evidentiary standards to evolve for review of supplemental indications.

The FDA should also be more flexible in terms of what it requires to support approval of a new use. Evidence may range from traditional well-controlled trials to "paper NDAs" (compilation of published, peer-reviewed, controlled trials), depending on the inherent risk in using the product, the prevalence of use, seriousness of the disease, need for alternative therapies, etc. To develop more flexible standards that are enforced fairly and uniformly, a separate staff should be responsible for review of supplemental efficacy NDAs.

Proposals to contract out review of supplemental applications to outside groups would be counterproductive to this effort, since it is "routine" applications that can be reviewed more easily outside the Agency against "standard" criteria.

Another approach to increase the likelihood of sponsors submitting more supplemental NDAs is to provide new incentives for industry to conduct controlled trials of approved drugs for new uses by extending marketing exclusivity for a period of time for each new indication. This approach would need to be carefully thought through in any specific proposal.

Comment: At the present time, a sponsor is prohibited from promoting a product for a use that has not been approved (i.e. in the labeling) so there is some incentive for the innovator company to conduct the trials to demonstrate safety and efficacy for a broad (high volume) new use, but the controlled trials required must compete for resources against trials to demonstrate the safety and efficacy of brand new drugs (NCE's) in the pipeline, and usually the latter wins.

As a result, many potential supplemental uses remain "off-label," although some, usually less rigorous, studies on the new uses may be conducted by academic centers or even by (the marketing arm) of the company itself. Publication of the results of these trials, *if favorable*, is a high priority, since it boosts off-label prescribing. Clearly, legal permission to disseminate these favorable trial results proactively, without independent review of all the data relating to the new use, would be profitable for the company, but potentially risky to consumers.

Attempts to improve the supplemental review process should not include abandonment of the efficacy standard or bypass of thorough, independent review of the data and information that exists relevant to the new use. FDA approval of supplemental indications should NOT be based primarily on "sound medical practice based upon reliable clinical experience and other confirmatory information." Use by clinicians does not by itself demonstrate either the safety or the efficacy of the product for the new use. The history of medicine is full of examples of well meaning physicians prescribing "standard" treatments that were shown later, through controlled trials, to be ineffective or harmful.

In addition, eliminating the efficacy standard for supplemental indications goes a long way toward undermining its justification for new drug approval. If it is deemed permissible to promote and sell a drug for supplemental indications without demonstrating efficacy or safety for those conditions, which may be much more serious and affect many more patients than the original indication, then what is the point in having an efficacy standard at all?

7. ENCOURAGING THE RAPID DEVELOPMENT AND APPROVAL OF NEW DRUGS FOR SERIOUS AND LIFE-THREATENING DISEASES WHILE IMPROVING THE QUALITY OF INFORMATION FROM POST-APPROVAL "CONFIRMATORY" CLINICAL EFFICACY STUDIES

Issue: Does the FDA have adequate authority to ensure that appropriate confirmatory clinical trials are performed following accelerated approval of new drugs for serious and life-threatening diseases?

Proposal: If the mission of the FDA is to promote, as well as to protect, the health of the American people, then its regulatory authority to compel drug sponsors to conduct and/or actively participate in appropriately designed post-approval trials "to verify and describe its clinical benefits" may need to be increased, rather than diminished. Retraction of marketing approval after a certain period of time if sponsors fail to conduct post-approval studies or if those studies are ambiguous in their interpretation is not a practical approach to solving the dilemma of how best to ensure that clinical efficacy is demonstrated for new drugs; nor is it in the best interest of patients. Civil monetary penalties for failing to conduct required post-approval studies "with due diligence" should be considered, with the money used to pay others (e.g. contract research organizations) to conduct the needed research.

Comment: The FDA has done a credible job over the past decade in shortening the approval time for all drugs (from an average of 33 to 19 months, as discussed in a recent GAO report). Special attention has been given to priority drugs intended for the treatment of serious and life-threatening diseases, for which a marked reduction in *pre-approval* regulatory requirements has occurred for data to demonstrate the safety and efficacy of the product for the proposed use. Many of these drugs are approved in less than six months of submission of the "accelerated" NDA. However, once a drug is approved for marketing it may be difficult to compel the sponsor to conduct controlled trials to confirm its clinical efficacy and expand upon the limited knowledge base that formed the basis of its rapid approval.

The earlier in drug development that approval occurs, the less is known about a new drug's safety and efficacy, and the harder it is to conduct adequate and well-controlled clinical studies. It is more difficult and expensive to enroll and retain patients in long-term controlled trials in which some patients get the new (approved) drug and others do not, especially in the context of a serious or life-threatening illness as the new drug becomes part of standard of care. In AIDS and other life-threatening progressive diseases requiring treatment with multiple drugs, the problem is compounded further by a continuing emphasis by pharmaceutical sponsors and the agency on traditionally designed "drug superiority" studies in narrow patient populations, rather than investigating the role of the new compound in the larger context of multiple drug regimens, which are the reality in the treatment of these diseases.

For those drugs/indications that are determined to be potential candidates for accelerated approval, the design of post-approval confirmatory clinical efficacy studies, and any anticipated generic problems with their prompt and adequate conduct and analysis, should be considered carefully before this approach is pursued. For complex diseases where multiple drugs are generally required to

control progression, such as AIDS and some types cancer, particularly careful consideration must be given to the design of post-approval studies, since they may require the participation of multiple companies.

8. PROVIDING THE FDA WITH SUFFICIENT RESOURCES TO FULFILL ITS MANDATES

Issue: Does the FDA have adequate resources to comply with all relevant statutes within desired time frames?

Proposal: The simple answer is no. The improvement in review times as a result of the increased resources (and better, more accountable management of the review process) from user fees demonstrates that inadequate resources is an impediment to optimal FDA performance. Appropriately, priority drugs that represent major therapeutic advances, particularly for serious or life-threatening conditions, get more attention and resources than other products, which, in a generally under-resourced environment, take longer to review.

Regulations that are "excessive" (unnecessary) should continue to be eliminated or appropriately modified and updated, as has recently occurred for certain biologics regulations, (e.g. elimination of the requirement for separate licensure of the manufacturing facility for some biologics) and some time ago for drugs (e.g. elimination of Form 5 for antibiotic applications).

Comment: An increase in the statutory requirements for more FDA reports, rigid time lines, and opportunities for excessive and prolonged appeals of any agency decision are resource intensive without any real likelihood of improved performance; in fact, because of the resource requirements, performance may well suffer. Regulation and oversight inevitably take time and resources, as does the appropriate planning and conduct of adequate and well controlled clinical trials, both constituting short-term costs for regulated businesses. In many respects, however, as the large pharmaceutical companies acknowledge, principled but flexible regulatory oversight is actually in their business interests as well as in the public health interest, by forcing potential drug marketers to generate scientific data and base their claims on more than (expensive) advertising techniques.

9. GUARANTEEING PATIENTS' RIGHTS

Issue: Are patients' rights protected adequately under current law and common practice?

Proposal: Patients are often not able to exercise their right of informed consent to drug treatment. This right includes a fair statement of the benefits of treatment, an understandable explanation of the risks, and discussion of available options, including forgoing treatment.

A major revision of the current system of regulations and tort law, which require drug manufacturers to make extensive disclosures to physicians but not to patients, would be necessary to protect patients' rights in this area. The voluntary scheme for patient package inserts has proved ineffective. Industry, organized medicine and the FDA should be charged with developing a plan to protect these rights on a routine basis.

Comment: Ultimately, a patient for whom a drug, biologic or medical device is prescribed for a particular medical problem should get a straightforward statement regarding the likely risks and possible benefits, based on the results of controlled clinical trials. They should receive a list of the known adverse effects and how they can be detected. When given a medication for pain, for example, some patients might choose a drug with a slightly smaller chance of benefit to avoid certain adverse effects.

The patient should be informed if the drug is not FDA approved for the medical purpose for which it is prescribed. Special disclosure and consent procedures should be provided if patients are taking partially tested drugs under early access or accelerated approval programs.

10. IMPROVING FDA COMMUNICATION WITH THE PUBLIC REGARDING REGULATORY ACTIONS AND REVIEW STATUS OF PRODUCTS

Issue: Are the limitations on public access to information at the FDA too restrictive?

Proposal: Too often, vital information about regulated products, such as the reasons for delays in product approval decision, reasons for withdrawals or shortages of approved products, etc., are not released to the public because of "confidentiality" concerns. The public has a right to know much information that is currently considered "trade secret," especially regarding the status of products intended for the treatment of serious or life-threatening conditions, because such information has the potential to affect important public health decisions outside the FDA.

The FDA should revise the regulations concerning disclosure of information regarding the review status of unapproved products and important safety and/or efficacy information regarding approved products that have been recalled or are otherwise subject to regulatory actions. The agency should only regard as "trade secret" that information pertaining to the composition or manufacturing methods for a drug, not that which otherwise applies to its safe and effective use.

Comment: FDA staff are extremely cautious about sharing any information that is deemed confidential, including that which has to do with the regulatory status of new products rather than with information submitted by the company about the product itself. Only when written permission from the company has been granted will the FDA discuss a specific product. This policy is not always in the best interest of the public.

Concern for unfair advantage by competitors from the release of product related information must be balanced against the public health advantages of clear and rapid dissemination of important information about certain pending or final regulatory actions.

THE PATIENTS' COALITION

An Independent Coalition of Patients With Serious And Life-Threatening Diseases Working Together For Responsible FDA Reform

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COMMENTS ON S. 1477 -- Chairman's Mark
March 15, 1996

SEC. 102. The Mission of the Food and Drug Administration

Reverse sections (1) and (2). The agency's first priority should be to do no harm and the second to get effective drugs out to people quickly, while striking an appropriate balance between the two.

SEC. 103. Performance Standards and Review

Strike Section (3)(A)(ii). Reasonable performance standards, with appropriate monitoring and reporting, are an appropriate management tool. However, to require the agency to set and monitor standards for such tasks as returning telephone calls and answering letters is an example of resource intensive micromanagement that can only detract from the agency's efficiency.

Improved Independent Oversight

We agree that in order for the agency to best fulfill its mission, better management practices and oversight to improve both agency and industry performance must be found. One possibility that we believe merits serious consideration and study is the establishment of a non-partisan oversight entity, modeled after the highly successful National Transportation Safety Board, to provide independent, non-political oversight of Agency management policies, and of industry performance in meeting their obligations. This Board could: investigate significant safety problems and other concerns or controversies with the potential to compromise the public health that involve drugs, medical devices, or biological products; inquire into allegations of FDA mismanagement, including delays in approval, arbitrary or unreasonable decisions, or retaliatory or punitive actions; collect and publish information about the overall performance of system, including statistics about deaths and injuries attributable to drugs, approval times, drug withdrawals, relabelling and product recalls; and make recommendations to FDA, the medical profession and the public for ways to achieve safer and more effective use of drugs, medical devices and biological products. Such a board could address the concerns of both consumers and regulated industry, which have complained that there is no independent, systematic oversight of the FDA except through Congress, which has many obligations and limited expertise in this complex area.

SEC. 105. Information System [PROPOSED ADDITION].

On page 10, line 13, strike the words "applicant or petitioner." and insert "applicant, petitioner, or public." Too often, vital information about regulated products, such as the reasons for delays in product approval decisions, reasons for withdrawals or shortages of approved products, etc., are not released to the public because of "confidentiality" concerns. The public has a right to know much of the information that is currently considered "trade secret", especially regarding the regulatory status of products intended for the treatment of serious or life-threatening conditions. Such information often has the potential to affect important public health decisions outside the FDA. Concern for unfair advantage by competitors from the release of product related information must be balanced against the public health advantages of clear and rapid dissemination of important information about certain pending or final regulatory actions.

SEC. 107. Scientific Review Groups
(c) Membership and Meeting Requirements
(2) Non-voting Members.
On page 12, strike lines 17-19 and insert: -- "Voting Members/A scientific review group shall include a voting public representative." Industry representatives should not sit on advisory committees, even as non-voting members, since there is an obvious conflict of interest (even if not from the company whose product is under consideration). There is ample opportunity for their advice and input at other points in the process. On the other hand, patient representatives have few other opportunities for meaningful input and should be empowered through voting membership on all advisory panels.

(6) Frequency of Meetings.
On page 13, strike lines 17-19 -- "The meetings shall occur not less than 3 times each year unless there are reasons for fewer meetings." A statutory requirement for meeting three times a year is arbitrary.

(7)Conflict of Interest
A provision should be added to the bill to strengthen conflict of interest protections regarding advisory group members. Individuals, whatever their expertise, who receive financial or other valuable compensation from a company whose profitability would be affected by the outcome of a regulatory decision should be barred from making or influencing that decision. While the intent of the current conflict of interest laws are clear, the current interpretation and enforcement have not proved adequate to prevent conflicts of interest among those non-FDA employees who are involved with the scientific evaluation of a drug or medical device in a paid or official capacity.

PROPOSED LEGISLATIVE LANGUAGE

INSERT -- On page 13, line 20, insert the following new paragraph:

> "(7) **Conflict of Interest** -- If a member of a scientific review group receives financial compensation from, other valuable compensation from, or is otherwise associated with a sponsor or applicant regarding whom a decision is pending before the scientific review group, that member shall abstain from the decision making process."

SEC. 108., SEC. 907. Appeals within the Food and Drug Administration.
(a) Employee Decisions.
On page 15 strike lines, 20-25 beginning with "As the final" and on page 16 strike lines 1-4, through "an evaluation." The scientific review group should not be the final step in the internal appeals process.

(b) Review by Scientific Review Group.
On page 16 strike lines 8-25 and on page 17 strike lines 1-6. In general, we are concerned that throughout the bill advisory committees (i.e. scientific review groups) are given enhanced authority to make what amount to regulatory decisions, rather than act primarily to give advice to the agency. The agency needs to be supported in its important and sensitive role as "gatekeeper" of new products rather than treated as incompetent and in broad need of outside experts to do its job. The overly enhanced authority of outside experts not only undermines the authority of the agency, but outside experts, with rare exceptions, have relatively little time to devote to these regulatory considerations, which are often much broader and more complex than may appear to the outside observer. Medical subspecialty expertise is an important part of the information and advice that the regulatory authorities need to consider, but such expertise alone is not sufficient to ensure good public health decisions.

The issues and decisions that could be appealed by *any* party to an advisory committee under SEC. 907 (b) are the regulatory decisions that agency personnel make as routine matters under present law. These decisions are the essence of the regulator's job -- to balance risks and benefits at various milestones in the clinical evaluation of a new drug (i.e. acceptability of an application for filing, whether an IND should be subject to a hold, protocol design recommendations, etc.). The authority of the FDA is undermined substantially if any or all of these routine decisions or actions are to be made subject to second-guessing by volunteer advisory groups, which have mixed expertise on these issues, little or no regulatory experience, and may have conflicts of interest (even if disclosed). Agency employees, who are held to very strict conflict of interest guidelines, are paid to do the work full-time, and have a historical perspective on what actions are most appropriate. The internal review and appeals process [described in SEC 907 (a)] should ensure that poor judgments or advice by agency personnel are minimized. The external appeals process outlined in SEC 907 (b) is likely to prolong the approval process.

(c) Additional Informal and Formal Procedures.
(2) Application of FACA.
Strike"not" on page 17, line 24. The Federal Advisory Committee Act (FACA) should apply to these advisory panels. Removing the applicability of FACA to the appeals panels is an invitation to conflict of interest. There is no role in regulatory decisions for anyone with real conflicts of interest, either financial or intellectual, even if publicly disclosed. This part of the bill proposes to mandate an external appeals process for all decisions to voluntary advisory bodies who are not required to adhere to the same strict conflict of interest policy as FDA employees.

TITLE II. "PATIENTS RIGHTS REGULATORY REFORM ACT".

In general, we feel that all patients, whether or not they have a serious or life-threatening disease, should have the right to be informed about the risks and benefits of drugs being described to treat their condition, and about other options. Procedures should be developed to guarantee this right for on-label, off-label, and experimental therapies.

SEC. 543. Expanded Access to Unapproved Therapies and Diagnostics.

(b) Protocols

Replace "may" on page 19, in line 19, with "shall." The FDA should be required to review and approve all expanded access protocols and should have the authority to terminate an expanded access program. In addition, the manufacturer must be required to pursue full product approval with "due diligence." As written, there are no requirements or real restrictions on expanded access under this section, except the willingness of the sponsor to provide the product. Who decides whether requirements (a) (1) and (2) are met is not specified. Requirement (2) involves a risk-benefit assessment in a situation where very little may be known about the risks of the investigational product being requested (e.g. it could be a drug in early phase 1 testing). The potential for overly zealous manufacturers to take advantage of sick and dying patients is too great without mandatory regulatory review and approval of proposals for expanded access to experimental products.

SEC. 204. Expediting Approval of New Drugs, Biologics, and Medical Devices for Serious Conditions

Strike this section. Mandating action in 120 days is impractical and unwise. According to the FDA, in FY95, the median time to review 15 priority drugs was six months, which included several AIDS drugs where review resources are relatively ample. Thus, to mandate that all priority drugs be acted on within four months is unrealistic from a resource perspective, unless the intent is to increase risk to patients through hasty approvals, or to increase the number of non-approval actions, which would then likely be appealed, causing the potential for considerable delay and consumption of additional resources.

TITLE III. REVITALIZING THE INVESTIGATION OF NEW PRODUCTS

SEC. 302 Timely Review and Reasonable Data Requirements for Clinical Research on Drugs and Biological Products

Improving the Quality of Information from Post-Approval "Confirmatory" Clinical Efficacy Studies ***A provision should be added to the bill to ensure that the Agency has the appropriate authority to ensure that confirmatory clinical trials are performed following expedited, or "accelerated," approval of new drugs for serious and life-threatening diseases. This authority should allow the agency to impose civil monetary penalties on companies that do not fulfill their post-approval obligations, and use that money to pay some other group to conduct the needed research.***

Many drugs for serious and life-threatening diseases have been approved in less than six months with the submission of an accelerated NDA. Their approval is based on a sparse database that leaves many important questions unanswered. The requirement that "the applicant study the drug further to verify and describe its clinical benefit" is critical, and the agency must be empowered to enforce this provision.. Experience has shown, however, that it is sometimes difficult for the Agency to compel the sponsor to conduct such controlled trials.

The agency's current authority to withdraw marketing approval after a certain period of time if sponsors fail to conduct post-approval studies or if those studies are ambiguous in their interpretation is not a practical approach to solving the dilemma of how best to ensure that clinical efficacy is demonstrated; nor is it in the best interest of patients. Rather, the regulatory authority of the agency to compel drug sponsors to conduct and/or actively participate in appropriately designed post-approval trials "to verify and describe its clinical benefits" must be increased.

PROPOSED LEGISLATIVE LANGUAGE:

On page 22, line 23 insert the following:

(a) SEC 505 (e) (21 U.S.C. 355) is amended --

by adding at the end thereof the following new paragraph [and making necessary conforming amendments]:

"(f) When new drugs for serious and life threatening diseases are approved, if the Secretary finds that at the time of approval additional data are necessary to confirm the initial submission data on which the approval under section 505(d) was made, the Secretary shall require the applicant to produce the necessary data. If the applicant fails to produce the necessary data within a time deemed reasonable by the Secretary or if the applicant fails to demonstrate due diligence in the production of the data, then Secretary may impose a fine under section 307."

(b) SEC 307 (a) (21 U.S.C. 355(b)) is amended --

(1) by adding at the end thereof the following new paragraph:

"(8) failed to comply with section 505(f)."

(3)(B)
Strike. It is inappropriate to force the FDA to meet with sponsors within 10 days of a clinical hold. It is also inappropriate to require that FDA provide to the sponsor a written list of conditions for withdrawal of a clinical hold within 10 days of such a meeting. Some INDs are unsafe or contain poor protocol plans. FDA should not be forced to use scare resources to meet with every sponsor who submits an IND no matter what the quality. In many cases, sponsors should make better use of outside experts before filing an application

Notification of Discontinuance
A post-marketing provision should be added to require that sole manufacturers of a licensed pharmaceutical, biologic, or medical device provide a one-year advance notification to the FDA if they discontinue manufacture of that product. In cases where a drug competes with other similar drugs on the market, there is usually no problem when one company stops production, as patients have other options. However, when a company stops manufacturing the only possible treatment for a disease, the morbidity and mortality can be considerable. In 1991, the Orphan Drug Act was amended by a similar requirement, and it has worked well. Failure to notify the agency could result in a monetary penalty to the manufacturer.

PROPOSED LEGISLATIVE LANGUAGE:

On page 24, line 24 insert the following:

(a) Chapter VII is amended:

(1) by adding the following new section:

"Notification of Discontinuance

712. When an applicant is the sole manufacturer of a drug, biologic or device, and (1) receives approval under 505(b) or 505(j) [parallel subsections for biologics and medical devices], then the manufacturer of the drug, biologic or device [or product] will notify the Secretary of any discontinuance of the production of the drug, biologic, or device at least one year before discontinuance, or (2) has not received approval under subsection 505(b) or 505(j) and if preclinical investigations or investigations under subsection 505(I) [**and parallel subsections**] are being conducted with the drug, biologic, or device the

manufacturer or sponsor of the drug, biologic, or device will notify the Secretary of any decision to discontinue active pursuit of approval of an application under subsection 505(b) [**and parallel subsections**]."

(b) Section 307(a) (21 U.S.C. 335 (b)) is amended:

(1) by adding at the end thereof the following new paragraph:

"(9) failed to comply with section 712."

SEC. 304. SEC. 544. Collaborative Research Design.

Strike entire SEC. While improved communication between the sponsors and the FDA throughout the development process should be encouraged, a certain distance or separation of functions must be maintained. The sponsor is responsible for planning and implementing the clinical trials to demonstrate safety and efficacy, and the FDA reviews them with the responsibility to decide whether the sponsor's claims are legitimately supported by the data. The FDA should review and provide advice on protocol designs to minimize potential misunderstandings about the appropriateness of endpoints, use of control groups, proposed methods of analysis, etc., but in the end the totality of the evidence regarding safety and efficacy for the proposed use must be considered by an independent and unbiased group of experts (i.e. Agency personnel). There must not be a presumption that agency involvement early in the process of drug development ensures, or makes more probable, a positive outcome for the sponsor when the final database may be marginal or inadequate to support the safety and efficacy of the product for the proposed use.

(a) Review of Design

We support improved communication between industry and the agency, but the 30-day deadline should be removed. It is unrealistic to expect that the Agency, with current resources, can meet with every company that requests such a meeting within 30 days, and provide a written review that is binding. These meetings would require active participation of FDA personnel at several levels, and there are far too many products under development to accommodate this section. The FDA should meet with the sponsor and provide feedback as soon as is reasonably possible.

(b) Modification of Agreements, (c) Modification of Agreements, and (d) Panel Review.

These provisions undermine FDA's authority to act to promote and protect the public health, and should be eliminated. The presumption here is that the day-to-day decisions of the FDA can be

appealed at any time. Rather, the concerns on the part of sponsors should be addressed within the internal appeals process to be established under Section 907..

TITLE IV -- EFFICIENT, ACCOUNTABLE AND FAIR PRODUCT REVIEW
SEC. 402., SEC. 741. **Content and Review of an Application**
(b) Filing Requirements
Strike. The proposed statute is unclear. Publication of guidance regarding filing requirements is appropriate, but establishing a mechanism in statute to ensure fair and consistent application is vague. Routine agency procedures, including an appropriate internal appeals process [see SEC. 907 (a)], should be adequate to promote fair and consistent application of all rules.

SEC. 403., SEC. 742 Contracts for Expert Review
A provision should be added to insure that outside contractors and consultants meet the same conflict of interest standards as full-time FDA employees. The current, strict conflict of interest provisions for FDA employees are at the core of the FDA's ability to make objective decisions. That objectivity must not be compromised by the external review process.

PROPOSED LEGISLATIVE LANGUAGE

On page 32, line 12, insert the following new subsection and renumber the following subsections accordingly:

"**(c) Conflict of Interest** -- Outside organizations and individuals with whom the Secretary contracts under this section are subject to the conflict of interest standards applicable to all Food and Drug Administration employees as provided in 45 CFR 73 subparts E, H, and I, as in effect on January 1, 1996. Outside organizations and individuals under this section are not subject to conflict of interest standards provided in 45 CFR 73 subpart J."

SEC. 404, SEC. 743. Prompt and Efficient Review.
(b) Review Procedures and Policies
Strike. To mandate a "collaborative review process" is inappropriate. The sponsor proposes (with the help of outside experts) and the agency reviews. These primary responsibilities of the regulator and the regulated industry must be kept separate, while improving communication. If the sponsor believes that an FDA employee is being unreasonable in insisting on a certain design or plan, that concern should receive prompt review within the internal appeals process to be established under SEC 907.

(2)
Strike. The frequency and/or timing of meetings between the sponsor and FDA should not be specified in the law. This is micromanagement that would impede the ability of FDA management to best utilize limited resources. This is one of many examples in the bill of requiring resource intensive micromanagement without any guidance as to where these resources are to be found.

(4)
Strike. The phrase "to bring the application into a form that would require approval," is inappropriate because not all drugs are approvable. It is the sponsor's responsibility to present an approvable package; it is not the FDA's responsibility to do the industry's work. Even it was appropriate, there are not enough resources.

(c) Approval, Disapproval and Classification
(1) Consideration of International Approvals
Strike. Language in the bill should tie improved performance to increased resources, not "hammers" that ultimately punish consumers when the agency does not meet unrealistically short and arbitrary timelines for action on applications. Provisions linking the U.S. marketing approval process to foreign approvals should be eliminated.

(2) Appeal
Strike. Judicial review of agency decisions is inappropriate.

(d) Contracts for Expert Review
(1) In General
Strike. Mandatory contracting out classes of applications for external review if at least 95% of applications do not meet unrealistic timelines is also an unwise strategy. In addition, there is no provision explaining who will pay for these external reviews. There is no evidence that external reviewers would work more quickly than internal reviewers, and they surely would not cost less.

The Agency has responded well in reducing review times when provided with increased resources and realistic performance goals (User Fee Act of 1992). There is no evidence that performance will be further improved by setting arbitrary and unrealistically short time lines, without providing additional resources.

SEC, 407, SEC. 746. Dissemination of information on drugs.
Strike. Our preferred solution to dissemination of information and reimbursement issues related to unapproved uses of approved drugs is to decrease disincentives and increase incentives for companies to perform research and submit new use supplemental efficacy applications to the agency. (See SEC. 749 below). It is unrealistic to claim that physicians receiving unsolicited information from manufacturers on new uses would carefully review the articles and have the background to question or put the results in appropriate context. If practicing physicians are typically too busy to initiate requests for information, read the literature, and/or attend meetings

to learn of new uses from less biased sources, they are unlikely to take the time (and many don't have the background or training) to evaluate carefully unsolicited information. Rather, the effects of exposure to the headline ("this drug is safe and effective for this new use") would influence his/her prescribing practices of the drug for the new use, which surely falls under the general heading of promotion.

SEC. 748. Policy on Information Dissemination

Strike. This provision should be omitted per changes to SEC. 746 eliminating the sponsor's authority to disseminate unsolicited information on off-label uses. We do not support a proposed compromise to allow dissemination once a supplemental efficacy application is filed, because that presumes approvability in advance if independent review.

SEC. 749. Approval of New Uses

Strike. It is inappropriate to allow routine approval of new uses of approved drugs based solely on common medical practice and "reliable clinical experience and other confirmatory information" per a sponsors petition reviewed by an advisory committee. This procedure undermines not only the authority of the FDA, as the advisory committee essentially makes the regulatory decision, but also calls into question the rationale for requiring evidence of efficacy from adequate and well controlled trials for *initial* uses. Flexibility in the types of proof are permissible for a subsequent use, but scientific standards should not be abolished. The history of medicine is replete with examples of therapeutics widely used by physicians that were shown, when appropriate and well-controlled trials were performed, to be of no use or even harmful. Allowing anecdotal observations to form the basis for FDA approval would elevate desire over science in the selection of marketing therapeutic products in this country.

However, we agree that off-label use and related issues of reimbursement and dissemination of information to practitioners and patients are not adequately addressed by current regulatory procedures. We recommend two important changes, both of which can occur without legislation.

First, review of supplemental efficacy applications for new uses must be reviewed more quickly at the FDA. Since it is rare that applications requesting approval of secondary uses of approved drugs are prioritized above review of original applications, we recommend that the agency review supplemental applications in a separate unit or division, where they would be a priority.

The FDA should also be more flexible in terms of what it requires to support approval of a new use. Evidence may range from traditional well-controlled trials to "paper NDAs" (compilation of published, peer-reviewed, controlled trials), depending on the inherent risk in using the product, the prevalence of use, seriousness of the disease, need for alternative therapies, etc. To develop more flexible standards that are enforced fairly and uniformly, a separate staff should be responsible for review of supplemental efficacy NDAs.

SEC. 408 Effectiveness, Outcome, and Cost-Effectiveness Standards
There are circumstances in which it may be appropriate for the agency to review a potential use not included in the labeling and the agency should not be prohibited from acting when it is appropriate.

(e)(2)
INSERT -- On page 49, in line 16 insert, following "in the labeling",

"unless --

(A) there is a compelling public health need to do so;"

SEC. 410 Alternative Approval of Supplemental New Drug Application
Strike. It is not appropriate to define the type of acceptable information in statute. The use of "may" is vague. A "paper NDA" is not necessarily adequate for approval and the FDA must make that judgement, not the sponsor. There is a range of potentially acceptable information, including paper NDAs, that could be outlined and published by the agency in guidance documents. [See Sec. 402 (d).]

SEC. 411 Pediatric Studies Marketing Exclusivity
Legislative clarification to follow. We support the intent of these provisions, though some clarification is necessary.

TITLE V -- DRUG, BIOLOGICAL PRODUCTS, DEVICES EXPORT REFORM
No changes.

TITLE VI -- DRUG AND BIOLOGICAL PRODUCTS REGULATORY REFORM

SEC. 602 New Drug Approval Standard.
We do not believe that this section of the current law needs to be amended to add another definition of substantial evidence. Clearly, the amendment as written effectively replaces the current standard, rather than just clarifying it, because it is a lesser requirement. The current standard requiring substantial evidence of efficacy from adequate and well-controlled clinical investigations (i.e., more than one) should not be replaced. Replication of experimental results is a basic tenet of good science, especially when the safety and well being of millions of potential users of a new drug depend on informed regulatory judgments. Borderline significant results from a single study cannot be confirmed or refuted with any confidence in the absence of a second controlled study. The second study increases the scientific credibility of the results and may broaden the initial approvable indication.

Most new drugs offer, at best, incremental improvement in the treatment of a given condition (e.g. improved convenience in dosing schedule) and should be thoroughly tested for safety and

efficacy before being marketed. Caution on the part of the FDA is appropriate in the evaluation of "routine" drugs, for the safety of patients is more important than getting a new, redundant agent on the market. For serious and life-threatening conditions, more risk-taking based on fewer data is appropriate, and the FDA has demonstrated its flexibility in approving such drugs on an expedited basis, best exemplified in AIDS.

When special circumstances dictate that it is in the public interest to do so, the FDA has approved drugs based on one investigation with confirmatory evidence. Such approval is technically contrary to the language of section 505 which states that "the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations..."

While the FDA has not been constrained by this provision in exceptional circumstances, if Congress is concerned that the FDA technically "breaks the law" by approving drugs based on one investigation, the law could be clarified by allowing for the exceptional circumstance where one investigation will fulfill the substantial evidence requirement. However, we are concerned that the proposed amendment in S. 1477 would make one investigation the general rule rather than the exception. In order to maintain the requirement that the efficacy standard is normally fulfilled by at least two investigations and that only in rare circumstances may one investigation meet the standard, we suggest the following amendment which parallels current law.

PROPOSED LEGISLATIVE LANGUAGE:

Section 602. New Drug Approval Standard

On page 70, delete lines 23, 24, and 25 and on page 71 delete lines 1 and 2, and insert the following:

(a) Section 505(d) (21 U.S.C. 355(d)) is amended -

(1) by adding at the end thereof the following new sentence:

"In the case of a drug to treat a serious or life-threatening disease or condition, the term "substantial evidence" may mean evidence consisting of data from a single adequate and well-controlled clinical investigation with confirmatory evidence if (1) such investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, demonstrates clear evidence of clinical efficacy based on positive impact on mortality or irreversible morbidity,

and (2) on the basis of such investigation, experts could fairly and responsibly conclude that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

■ The FACTS on the FDA's record

FACT ***The FDA evaluates new drugs, and in particular important new drugs, faster than regulatory agencies in other countries.***

The Government Accounting Office recently reported that drugs used to treat serious or life threatening conditions or that provide benefits significantly beyond those of existing products (as opposed to drugs that duplicate therapies already available to patients) are generally approved by the FDA *as quickly as or even faster than* they are approved in the U.K., Germany or Japan.

FACT ***The FDA has the premier record on keeping unsafe drugs off the market.***

From 1970 to 1992, while the U.S. withdrew approval of nine drugs for public safety reasons, the U.K. was forced to withdraw 23, Germany 30 and France 31. While none of the drugs withdrawn for health and safety reasons offered significant therapeutic advances over drugs already on the market, adverse reactions to them led to deaths and serious injuries. For example, drugs marketed as aspirin substitutes were found to cause significant adverse effects such as fatal internal bleeding, fatal skin rashes and hepatitis.

FACT ***The FDA stands alone in the world in the area of medical device protection.***

Our medical device laws were first enacted in 1976. Congress passed the laws in the wake of the Dalkon Shield disaster, in which thousands of women were rendered infertile or otherwise seriously injured by an unsafe product and its manufacturer, which delayed taking the device off of the market even after the device's dangers became apparent.

Most other countries, including the U.K., do not now have or are only now implementing medical device laws. Although comparison in terms of review times is therefore impossible, the decisions of countries such as the U.K. to enact such laws now attest to the importance of our system of rigorous product review.

FACT ***Internal FDA reform has effectively decreased the evaluation time for the vast majority of new devices.***

Ninety percent of new medical devices enter the market based on a finding of "substantial equivalence" to a product on the market before the medical device laws were enacted in 1976. Although the FDA had a substantial backlog of applications for these devices in the early 1990s, it has since eliminated the backlog.

* * * * *

DRUGS MARKETED AND WITHDRAWN IN OTHER COUNTRIES, BUT NOT APPROVED IN THE UNITED STATES AFTER 1970 AND BEFORE 1992

from Sidney M. Wolfe, MD, *Differences in the Number of Drug Safety Withdrawals*
(Public Citizen's Health Research Group, February 2, 1995)

DRUG Year Withdrawn Country	THERAPEUTIC USE	SAFETY PROBLEM
Cinepazide 1992 France	Peripheral vasodilator to increase blood flow	Caused blood disorders such as decreased production of white blood cells
Germander Extracts 1992 France	Diet aid	Liver damage
Terodilene 1991 Germany, U.K.	Bladder disorders such as incontinence	**14 deaths**; 69 serious cardiac arrhythmias (irregular heart rhythms)
Fipexide 1991 France	Psychostimulant; used for treating lethargy	Liver failure: of three persons who received liver transplants, two survived
Pirprofen 1990 France, Germany	Pain reliever; non-steroidal anti-inflammatory drug (NSAID)	Liver damage, liver failure, hepatitis resulting in **death**
Gangliosides (from cattle brain) 1989 Germany	Dementia, memory loss, nervous system failure	Drug-induced paralysis (Guillian Barre syndrome)
Exifone 1989 France	Mental function disorders in the elderly	Liver damage, hepatitis resulting in **death**
Muzolimine 1987 France, Germany	Diuretic (water pill)	Severe nervous system problems
Cyclofenil 1987 France	Fertility drug	Liver damage
Clometacin 1987 France	Pain reliever; non-steroidal anti-inflammatory drug (NSAID)	**Nine deaths** from hepatitis; 130 reports of hepatitis
Domperidone Injectable 1986 France, Germany, U.K.	Used to prevent nausea	Cardiac arrhythmia (irregular heart rhythms); **deaths reported**

DRUG Year Withdrawn Country	THERAPEUTIC USE	SAFETY PROBLEM
Bucetin 1986 Germany	Pain reliever	Kidney damage; possible kidney failure
Beta-Ethoxylacetanilanide 1986 Germany	Pain reliever	Kidney damage or failure; cancer in laboratory animals
Suloctidil 1985 France, Germany	Improve circulation, treat poor memory, dementia	67 cases of hepatitis including some deaths
Isoxicam 1985 France, Germany	Pain reliever; non-steroidal anti-inflammatory drug (NSAID)	Skin reactions such as severe skin blistering, burning, rashes, hives, or peeling
Indalpine 1985 France	Antidepressant	Blood disorders
Cianidanol 1985 France, Germany	Liver protecting agent	Breakdown of red blood cells; deaths reported
Canthaxanthin 1985 France, Germany	Skin product (dermatological)	Deposits in retina of the eye leading to loss of vision
Nitrefazole 1984 Germany	Alcohol (drinking) deterrent	Liver failure and blood disorders
Isaxonine 1984 France	Brain stimulant	Liver failure or damage
Feprazone 1984 Germany, U.K.	Pain reliever; non-steroidal anti-inflammatory drug (NSAID)	Skin problems; blood problems
Fenclofenac 1984 U.K.	Pain reliever; non-steroidal anti-inflammatory drug (NSAID)	Seven deaths; 895 adverse reaction reports including severe skin irritation reactions
Antrafenine 1984 France	Aspirin substitute	Found toxic to intestines in laboratory animals

DRUG Year Withdrawn Country	THERAPEUTIC USE	SAFETY PROBLEM
Alphaxalone and Alphadolone 1984 France, Germany, U.K.	Anesthetic agent to prevent pain	Allergic shock
Zimeldine 1983 Germany, U.K.	Antidepressant	Nerve problems, paralysis
Proglumide 1983 France, Germany	Prevent ulcers in hospitalized patients	Lung problems
Indoprofen 1983 Germany, U.K.	Pain reliever; non-steroidal anti-inflammatory drug (NSAID)	Gastrointestinal problems
Indomethacin R 1983 Germany, U.K.	Pain reliever; non-steroidal anti-inflammatory drug (NSAID)	Gastrointestinal problems; 36 deaths; 717 adverse drug reactions
Pyrovalerone 1979 France	Psychostimulant; treats lethargy	Highly addictive
Pifoxime-Pixifenide 1976 France	Pain reliever; non-steroidal anti-inflammatory drug (NSAID	Neuropsychiatric (psychiatric problems)
Practolol 1975 France, Germany, U.K.	Beta-blocker used for high blood pressure, chest pain (angina)	Serious adverse effects on the skin, eyes and mucous membranes; deafness; lupus; inflammation of the abdomen which may be fatal
Polidexide 1975 U.K.	Lower fat in the blood (anti-hyperlipidemic)	Found to cause harm in laboratory animals
Alclofenac 1975 Germany, U.K.	Pain reliever; non-steroidal anti-inflammatory drug (NSAID)	Skin problems, kidney damage, toxicity in laboratory animals
Suprifen and Tussilax 1972 France, Germany	Cough suppressant	Liver damage

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Joan Claybrook, President

FDA ROLLBACK BILLS COULD LET MANUFACTURERS OF BAD DRUGS AND COSMETICS OFF THE HOOK FOR CONSUMER INJURIES

"NATIONAL UNIFORMITY" PROVISION COULD ELIMINATE PRODUCT LIABILITY LAWSUITS

FDA ROLLBACK BILL IS LIABILITY LEGISLATION DU JOUR

With the ink barely dry on President Clinton's principled veto of the product liability bill, the Republican-controlled Congress is expanding its hypocritical attempts to deprive state judges and jurors of their legitimate rights to establish and enforce liability laws. The liability limits legislation du jour is the Food and Drug Administration (FDA) rollback bill, which goes beyond the vetoed product liability legislation by proposing total legal immunity for drug, food and cosmetic companies -- no matter how egregious or intentional the conduct.

For decades, manufacturers of bad products -- like pesticides -- have been arguing that compliance with certain federal laws and regulations immunizes them from liability in state court -- in other words, lets them off the hook for compensation to injured consumers.

Now, drug and food manufacturers are trying to weaken the FDA's regulations and then force state courts to accept the output of the crippled agency as the standard in product liability cases. This does not serve the public interest.

HIDDEN "GET OUT OF JAIL FREE CARD"

In both the House and Senate's anti-consumer legislation to rollback the safety functions of the FDA, the drug manufacturers have cleverly hidden a "get out of jail free card." The bills seek to provide uniform rules by preventing state and local governments from issuing "requirements" that conflict with federal laws and regulations. In the House bill, the uniformity provision applies to food, drugs and cosmetics. In the Senate bill, the uniformity provision applies only to non-prescription drugs.

COMPLEX LANGUAGE

Although the clear intent of the bills' authors seems to have been to provide for uniform regulatory requirements, the bills' complex language could prevent anyone injured or killed by a defective drug or cosmetic from bringing a product liability lawsuit to recover their damages. The reason is that the word "requirement" could be

interpreted to include product liability cases -- in other words, a product liability lawsuit would be interpreted as a conflicting state regulatory "requirement."

SIMILAR LANGUAGE BEING CHALLENGED IN U.S. SUPREME COURT

In fact, manufacturers of medical devices have argued that nearly identical language in the Medical Device Amendments of 1976 has precisely this effect and have sought to eliminate hundreds of claims brought by consumers injured by defective medical devices. The Supreme Court is currently considering this exact issue in the case of Medtronic v. Lohr, which was argued by Public Citizen's Litigation Group in April of this year.

INJURED CONSUMER TOTALLY BARRED FROM RECOVERING DAMAGES

No matter what the result in Medtronic, there could be two devastating consequences for consumers if this language is not removed or clarified. First, years of litigation will inevitably arise over whether the prohibition on state "requirements" bars all lawsuits against defective food, drugs and cosmetics that are federally regulated. Second, if the bill does bar these lawsuits, then those injured by the dangerously defective food, drugs and cosmetics will go uncompensated.

MORE SEVERE THAN RECENTLY VETOED PRODUCT LIABILITY BILL

The effect of this provision could go far beyond the recently vetoed product liability bill -- which, in most circumstances, limited the amount of damages an injured consumer could receive. If product liability claims are pre-empted by the FDA rollback legislation, then an injured consumer could not receive any compensation for damages.

For example, drug manufacturers would likely argue that an individual could not be compensated if her headache medicine caused liver damage; or, a senior citizen could not be compensated if she was poisoned by an arthritis medicine that was contaminated during production due to poor manufacturing processes; or, an individual could not sue for injuries caused by unsafe allergy medicine for which the manufacturer obtained FDA marketing approval only by hiding information from the FDA.

WHERE THERE IS SMOKE THERE IS FIRE

One of main forces behind the FDA rollback legislation is the tobacco industry -- longtime leader of the liability limits movement and currently the target of both FDA proceedings and liability trials.

ATTACKING THE INDEPENDENCE OF THE CITIZEN JURY

The motivation for the manufacturers' effort lies in the independence of the jury

system. Unlike legislators, judges are rarely influenced by campaign contributions and bribing jurors is illegal. Judges and jurors are also free from the influence of corporate lobbyists -- who wine and dine regulators and use their gross imbalance of advocacy resources to weaken regulations -- and the lure of the corporate revolving door. Indeed, America's civil justice system is often the only place where an individual citizen can effectively challenge raw corporate financial and political power.

WASHINGTON KNOWS BEST

This is the preemption game at its cruelest. Consolidate power in the hands of Washington lawmakers and bureaucrats, use that power to pass laws to weaken health and safety regulations, and then use the federal laws and regulations to deny state legislators, judges and citizen jurors from exercising their legitimate states' rights.

PRODUCT LIABILITY LAWSUITS COMPLEMENT FDA REGULATIONS

FDA regulations are not a substitute for product liability lawsuits: the FDA regulates while courts compensate.

NO JUSTIFICATION

There is simply no justification for this extraordinary step of statutory immunity that would reverse long-established state protections for consumers -- especially for the thriving, highly profitable pharmaceutical industry. Congress should reject this extreme legislation.

For more information, contact Public Citizen's Congress Watch at (202) 546-4996.

CSPI CENTER FOR SCIENCE IN THE PUBLIC INTEREST
Publisher of *Nutrition Action Healthletter*

S. 1477: FOOD SAFETY & THE FUTURE OF FDA

In mid-May the Senate will vote on Senate bill 1477, the Food and Drug Administration (FDA) Performance and Accountability Act. The bill is an aggressive attack on FDA and it's authority to maintain tough U.S. food-safety standards.

The food and drug industries are trying to privatize as many FDA functions as possible. They want to get FDA off their backs and turn some of its key public health responsibilities -- like inspecting food processors for unsafe conditions or approving new food additives -- over to outside groups. These groups could be largely made up of scientists and companies with ties to the food and drug industries.

S. 1477 is the single biggest threat to the independence of FDA that we have seen in the history of the agency's existence. In the era of Mad Cow Disease we need stronger -- not weaker -- government agencies protecting us from unsafe food.

S. 1477 allows FDA to certify outside groups to conduct food safety inspections. This means that Congress would rather privatize inspections than increase FDA's funding to improve it's ability to keep our food supply safe. And companies could get inspectors-for-hire to check their companies for food-safety violations. Only the FDA should do government sanctioned food-safety inspections.

S. 1477 would privatize the approval of new food additives. Whenever FDA falls behind in approving new additives, private review panels would get to decide whether the new additives are safe. The panel could be largely composed of scientists who work directly for or receive grants from the food industry. You don't have to be a rocket scientist to figure out that a panel stacked with industry consultants will likely favor companies seeking product approvals.

Finally, S. 1477 would reduce the FDA's policing authority over misleading health claims. S. 1477 could result in a plethora of inconsistent and potentially misleading health claims on food. Now, only FDA can approve health claims. It should stay that way.

CSPI also opposes two amendments that will be offered by Sen. Judd Gregg (R-NH) that would make S. 1477 even worse. The first amendment provides that the safety findings of a third-party panel regarding a new food additive creates a "presumption of approvability," shifting the burden of proof. Instead of forcing a company to prove that the new additive is **safe**, FDA would have to demonstrate that the food additive is dangerous.

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Executive Director: *Michael Jacobson, Ph.D.*

The second Gregg amendment would prohibit states from issuing their own food labeling laws. It would void Vermont's disclosure requirement regarding bovine growth hormone in milk, Ohio's freshness dating law, California's requirement for label warnings about dangerous contaminants, and kosher food labeling laws in New York, Massachusetts, Rhode Island, and Illinois.

For more information, contact Caroline Smith DeWaal, Director of Food Safety, (202) 332-9110, ext. 366.

Public Citizen

FDA ROLLBACK PROPOSALS (S. 1477) AND WOMEN'S HEALTH

Senator Nancy Kassebaum (D-KS) has introduced a bill, S.1477, which would diminish the Food and Drug Administration's authority to protect the public from unsafe and ineffective drugs and medical devices. Although all Americans face significant dangers if the legislation is passed, the Kassebaum proposal presents a number of concerns particular to women.

I. The FDA's Current Authority Is a Direct Response to Corporate Indifference to Women's Health: Much of the FDA's current authority traces its roots to two health care disasters, both of which involved products marketed almost exclusively to women.

First, the 1962 amendments to the Food, Drug, and Cosmetic Act, which expanded the agency's power to require it to consider the effectiveness of new drugs, as well as safety, were written in the wake of the thalidomide tragedy. Between 1959 and 1961, thalidomide was widely prescribed overseas as a morning sickness sedative for pregnant women. The drug caused gruesome birth defects in approximately 10,000: some babies were born with no arms, just flippers extending from the shoulders; others had limbless trunks with toes extending from their hips; others were born with just a head and a torso.

This tragedy was averted in the United States by the careful review of a skeptical medical officer, who delayed approval of the drug's marketing application. (Some American women received the drug in investigational trials.) Then, following reports that thalidomide was causing thousands of severely deformed babies, Congress held hearings and passed amendments requiring that companies meet stringent scientific standards of proof that drugs are safe and effective before they can be sold in the U.S.

Second, medical devices -- from pacemakers, to bone screws, to tampons -- were essentially unregulated until 1976, when Congress passed the Medical Device Amendments. That law was enacted in response to the Dalkon Shield disaster, wherein A.H. Robins marketed a defective contraceptive intrauterine device to 2.3 million American women. By the time the company withdrew its product from the market, tens of thousands of women had been rendered infertile or otherwise injured by the device. At least 15 women died of their injuries. In the wake of this fiasco, Congress gave the FDA authority to regulate medical devices.

II. The Kassebaum Proposal Threatens To Take Women's Health Back To The Days When Poorly Tested Products Caused Serious Harm

A. Semi-automatic Approval Of U.K. or European-Approved Medical Products Will Increase The Likelihood That Unsafe Products Reach American Patients.

The Kassebaum proposal would force the FDA to reduce the review time for new

products by one-third or more, without providing any additional funding to hire staff. If the FDA missed a deadline for making a final decision on a new product application, the manufacturer could petition the FDA for automatic approval of that product if it had been approved in the U.K. or a European country. Unless the FDA specifically denied the entire application within 30 days, the medical product would be marketed here.

Yet, the FDA has done a much better job keeping unsafe drugs off the market than have European governments. From 1970 to 1992 the U.S. withdrew approval of 9 drugs for public safety reasons, the U.K. was forced to withdraw 23, Germany 30, and France 31. The European safety withdrawals included a number of drugs prescribed primarily for women, with serious and sometimes fatal consequences:

- **Cyclofenil**: Cyclofenil was marketed in France to enhance fertility in women. Because the drug caused liver damage in a number of women, France withdrew marketing approval in 1987.

- **Terodiline**: Urinary incontinence affects women far more often than men, particularly elderly women, pregnant women, and women immediately post-partum. Terodiline was marketed in Germany and the U.K. as a treatment for urinary incontinence, but withdrawn after 69 reports of serious cardiac arrhythmias, including 14 deaths.

- **Zimeldine and Indalpine**: Women are almost twice as likely as men to be diagnosed with depression. In Europe, at least two unsafe anti-depressants received marketing approval in the 1980s. The U.K. approved the anti-depressant Zimeldine and then, in 1983, withdrew marketing approval because the drug caused liver toxicity and was associated with Guillain Barre paralysis, which causes numbness and paralysis in the hands, feet, arms and legs. France approved the anti-depressant Indalpine and then, in 1985, withdrew approval because the drug caused blood disorders.

Thus, the Kassebaum proposal would replace the standards of the FDA, the premier drug safety agency in the world, with European standards that have a significantly worse track record in protecting women from unsafe products.

Moreover, the EC is converting to a Europe-wide approval system, based on a new and untested organization for drug approval. Our effective product review process cannot be sacrificed to a European experiment with no track record at all.

B. The Kassebaum Bill Will Sharply Reduce The "Effectiveness" Testing Requirements for New Prescription Drugs.

Less clinical testing means we will know less about the physiological differences and less about gender-specific responses to drugs between men and women. For example, women tend to metabolize certain anti-hypertensive and cardiovascular drugs at a slower rate than men, and both naturally-occurring female hormones and oral contraceptives cause other drugs to act differently in women than in men. Yet drug

companies and other researchers have historically slighted the specific needs of women when studying drug safety and efficacy.

In 1992, the General Accounting Office released a study of drugs approved by the FDA over a 3 1/2 year period, and found that although women were included in clinical trials for all the drugs surveyed, they were generally under-represented in those trials. Of the drugs studied, one-third had too few women enrolled in trials to yield accurate information on differences in gender response to the drug. Moreover, even when enough women were included, manufacturers often did not analyze whether women responded differently to the drug than did men.[1]

The Kassebaum bill would allow the FDA to accept the results of a single clinical trial to prove the "effectiveness" of a new drug and even that trial could be waived. Given the already insufficient attention to women's health in clinical testing, reducing the number of trials would increase the likelihood that inadequate data on proper dosages for women and safety and efficacy problems peculiar to women will be collected and analyzed.

C. Promotion of Unapproved Uses Invites Disaster

FDA approves drugs to be used for specific conditions. Although physicians may nonetheless prescribe drugs for any use, critics of the agency argue that patients are denied life-saving therapies because pharmaceutical companies may not promote their products for unapproved uses. Responding to this criticism, the Kassebaum bill would change the restrictions on off-label promotion by allowing companies to distribute studies purporting to show the effectiveness of drugs for off-label uses.

Such a change would undermine the approval process and allow companies to substitute preliminary research for the sound science required by the FDA approval process. This inevitable consequence is particularly dangerous in the case of women's health, because so many products are used "off-label" in treating women.

For example, obstetrician-gynecologists routinely prescribe Terbutaline to stop pre-term labor. Approved by the FDA for treatment of asthma, Terbutaline relaxes the smooth muscles of the body. Yet at least 14 deaths are associated with use of Terbutaline and a similar pregnancy drug.

Allowing promotion of drugs for off-label uses will increase the chance of harm to patients, both because the drug may not be safe for the off-label use and because the drug may be ineffective for that use and, thus, leave the condition untreated. If the manufacturer has evidence that the drug is in fact safe and effective for the unapproved use, the company should be encouraged to submit a supplemental use applications to the

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[1] *Women's Health: FDA Needs to Ensure More Study of Gender Differences in Prescription Drug Testing*, Washington, U.S. General Accounting Office GAO/HRD-93-17, Oct. 1992, at 3.

AIDS Clinical Trials Information Service

Providing the Latest Information on Clinical Trials for HIV and AIDS

1-800-TRIALS-A

The AIDS Clinical Trials Information Service (ACTIS) is a central resource providing current information on federally and privately sponsored clinical trials for AIDS patients and others infected with HIV. This free service is a Public Health Service (PHS) project provided collaboratively by the Centers for Disease Control and Prevention, the Food and Drug Administration, the National Institute of Allergy and Infectious Diseases, and the National Library of Medicine.

AIDS clinical trials evaluate experimental drugs for adults and children at all stages of HIV infection—from patients who are HIV-positive with no symptoms to those with various symptoms of AIDS. Clinical trials also evaluate vaccines for adults at all stages of HIV infection and for adults who are not HIV positive.

Access Up-to-Date, Accurate Information

The AIDS Clinical Trials Information Service is free and easy to use—one toll-free number puts callers in touch with experienced health specialists who provide information about AIDS clinical trials. These specialists access a database featuring information on AIDS studies currently underway.

The Service's health specialists are available to answer questions from individuals infected with HIV, their families, and health professionals. A bilingual specialist is available to talk to Spanish-speaking callers. Specialists provide information on:

- Purpose of the study protocol
- Studies that are open
- Eligibility requirements (inclusion/exclusion criteria)
- Participating centers
- Names and telephone numbers of contact persons
- Study drugs
- Results of trials which have been completed

Callers can receive this information over the telephone; also available, on request, are searches of the clinical trials database. The information can also be accessed directly through two online databases, AIDSTRIALS and AIDSDRUGS, available through the National Library of Medicine, by calling 1-800-638-8480 or 301-496-6193 in Maryland.

1-800-TRIALS-A (1-800-874-2572)

The toll-free line is available in the U.S., U.S. territories, and Canada

International number: 1-301-217-0023

Deaf access number: 1-800-243-7012 (TDD)

A service of the U.S. Department of Health and Human Services, Public Health Service. The National Institute of Allergy and Infectious Diseases, the Food and Drug Administration, the National Library of Medicine, and the Centers for Disease Control and Prevention have collaborated to provide this service.

A Cooperative Project of PHS Agencies

The AIDS Clinical Trials Information Service, provided free of charge as a public service, is a cooperative effort by several PHS agencies:

- **National Institute of Allergy and Infectious Diseases (NIAID).** NIAID has the major responsibility for funding federally sponsored AIDS clinical trials and supports a nationwide network of AIDS Clinical Trials Units, enrolling thousands of patients. The database includes all NIH-sponsored AIDS clinical trials as well as studies sponsored by other institutes.
- **Food and Drug Administration (FDA).** As the Federal agency responsible for evaluating and approving new therapies, the Food and Drug Administration grants permission to pharmaceutical companies to test experimental drugs and biologic products in humans, monitors the progress of those trials, and reviews the results of the studies. Every experimental treatment undergoing clinical testing for effectiveness in treating AIDS or AIDS-related conditions in FDA-approved trials is included in the ACTIS database.
- **National Library of Medicine (NLM).** The National Library of Medicine makes the information in the database available to its world-wide network of users through its online services.
- **Centers for Disease Control and Prevention (CDC).** The CDC National AIDS Clearinghouse, sponsored by the Centers for Disease Control and Prevention, operates the toll-free AIDS Clinical Trials Information Service.

What Is an AIDS Clinical Trial?

An AIDS clinical trial is a study conducted to help find effective therapies to treat people infected with HIV, the virus that causes AIDS.

Patients choose to take part in clinical trials for many reasons. Usually patients hope for benefits for themselves—a cure for the disease, a longer time to live, a way to feel better. Joining a study means taking positive action. Many want to contribute to a research effort that may help others.

AIDS clinical trials for experimental therapies follow strict guidelines to protect participants' privacy and safety.

Why Are Clinical Trials Important?

AIDS clinical trials fill an urgent need to find ways to treat the millions of people who are or who will be infected with HIV. Clinical trials provide important information about new treatments—benefits and risks, effectiveness, and dosages.

Clinical studies also help improve patient care by identifying which treatments and drugs work best. Many new therapies are designed on the basis of what has worked in past trials.

Can Anyone with HIV Infection Join a Clinical Trial?

To be eligible to participate in an AIDS clinical trial, an individual must meet the study's eligibility criteria. Eligibility criteria are different for each study and may include a person's age, symptoms of HIV infection or other illnesses, laboratory test results, and past treatments. Applicants for clinical trials are evaluated on an individual basis by the study's clinical investigator and other health care providers.

CDC NAC Inventory No. B515

June 1995

NEW INFORMATION FROM ACTIS

The AIDS Clinical Trials Information Service (ACTIS) is a central resource providing current information on federally and privately sponsored clinical trials for AIDS patients and others infected with HIV. This service is a Public Health Service project produced collaboratively by the Centers for Disease Control and Prevention, the Food and Drug Administration, the National Institute of Allergy and Infectious Diseases, and the National Library of Medicine. NAC ONLINE, the computerized information service of the CDC National AIDS Clearinghouse, will alert you to any new information collected by ACTIS.

A description of the most recent clinical trial added to the ACTIS database is provided below.

For more information, call the ACTIS toll-free number to talk with a health specialist. On request, you can also obtain a printout of a customized search of the clinical trials databases. The information can also be accessed directly by subscribers through two online databases, AIDSTRIALS and AIDSDRUGS, available through the National Library of Medicine.

AIDS CLINICAL TRIALS INFORMATION SERVICE
1-800-TRIALS-A
(1-800-874-2572)
FAX: 1-301-738-6616
TTY/TDD: 1-800-243-7012
International Line: 1-301-217-0023

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PROTOCOL NUMBER: NCI 95 C-183.

TITLE: A Pilot Study of Recombinant Interleukin-2 (IL-2) in Children and Adolescents With Human Immunodeficiency Virus Infection.

PHASE: Pilot Study.

DISEASE STATUS:
Patients have the following symptoms and conditions: 1. Documented HIV infection. 2. No new or active opportunistic infection at study entry requiring acute intervention. 3. CD4 count 500-1000 cells/mm3 if 2-5 years of age or 200-500 cells/mm3 if 6 years or older. 4. Either asymptomatic with CD4 count that renders them at risk for AIDS-related opportunistic infection OR mild to moderately symptomatic. NOTE: Previously treated patients may have progressive disease or intolerance to prior therapy.

PATIENT INCLUSION CRITERIA

SPECIFICATION CRITERIA:
Patients must have:
1. HIV infection.

2. No new or active opportunistic infection.
3. CD4 count 500-1000 cells/mm3 if 2-5 years of age or 200-500 cells/mm3 if 6 years or older.
4. Consent of parent or guardian unless over the age of consent or an emancipated minor.

AGE: 02 Years - 21 Years.
SEX: M. F.

REPRODUCTIVE SPECIFICATION:
Not pregnant. Negative pregnancy test within 14 days of study entry.

LABORATORY VALUES AT ENTRY

CD4 (T4 CELL) COUNT: 500 - 1000 cells/mm3. if two-five years old. (500 - 600 - 700 - 800 - 900 - 1000). OR 200 - 500 cells/mm3 if six years or older. (200 - 300 - 400 - 500).

PATIENT EXCLUSION CRITERIA

SPECIFICATION CRITERIA:
Patients with the following prior conditions are excluded:
1. Prior intolerance to AZT at 90 mg/m2 every 6 hours or ddI at 60 mg/m2 every 12 hours.
2. Prior need for therapy to maintain hemoglobin > 8.0 g/dl or neutrophils > 1000 cells/mm3 while on antiretrovirals.

AGE: 01 Days - 01 Years. 22 Years - 99 Years.

REPRODUCTIVE SPECIFICATION:
Pregnant. Positive pregnancy test within 14 days of study entry.

CO-EXISTING CONDITIONS OR DISEASES:
Patients with the following symptoms or conditions are excluded:
1. Critically ill or medically unstable.
2. Current clinical HIV disease progression on combination AZT/ddI.
3. Allergic symptoms to AZT or ddI.
4. Active peripheral neuropathy.
5. Static or progressive encephalopathy.
6. Seizure disorder.
7. Concurrent malignancy or significant autoimmune disease.
8. Concurrent participation in an HIV vaccine trial.
9. Lymphoid interstitial pneumonitis (LIP) requiring treatment with systemic corticosteroids.
10. Pancreatitis.

GENERIC DRUG NAME

Drug 1: Aldesleukin. Immunomodulator.

Drug 2: Zidovudine. Antiretroviral.
Drug 3: Didanosine. Antiretroviral.

DRUG TRADE NAME

Drug 1: Proleukin.
Drug 2: Retrovir.
Drug 3: Videx.

DRUG COMPANIES

Drug 1: Chiron Corporation
4560 Horton Street
Emeryville, CA 94608
Contact: Professional Services (510) 601-3440.

Drug 2: Glaxo Wellcome
5 Moore Drive / PO Box 13398
Research Triangle Park, NC 27709
Contact: Department of Consumer Affairs (800) 437-0992 X 7900.

Drug 3: Bristol - Myers Squibb Company
2400 West Lloyd Expressway
Evansville, IN 47721-0001
Contact: Information (800) 662-7999.

END POINT

Toxicity, pharmacokinetic profile.

DISCONTINUE TREATMENT

Patients discontinue treatment for the following reasons:
1. Cessation of antiretroviral treatment.
2. Unacceptable toxicity.
3. Development of infection that delay IL-2 therapy.
4. HIV disease progression after 12 weeks of IL-2.
5. Development of malignancy that requires systemic therapy.
6. Pregnancy.
7. Patient noncompliance or desire to withdraw from study.

PARTICIPATING UNITS

0000001821:
National Cancer Institute

9000 Rockville Pike Clinical Center
Bethesda, MD 20892
Contact: Susan Sandelli (301) 402-1391
Contact: (301) 402-1387
OPEN / USA accrual 951201.

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AIDS CLINICAL TRIALS INFORMATION SERVICE
CUSTOM SEARCH SERVICE

DATE: Jun 12, 1996

REQUESTOR: Jess Bloom

SEARCH: Sample - Open Adult Trial

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The Public Health Service makes this information available on AIDS clinical trials as a public service only. The Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), and the National Institute of Allergy and Infectious Diseases have coordinated their efforts and resources to make this information easily available. Included are trials that are federally funded, as well as those sponsored by drug companies and other private or public sources.

Information submitted to this database through the FDA is determined in part by the requirements of the Health Omnibus Programs Extension Act of 1988 which requires sponsors of AIDS clinical trials that are tests for efficacy to submit certain information. Sponsors may also submit additional information voluntarily and may include information on trials other than those for efficacy. As a result, variations will be noted in the amount and type of information included in the protocols.

While every attempt is made to include the studies most relevant to the requester, inclusion of specific protocols does not guarantee eligibility or patient entry. Also, inclusion does not imply that these protocols are the appropriate treatment for a particular patient or that the safety or the effectiveness of the product is established. Listing of a trial in this database does not reflect judgements by FDA about the outcome of the study, or guarantee approval of the drug(s) involved.

The database is updated regularly by information provided by the sponsoring agencies in order to keep the information as current and accurate as possible. However, the contact persons listed in this search are the best sources of information on the most current status of the studies. Individuals should discuss their treatment options with their physician prior to enrolling in a trial.

Protocol Number:
NINDS 93 N-30.
Version Number and Approved Date:
(940520).
Other Applicable Identification Numbers:
None given.
Title:
The Efficacy of Oral Levocarnitine (L-Carnitine) Therapy on Zidovudine-Induced Myopathy: A Double-Blind, Placebo-Controlled Trial.
Categories of Trials:
Neurologic Manifestations.
Asymptomatic.
Protocol Chair:
Dulakas M.
Protocol Co-Chair:
Cupler E.
Protocol Summary:
Purpose:
To evaluate the effects of levocarnitine (L-carnitine) on zidovudine (AZT)-induced myopathy in patients currently receiving AZT therapy for HIV infection.
Rationale:
Some HIV-infected patients receiving AZT therapy develop a medication-induced muscle disease called myopathy. Current recommendations usually are to decrease or discontinue AZT therapy, but since AZT is the most effective treatment of HIV infection currently available, a therapy for the side effect of muscle disease would be highly beneficial.
Methodology:
Patients who are receiving AZT and experiencing myopathy are randomized to receive either oral L-carnitine or placebo thrice daily for 6 months. Patients will undergo two muscle biopsies in addition to EMG and nerve conduction studies, blood studies, and muscle strength and function assessments. A total of five clinic visits (visits for screening, for the initial biopsy, and at months 2, 4, and 6) will be required. Patients will also need to complete questionnaires at home every 2 weeks. At the end of 6 months, patients on the placebo arm may receive 6 months of L-carnitine on an optional basis, provided benefit was shown.
Sponsoring Agency(ies):
National Institute of Neurological Disorders & Stroke.
Phase:
Phase II.
Study Intent:
Drug efficacy.
Study Design:
Randomized; Double-Blind; Placebo-Controlled.
Hospitalization:
Outpatient.
Protocol Status:
Open: Actively accruing patients (940520).
Projected Accrual:
OPEN patients.
Duration of Patient on Study:
Minimum of 6 months.

Number of Participating Agencies:
1 unit.
MESH Headings:
AIDS-Related Complex -- *complications.
Acquired Immunodeficiency Syndrome -- *complications.
Adult.
Aged.
Carnitine -- *therapeutic use.
Female.
HIV Infections -- *complications.
Human.
Male.
Middle Age.
Muscles -- *pathology.
Muscles -- drug effects.
Muscular Diseases -- *chemically induced.
Muscular Diseases -- complications.
Muscular Diseases -- pathology.
Zidovudine -- adverse effects.
Disease(s) Studied:
Myopathy.
Eligibility:
ASYM. ARC. AIDS.
Disease Status:
Patients have the following symptoms and conditions:
1. Current AZT therapy for HIV infection and intending to remain on AZT therapy for the duration of the study.
2. Biopsy-proven AZT-induced myopathy. Clinical signs of AZT-induced myopathy may include muscle weakness, muscle shrinkage, fatigue, decreased endurance, muscle pain, abnormal elevation of creatine kinase, or evidence of muscle disease by EMG.
Inclusion Specification Criteria:
Patients must have:
1. Current AZT therapy for HIV infection.
2. Diagnosis of AZT-induced myopathy.
[Refer to Laboratory values for additional requirements.]
CD4 (T4 Cell) Count:
Unspecified cells/mm3.
Inclusion Age:
18 Years - 99 Years.
Inclusion Sex:
M. F.
Inclusion Prior Medication:
Required: Prior AZT.
Inclusion Concurrent Medication:
Required: AZT.
Exclusion Specification Criteria:
[Refer to Laboratory values for additional requirements.]
Exclusion Age:
01 Days - 17 Years.
Drug Accession Number(s):
Drug 1: DRG-0211.
Generic Drug Name:
Drug 1: Levocarnitine. Antihyperlipoproteinemic.
Dosage Schedule:
Drug 1: Drug or placebo thrice daily for at least 6 months.

Mode of Delivery:
Drug 1: Oral.
Duration of Drug Administration:
6 months.
Drug Company(ies):
Drug 1: Drugs are provided by each participating unit site
.
Participating Units:
0000003108:
National Institute of Neurological Disorders & Stroke
9000 Rockville Pike / Clinical Center / Room 4N248
Bethesda, MD 20892
Contact: Dr Edward Cupler (301) 402-1931
OPEN / USA Accrual 940520.
Verification Date:
940607.

AIDS CLINICAL TRIALS INFORMATION SERVICE
CUSTOM SEARCH SERVICE

DATE: Jun 12, 1996

REQUESTOR: Jess Bloom

SEARCH: Sample - Drug Record Used in the Trial

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The National Institute of Allergy and Infectious Diseases makes this information available as an adjunct to the Protocol Database. Information on the drugs used in the AIDS Clinical Trials Information Service (ACTIS) Protocol Database has been compiled from public sources as a service to ACTIS users. This information is also available through the National Library of Medicine's MEDLINE information service under the file name AIDSDRUGS.

Information contained in this drug record has not been reviewed by the Food and Drug Administration and should not be construed as representing FDA-approved product information. None of the investigational products listed in the Drug File have been proven safe or effective for the indication under investigation.

Accession Number:
DRG-0211.

Generic Name:
Levocarnitine (USAN 1996 p 397).

Alias/Trade Name:
L-carnitine (CHEMLINE). Vitamin BT (Merck Index 1989 p 281). Cardiogen (Merck Index 1989 p 281). Carnitene (Merck Index 1989 p 281). Carnicor (Merck Index 1989 p 281). Carnitor (USAN 1996 p 397). Carrier (Merck Index 1989 p 281). Levocarnil (Merck Index 1989 p 281). Metina (Merck Index 1989 p 281). VitaCarn Liquid (Drug Evaluations Annual 1995 p 2505). Carnitine (L-Form) (CHEMLINE).

Therapeutic Classification:
Antihyperlipoproteinemic (Merck Index 1989 p 281).

AIDS-Related Uses:
Zidovudine-induced myopathy resulting from carnitine deficiency. (NINDS 93 N-30)

Drug Company(ies):
Drugs are provided by each participating unit site

Pharmacology:
MODE OF ACTION: Carrier molecule in the transport of long chain fatty acids across the inner mitochondria, delivering substrate for oxidation and subsequent energy production. Fatty acids are utilized as an energy substrate in all tissues except the brain. The mean distribution half-life for a 20 mg/kg IV dose was 0.585 h and the mean apparent terminal elimination half-life of total levocarnitine was 19.4 h. Mean renal clearance was about 3.0 L/h; 85% of the dose was excreted as total levocarnitine in 24 h.
(PDR 1995 p 2340; J Pharm Sci 1995 Apr;84(5) p 634-35)

Drug Interactions:
Levocarnitine can be competitively inhibited by D,L-carnitine; requirements for levocarnitine may be increased in patients receiving valproic acid.
(Drug Evaluations Annual 1992 p 2190; USP DI 1995 p 1715)

Adverse Effects/Toxicity:
Adverse effects include mild gastrointestinal complaints, including transient nausea and vomiting, abdominal cramps, and diarrhea; and drug-related body odor.
(PDR 1995 p 2340)

Dosage Form:
330 mg tablets; oral solution, 1 g/10 ml; 5 ml ampuls (1 g/5 ml) for injection.
(PDR 1995 p 2340-41)

Mode of Delivery:
Oral; intravenous. (PDR 1995 p 2340-41)

Storage Instructions:
Tablets, injections and oral solutions; store at 25 C. Protect ampules from light.

(USP DI 1995 p 1715-16)

Bibliographic References:

Mintz M. Carnitine in human immunodeficiency virus type 1 infection/acquired immune deficiency syndrome. J Child Neurol. 1995 Nov;10 Suppl 2:S40-4.

Famularo G, De Simone C. A new era for carnitine? Immunol Today. 1995 May;16(5):211-3.

Vitale G, Parente R, Melotti C. Carnitine supplementation in human idiopathic asthenospermia: clinical results. Drugs Exp Clin Res 1995;21(4):157-9.

Semino-Mora MC, Leon-Monzon ME, Dalakas MC. Effect of L-carnitine on the zidovudine-induced destruction of human myotubes. Part I: L-carnitine prevents the myotoxicity of AZT in vitro. Lab Invest. 1994 Jul;71(1):102-12.

Semino-Mora MC, Leon-Monzon ME, Dalakas MC. The effect of L-carnitine on the AZT-induced destruction of human myotubes. Part II: Treatment with L-carnitine improves the AZT-induced changes and prevents further destruction. Lab Invest. 1994 Nov;71(5):773-81.

De Simone C, Famularo G, Tzantzoglou S, Trinchieri V, Moretti S, Sorice F. Carnitine depletion in peripheral blood mononuclear cells from patients with AIDS: effect of oral L-carnitine. AIDS. 1994 May;8(5):655-60.

Dalakas MC, Leon-Monzon ME, Bernardini I, Gahl WA, Jay CA. Zidovudine-induced mitochondrial myopathy is associated with muscle carnitine deficiency and lipid storage. Ann Neurol. 1994 Apr;35(4):482-7.

De Simone C, Tzantzoglou S, Famularo G, Moretti S, Paoletti F, Vullo V, Delia S. High dose L-carnitine improves immunologic and metabolic parameters in AIDS patients. Immunopharmacol Immunotoxicol. 1993 Jan;15(1):1-12.

Grau JM, Casademont J, Pedrol E, Fernandez-Sola J, Cardellach F, Barros N, Urbano-Marquez A. Chronic fatigue syndrome: studies on skeletal muscle. Clin Neuropathol. 1992 Nov-Dec;11(6):329-32.

De Simone C, Tzantzoglou S, Jirillo E, Marzo A, Vullo V, Martelli EA. L-carnitine deficiency in AIDS patients. AIDS. 1992 Feb;6(2):203-5.

SENATE REPORT

these approaches may also be useful for nonscientific issues that may arise during the regulatory process. The provisions of the Federal Advisory Committee Act, which require a Federal charter and public meetings, do not apply under these circumstances.

For the same reasons that prompt decisions are required after scientific review group meetings, a decision must also be made within 60 days after any matter that is presented for resolution as part of the internal appeal system has been the subject of conclusions and recommendations.

Appointment and term of the commissioner of food and drugs

At present, the commissioner of Food and Drugs is appointed by the President, with the advice and consent of the Senate, to serve an unlimited term and serves at the pleasure of the President. As part of the provisions to achieve greater FDA accountability to the American public and to congress, the legislation imposes a limit of 1 term, for 5 years, on future commissioners. The President could elect to reappoint a commissioner to another term, but the appointment would be subject to Senate reconfirmation. To insulate the position of the commissioner from political considerations, the legislation provides that the President may remove a Commissioner only on a finding of neglect of duty or malfeasance. These provisions do not apply to the individual serving as commissioner when this legislation is enacted.

TITLE II—EXPEDITED ACCESS TO PRODUCTS FOR SERIOUSLY ILL PATIENTS

Access to unapproved therapies

For many years, the rights of patients who need access to unapproved therapies went unrecognized under the Federal Food, Drug and Cosmetic Act. The FDA established informal policies relating to compassionate use of investigational products shortly after enactment of the 1938 act, but these policies remained informal and outside FDA regulations until recently.

The committee commends the FDA for the programs it has put in place to ensure that individuals with AIDS have access to promising new investigational therapies and for its recently announced initiative to expand access to experimental therapies for cancer patients.

The committee wishes to extend opportunities of this nature to every individual with a life-threatening or seriously debilitating illness for which there is not an effective, approved therapy. The legislation establishes in statute, the right of any person, through a licensed health care practitioner or licensed health care professional, to request access to an unapproved therapy, and the right of any manufacturer or distributor to provide that unapproved therapy, if it is for the diagnosis, monitoring, or treatment of a serious disease or condition, an immediately life-threatening or seriously debilitating disease or condition, or any other disease or condition designated by the FDA as appropriate for expanded access.

The person requesting the unapproved therapy must show that there is no comparable or satisfactory alternative, the risk from the investigational product is not greater than the risk from the disease, there is an investigational protocol in effect under the Federal Food, Drug, and Cosmetic Act, and an expanded access protocol has been approved by the FDA. A manufacturer or distributor may decline to make an investigational product available under such a program.

To induce manufacturers and distributors to make investigational therapies available for patients who need them under these circumstances, the legislation provides that they may charge for up to the amount necessary to recover the costs of manufacture and handling of the unapproved drug or device, provided the Secretary is notified in advance of assessing such charges.

Consistent with the desire of the committee to help ensure that patients with serious conditions and no realistic alternative treatments have available to them investigational products that may offer some promise of help, the legislation requires the Commissioner to inform the medical profession and such groups as voluntary health associations about the availability of investigational products for expanded access use. Too often, patients and their physicians are unaware that new therapies are under investigation and are available for expanded use pending review by the FDA. This provision will help to ensure that all patients will have equal knowledge of and access to investigational products.

The committee emphasizes that it has purposely used broad language in this section relating to "serious" conditions, without attempting to define them, in order to permit wide flexibility in implementation. Illnesses that do not cause death can nonetheless destroy the lives of both patients and their families. The committee therefore intends that the seriousness of an illness be given broad consideration, to take into account all of the circumstances involved.

Expanding humanitarian use of devices

The Safe Medical Devices Act of 1990 included a new provision authorizing the use of devices for humanitarian purposes for small populations of targeted patients for whom products are not generally available to treat or cure a condition or disease. This provision permits device approval based on specified safety criteria and exempts effectiveness showings from approval requirements. The provision requires the Secretary to issue implementing regulations within 1 year. The Secretary proposed regulations in December 1992 but has not promulgated final regulations in the intervening 3½ years, despite repeated assurances that the regulations would be forthcoming. The legislation therefore terminates the requirement for final regulations and provides that the Secretary must approve or deny an application for a humanitarian device within 30 days—the same time period required for a response to an investigational device exemption application, which similarly requires a finding of safety by the agency.

The legislation also eliminates current-law provisions that provide for an 18-month limit on the period that a humanitarian device exemption may be in effect and the current-law limitation of 5 years on the authority of the Secretary to provide humanitarian

make grants to, and enter into contracts with, public and nonprofit private entities to assist such entities in planning, establishing, or strengthening, and providing basic operating support for, centers for basic and clinical research into, and training in, advanced diagnostic, prevention, and treatment methods for acquired immune deficiency syndrome.

(2) A grant or contract under paragraph (1) shall be provided in accordance with policies established by the Secretary, acting through the Director of the National Institutes of Health, and after consultation with the advisory council for the National Institute of Allergy and Infectious Diseases.

(3) The Secretary shall ensure that, as appropriate, clinical research programs carried out under paragraph (1) include as research subjects women, children, hemophiliacs, and minorities.

(b) USE OF FINANCIAL ASSISTANCE.—

(1) Financial assistance under subsection (a) may be expended for—

(A) the renovation or leasing of space;

(B) staffing and other basic operating costs, including such patient care costs as are required for clinical research;

(C) clinical training with respect to acquired immune deficiency syndrome (including such training for allied health professionals); and

(D) demonstration purposes, including projects in the long-term monitoring and outpatient treatment of individuals infected with the etiologic agent for such syndrome.

(2) Financial assistance under subsection (a) may not be expended to provide research training for which National Research Service Awards may be provided under section 487.

(c) DURATION OF SUPPORT.—Support of a center under subsection (a) may be for not more than five years. Such period may be extended by the Director for additional periods of not more than five years each if the operations of such center have been reviewed by an appropriate technical and scientific peer review group established by the Director and if such group has recommended to the Director that such period should be extended.

(d) AUTHORIZATION OF APPROPRIATIONS.—For the purpose of carrying out this section, there are authorized to be appropriated such sums as may be necessary.

SEC. 2317. [300cc-17] INFORMATION SERVICES.

(a) ESTABLISHMENT OF PROGRAM.—The Secretary shall establish, maintain, and operate a program with respect to information on research, treatment, and prevention activities relating to infection with the etiologic agent for acquired immune deficiency syndrome. The program shall, with respect to the agencies of the Department of Health and Human Services, be integrated and coordinated.

(b) TOLL-FREE TELEPHONE COMMUNICATIONS FOR HEALTH CARE ENTITIES.—

(1) After consultation with the Director of the Office of AIDS Research, the Administrator of the Health Resources and

Services Administration, and the Director of the Centers for Disease Control and Prevention, the Secretary shall provide for toll-free telephone communications to provide medical and technical information with respect to acquired immune deficiency syndrome to health care professionals, allied health care providers, and to professionals providing emergency health services.

(2) Information provided pursuant to paragraph (1) shall include—

(A) information on prevention of exposure to, and the transmission of, the etiologic agent for acquired immune deficiency syndrome; and

(B) information contained in the data banks established in subsections (c) and (d).

(c) DATA BANK ON RESEARCH INFORMATION.—

(1) After consultation with the Director of the Office of AIDS Research, the Director of the Centers for Disease Control and Prevention, and the National Library of Medicine, the Secretary shall establish a data bank of information on the results of research with respect to acquired immune deficiency syndrome conducted in the United States and other countries.

(2) In carrying out paragraph (1), the Secretary shall collect, catalog, store, and disseminate the information described in such paragraph. To the extent practicable, the Secretary shall make such information available to researchers, physicians, and other appropriate individuals, of countries other than the United States.

(d) DATA BANK ON CLINICAL TRIALS AND TREATMENTS.—

(1) After consultation with the Commissioner of Food and Drugs, the AIDS Research Advisory Committee established under section 2304, and the Director of the Office of AIDS Research, the Secretary shall, in carrying out subsection (a), establish a data bank of information on clinical trials and treatments with respect to infection with the etiologic agent for acquired immune deficiency syndrome (hereafter in this section referred to as the "Data Bank").

(2) In carrying out paragraph (1), the Secretary shall collect, catalog, store, and disseminate the information described in such paragraph. The Secretary shall disseminate such information through information systems available to individuals infected with the etiologic agent for acquired immune deficiency syndrome, to other members of the public, to health care providers, and to researchers.

(e) REQUIREMENTS WITH RESPECT TO DATA BANK ON CLINICAL TRIALS AND TREATMENTS.—The Data Bank shall include the following:

(1) A registry of clinical trials of experimental treatments for acquired immune deficiency syndrome and related illnesses conducted under regulations promulgated pursuant to section 505 of the Federal Food, Drug and Cosmetic Act that provides a description of the purpose of each experimental drug protocol either with the consent of the protocol sponsor, or when a trial to test efficacy begins. Information provided shall include eligibility criteria and the location of trial sites, and must be

forwarded to the Data Bank by the sponsor of the trial not later than 21 days after the approval by the Food and Drug Administration.

(2) Information pertaining to experimental treatments for acquired immune deficiency syndrome that may be available under a treatment investigational new drug application that has been submitted to the Food and Drug Administration pursuant to part 312 of title 21, Code of Federal Regulations. The Data Bank shall also include information pertaining to the results of clinical trials of such treatments, with the consent of the sponsor, of such experimental treatments, including information concerning potential toxicities or adverse effects associated with the use or administration of such experimental treatment.

SEC. 2318. [300cc–18] DEVELOPMENT OF MODEL PROTOCOLS FOR CLINICAL CARE OF INFECTED INDIVIDUALS.

(a) IN GENERAL.—

(1) The Secretary, acting through the Director of the National Institutes of Health and after consultation with the Administrator for Health Care Policy and Research, may make grants to public and nonprofit private entities for the establishment of projects to develop model protocols for the clinical care of individuals infected with the etiologic agent for acquired immune deficiency syndrome, including treatment and prevention of HIV infection and related conditions among women.

(2) The Secretary may not make a grant under paragraph (1) unless—

(A) the applicant for the grant is a provider of comprehensive primary care; or

(B) the applicant for the grant agrees, with respect to the project carried out pursuant to paragraph (1), to enter into a cooperative arrangement with an entity that is a provider of comprehensive primary care.

(b) REQUIREMENT OF PROVISION OF CERTAIN SERVICES.—The Secretary may not make a grant under subsection (a) unless the applicant for the grant agrees that, with respect to patients participating in the project carried out with the grant, services provided pursuant to the grant will include—

(1) monitoring, in clinical laboratories, of the condition of such patients;

(2) clinical intervention for infection with the etiologic agent for acquired immune deficiency syndrome, including measures for the prevention of conditions arising from the infection;

(3) information and counseling on the availability of treatments for such infection approved by the Commissioner of Food and Drugs, on the availability of treatments for such infection not yet approved by the Commissioner, and on the reports issued by the AIDS Research Advisory Committee under section 2304(e)(2)(B);

(4) support groups; and

(5) information on, and referrals to, entities providing appropriate social support services.

The Cure That Could Kill You

FDA Reforms Are Bad Medicine

By Morton Mintz

HERE'S A true story you won't hear from House sponsors of three complementary bills to "reform" the Food and Drug Administration, or from free-marketeer think tanks, or from the regulated industries that contribute generously to the lawmakers and think-tankers:

In 1960, a then-new sedative was being widely sold abroad. The William S. Merrell Co. sought FDA approval to sell the drug here, claiming its safety for the morning sickness of early pregnancy was "firmly established." FDA medical officer Frances Kelsey, seriously doubting the drug's safety, stalled. Two studies vindicated her. The first found that some adult users suffered nerve damage that impaired their ability to walk, with ominous implications for fetal development. The second—coming after the infuriated manufacturer had waited 14 months for approval—revealed that West German women who had taken the sedative in early pregnancy had given birth to armless, legless or limbless infants.

The drug was thalidomide. In the 20 countries where government officials didn't demand substantial evidence of safety (including Germany, England, Canada, Australia, Japan and Brazil) an estimated 7,000 to 11,000 thalidomide babies were born. Had the FDA approved thalidomide, thousands more of these limbless babies would have been born in the United States.

Why didn't the FDA approve the drug? Helen Taussig, a

See FDA, C5, Col. 1

Morton Mintz, a former Washington Post reporter, is the author of "By Prescription Only," about the FDA and the pharmaceutical industry, and "At Any Cost" about the Dalkon Shield.

we think they are.

PHOTO COLLAGE BY PETER ALSBERG—THE WASHINGTON POST

The Cure That Could Kill

FDA, From C1

Johns Hopkins pediatrician who investigated the catastrophe in Germany, said at the time that the explanation was "a lucky combination of circumstances" and Kelsey's alertness.

What if the three bills—one for drugs, one for food, and one for medical devices—now being considered by Congress had been law in the 1960s? Pediatric cardiologist John Nestor, a FDA colleague of Kelsey who had reinforced her skepticism about thalidomide, reviewed the drug bill at my request. "It is my opinion that thalidomide would have been approved . . . and that a catastrophe would have occurred," said Nestor, now retired. "If the bill becomes law we can expect more drug catastrophes."

The FDA reformers, emboldened by the Republican takeover of Congress, want nothing less than to transform the way food and drugs have been regulated in the United States since the 1930s. They hope to speed the process of approving regulated products, proposing that the reviews now conducted by the FDA be replaced by reviews paid for by industry. FDA bureaucrats, says Rep. James Greenwood (R-Pa.), the floor manager for the bills, must be stopped from "nitpicking" new-drug applications by "saying 'not yet, not yet, not yet' for years and years and years."

The reformers' pitch sounds appealing. Victims of terrible diseases want relief for their suffering quickly and companies want their drugs and devices to get to market without undue delay. But, in their desperation, victims and their families may, for very human and understandable reasons, put their faith in a nostrum or unproved drug or device. Drug companies and politicians are exploiting these hopes in their campaign to remake the FDA. The bills could all but dismantle the agency as the guarantor of the safety and effectiveness of medicines and medical devices and of the safety of foods.

For starters, the FDA's clear-cut mission—"protect the public health and safety"—would be eroded by a "yes, but" directive. The new proposed mission statement asserts that clinical research should be reviewed "promptly and efficiently" and "take appropriate action on the marketing of regulated products" so as not to "unduly impede innovation or . . . availability." Last week, with action by the House Commerce Committee apparently imminent, the drug and medical-device bills were shorn of some extreme provisions.

Even so, key FDA functions would be transferred to private contractors. Unapproved drug uses could be promoted to physicians with unreliable information on safety and effectiveness, but the agency is forbidden from requiring that patients receive brochures containing FDA-approved information with their drugs. Supplemental uses of a drug could be approved without clinical testing for safety and effectiveness. A requirement that hospitals inform the FDA of deaths and serious injuries associated with medical devices would be weakened. New regulatory mechanisms could threaten food safety and sanitation.

The proposed privatization of reviews for scientific trials for safety and effectiveness would create new risks for public health and safety. Makers of medical devices, food additives and colorings, and, when the FDA is willing, drugs, could retain nominally independent third parties to review their new products. On paper, the third parties would be accountable to the public. In reality, they would face pressures to please well-paying clients free to take their patronage elsewhere. The FDA would have a perilously brief period to examine their recommendations.

For 34 years, 26 of them as a Washington Post reporter and then as an author, I've written about FDA-related issues and drug and medical-device disasters, starting with thalidomide in 1962. Two questions about the pending bills strike me as basic: Whom do you trust? Who benefits?

■ *The manufacturers.* The FDA has found that the nation's top pharmaceutical houses—the ones that provide life-preserving medicines—sometimes engage in life-threatening practices that violate the FDA law. These manufacturers need more scrutiny, not less. Consider just one key FDA requirement: to report alarming drug reactions within 15 days. Violators include G.D. Searle, Hoffmann-LaRoche and Johnson & Johnson. In 1994-95, Pfizer was 44 to 514 days late in reporting alarming reactions from no fewer than eight drugs. Criminal violations were admitted by SmithKline Beecham in 1984, Eli Lilly in 1985, Hoechst AG in 1991 and Warner-Lambert in 1995. Recently, the FDA admitted it "should have" referred Upjohn's reporting and nonreporting of problems with its Halcion sleeping pill to the Justice Department for criminal investigation four years ago.

■ *The sponsors.* In the three years ending last Dec. 31, according to the Center for Responsive Politics, the political action committees of FDA-regulated companies invested $881,635 in 33 Republican and 10 Democratic sponsors of the reform bills. The tobacco industry, striving to block FDA regulation of advertising of tobacco products to children, invested an additional $428,449. Of the combined total of $1,310,084, the three lead sponsors—GOP Reps. Richard Burr (N.C.), Joe Barton (Tex.), (devices), and Scott Klug (Wis.), (food)—got $121,500.

■ *The guru.* In 1994, Newt Gingrich asked the Progress and Freedom Foundation to design a replacement for the FDA. Gingrich is close to foundation president Jeffrey Eisenach, who acknowledged to the Wall Street Journal that drug companies help finance the foundation. In 1995, the foundation revealed initial proposals—mirrored in the bills—for privatizing review and approval of FDA-regulated products and stripping the FDA of all but limited power to block unsafe or ineffective products. Gingrich has called the FDA "the leading job-killer in America."

■ *The opponents.* Impressively, foes of the pending legislation include fierce critics of the FDA. Over the last 25 years, the nonprofit Public Citizen's Health Research Group, has filed more than 50 petitions with the FDA to force warning labels onto dangerous drugs or devices or to take other strong actions. Yet Sidney Wolfe, the group's founder and director, says the reform bills "would cripple [the FDA's] ability to adequately protect Americans."

At the heart of the reformers' argument is the assumption that new drugs waiting to get on the market are better drugs. In fact, most new drug applications are not for therapeutic breakthroughs, but for "copy-cats" offering little or no gain for public health. And new can sometimes be worse. Thalidomide was new in 1961. The Dalkon Shield was new in 1971, but those FDA nitpickers had no opportunity to say "not yet" to the disastrously defective IUD. Why? Congress declined numerous presidential appeals to require a pre-marketing showing of safety and efficacy for devices until 1976—after the device had sterilized of tens of thousands of women.

In the late 1980s, without FDA approval, physicians hoping to prevent sudden death in high-risk heart patients began prescribing a certain group of drugs to suppress mild irregular heartbeat. Then a National Institutes of Health study demonstrated that instead of preventing cardiac arrest, two of the medicines, 3M's Tambacor and Bristol-Myers' Enkaid, sometimes caused it. Under the current drug bill, this off-label use for this group of medicines could have been heavily promoted. "At least 50,000" deaths in the United States attributable to these drugs have already occurred, according to Thomas Moore, a senior fellow at George Washington University's Center for Health Policy Research. Under the proposed legislation, "thousands more unnecessary deaths would have occurred," David Kessler, commissioner of the FDA, told Congress in May.

The reformers complain that foreigners get new drugs faster than we do. Is this necessarily bad? Between 1970 and 1992, 56 new drugs marketed in the United States, United Kingdom, Germany and France were withdrawn for safety reasons in at least one of those countries. There were 31 withdrawals in France, 30 in Germany, 23 in the United Kingdom, and 9 in the United States. Sidney Wolfe, who assembled the data, testified that FDA regulation weakened by the drug bill to Europe's level would have led to "thousands of serious injuries or deaths" from these drugs here.

In any case, the General Accounting Office says, the FDA has been sharply shortening approval times for new-drug applications. The 1987 average was 33 months; 1992's was 19 months. In 1995, the FDA approved 82 applications in an average of 16.5 months. More importantly, the approval time for the 15 drugs given priority because they were deemed major therapeutic advances was only six months. "We already have achieved one of the major 1997 performance goals," Kessler testified. "We achieved it in 1994." These improvements flowed significantly from a benign reform, a 1992 law giving the FDA more resources financed by drug company "user" fees.

It's possible that "not yets" have undesirably delayed marketing of certain promising products. But consider this: Every day, diabetics prick a finger to draw a drop of blood to test in one of many available blood-sugar meters. Unpleasant, certainly for small children. But they almost always get accurate measurements of their blood sugar to use in adjusting their dosage of insulin. This is literally vital: Inaccuracy can lead to coma, dehydration, even death.

A device that measures blood sugar by looking through the skin would be a blessing. It exists—the Diasensor. Is the FDA blocking it, as some critics claim? No. To expedite the marketing application, the FDA summoned a panel of outside experts. At the manufacturer's request, they delayed meeting for five months, until last February. Even then, however, complete test information was available on only eight patients. The advisers judged eight patients too few to justify mass-marketing. Effectively, they said, "not yet." So did the company: It is testing a new model.

It took a 25-year crusade by Harvey Wiley to win passage of the Pure Food and Drug Act of 1906. He became the first head of what is now the world's most admired regulatory agency. Wiley sounded this warning in 1930: "There is a distinct tendency to put regulations and rules for the enforcement of the law into the hands of the industries engaged in food and drug activities. I consider this one of the most pernicious threats to pure food and drugs."

The current legislation poses just such a threat. It is as if numerous drug and device catastrophes had never occurred, or had taught nothing. Or are the GOP sponsors out to prove Wiley right about the Republican Party? He had given it "unswerving loyalty," his biographer wrote, but finally became convinced that it "had become the shield of the cheat and the adulterator."

THE FEDERAL PAGE

F)A Often Blamed for Problems That Aren't Agency's Fau lt

By John Schwartz
Washington Post Staff Writer

Kay Holcombe recalled the meeting as very sad—and very troubling.

More than a dozen people came to her office one day last spring to ask her to urge her boss, Rep. John D. Dingell (D-Mich.), to support efforts to reform the Food and Drug Administration. The visitors or their relatives were afflicted with dire diseases, and they wanted laws passed that would speed promising new therapies to market.

What Holcombe, the House Commerce Committee's top Democratic staff member on FDA issues, did not learn until well into the meeting was that her guests' trip to Washington had been paid for by the leading trade organization for the pharmaceutical , the Pharmaceutical Research and Manufacturers of America (Pharma).

They were among approximately 140 victims or family members who in to visit lawmakers during recent months as part of a lobbying effort by the industry in support of bills that would scale back the power of the FDA.

The industry contends that changing the way the FDA operates would get new medicines to market faster. The bills would set tight deadlines for drug approvals, reduce the number of clinical trials required to test drugs and shift some of the responsibility for evaluating such products to FDA-accredited private companies.

Yet, Holcombe said, the visitors to her office failed to make a persuasive case that their problems in obtaining treatment were really the fault of the FDA. She said that, although they blamed the agency, most often they were caught up in struggles with insurance companies over reimbursement or were simply frustrated by the lack of a anywhere in the world for what ailed

For example, a woman complained that the FDA was not releasing therapies for Parkinson's disease, a disorder of the ner- for which no cure exists. Another visitor was distraught over state budget cuts that would mean a lower quality of nursing home care for his Alzheimer's-afflicted wife. The FDA does not regulate homes.

Only one visitor had a problem that Holcombe could lay at the feet of the FDA: a woman who described repeated disputes with a local FDA official over paperwork required for her to import dietary supplements to treat her son.

BY TOM GANNAM—ASSOCIATED PRESS

Julie Full-Lopez, who has multiple sclerosis, carries Olympic torch through Crestwood, Mo. She credits a new drug with saving her life.

"They truly believed that all of their problems will be solved by FDA reform," Holcombe said, "and I truly believe that they won't." She said she ended the meeting feeling that the patient lobbyists were "a little bit victimized" by the industry that had paid their way.

Patrick Korten, until last month Pharma's chief spokesman, acknowledged that many of the patients' problems were not the fault of the FDA, but said, "We brought them to Washington because they're really people. If we wanted lobbyists, we would have brought them from here."

Pharma provided The Washington Post with the names of some of the people it had brought to Washington to meet with law- . All of those contacted by a reporter told of problems in obtaining treatment for themselves or family ers, but it appeared that none of those problems would be addressed by FDA reform proposals.

Julie Full-Lopez teaches English at Southern Illinois University in Edwardsville, Ill. A single mother with a 13-year-old, she suffers from multiple sclerosis, a degenerative disease of the nervous system that slowly robs its victims of the use of their muscles. Her heroic fight for better MS treatments earned her a singular honor this year: On May 28, she carried the Olympic torch in St. Louis as one of the "community heroes" selected to show the American spirit.

In the weeks before that run, Lopez came to Washington to lobby lawmakers on behalf of FDA reform proposals. Along with other people suffering from Lopez said, she was asked to tell her story and to encourage the lawmakers to make the FDA work faster by passing the bills.

But the drug Lopez credits with saving her life, Betaseron, was approved in the United States before it became available in any other country. When asked about this, she explained, "I was sort of the poster child of how a drug can be successful if it's approved in time."

Stephanie Hudson, of St. Louis, whose child suffers from sickle cell anemia, is upset that the FDA has not officially approved the drug hydroxyurea for the disease. Hydroxyurea has been approved for other uses since the 1960s, and doctors are free to prescribe it as they see fit. Hudson complains, however, that many insurance companies don't reimburse patients for such "off-label" prescriptions.

But Hudson's problems are not with the FDA. The agency has little i over insurers' policies, and Bristol-Myers Squibb Co., which holds the patent on the drug, has never applied for the new use to be approved, although a company spokesman said that "there are conversations going on with the FDA."

Janet McDermott, of Marshfield, also came to Washington to lobby legislators for FDA reform and was the subject of a profile in the Boston Globe. Her daughter has epilepsy so severe that she can suffer 100 seizures in a single day and is using four medications—and taking 21 pills each day—to bring the seizures to a few per week. "It's been a roller coaster for the past six years," she says.

McDermott wants her daughter to be able to take Sabril, a promising anti drug available in Europe and Canada but not yet approved in this country. She obtained an initial supply of the drug on a recent trip to Canada but says her family can ill afford the expense of such a trip on her husband's wages as an ironworker, and cannot depend on being able to obtain a reliable source of the medicine.

McDermott is worried about some provisions of the FDA reform bills. But she believes that "they could cut out a lot of red tape."

Sabril is manufactured by Hoechst Marion Roussel. Company spokesman Charles F. Rouse III said the drug has only available in Canada for about a year, and added that, although his company believes some drug approvals are slowed by FDA policies, the company bears responsibility for the current Sabril delay because it is gathering data requested by the FDA. "The ball is in our court, now, so to " he said.

His company denied McDermott's request for special access to the drug under FDA's "compassionate use" procedures because, Rouse said, it would divert es from the ongoing large clinical trials and "that would delay the ability to get the drug approved for the population at large that could benefit from it."

Lopez, Hudson and McDermott's names were supplied by Pharma as whose stories best illustrated the need for FDA reform. When asked why Pharma chose those examples, Korten said, "I was counting on the fact that our folks upstairs would have vetted the list pretty well" for the people whose problems were most on point. He added, "It's possible that what they gave me instead were the people wh were the most articulate."

FDA Reformers Race the Calendar

Sponsors of New Plan Expect Legislation to Reach House Floor Before August Recess

By John Schwartz and Ruth Marcus
Washington Post Staff Writers

After months of inertia, proponents of reforming the Food and Drug Administration—the government's chief consumer protection agency for food and medical products—are trying to build eleventh-hour momentum in Congress.

The latest version of a House plan to revamp the FDA was unveiled Wednesday at a briefing for reporters. The package's sponsors said they expect to move it through the Commerce Committee over the next two weeks and send it to the House floor before the August recess. A similar reform plan is pending in the Senate.

To drug companies, medical device makers, biotechnology firms and food producers, FDA reform is a critical issue and they have been pouring money into an all-out lobbying effort. The agency's vast bailiwick includes the regulation not just of food, drugs and medical devices, but also of blood, veterinary feeds and other products that, taken together, comprise 25 cents of each consumer dollar spent.

Supporters of legislative change at the FDA argue that for decades overregulation has stifled medical innovation and delayed new therapies. "Patients are waiting needlessly—patients are dying needlessly—while they wait for the wheels in the FDA to turn," Rep. James C. Greenwood (R-Pa.), who is managing the House package, said Wednesday.

"The purpose of FDA reform is to try to modernize the agency to assure that they can keep up with the pace of technological innovation, which in turn assures that products will get to patients in a timely fashion," said Alan H. Magazine, head of the Health Industry Manufacturers Association, whose members make medical devices.

Studies on drug approval by the General Accounting Office and others suggest that the FDA generally approves new medicines about as quickly as its counterparts in other developed countries. But it remains slow to act on some medical devices. Although the FDA has made strides in reducing the backlog of applications for most kinds of medical devices, it still takes more than 700 days, on average, to gain approval for new devices, far more than the statutory deadline of 180 days.

The bills under consideration—one in the Senate and three in the House—would force the FDA to hand over much of its work in evaluating drugs, devices and new food additives to agency-accredited private companies. In some cases, companies would be selected and paid by the makers of the products seeking agency approval. The four bills would set tighter deadlines for all drug and device approvals.

The bills also would relax the requirements for testing drugs and devices for safety and effectiveness by requiring fewer clinical trials and by reducing the amount of data companies would have to supply the FDA. The House bills also would loosen restrictions on the ways companies may promote unapproved uses for drugs and devices that are already on the market.

Congressional sources last week expressed pessimism about the passage of such complex legislation so late in the session. Rep. Fred Upton (R-Mich.), who pressed for reforms of FDA export rules as part of the continuing resolution in April, said, "There's not a lot of sand in the hourglass. . . . Though people said, 'It's on the respirator' a couple of weeks ago, they do have a chance to get out of the hospital door."

The Congressional Budget Office estimates that implementing the Senate bill would cost the government an additional $555 million over six years. No estimate on the cost of implementing the House bills is available.

Food and Drug Commissioner David A. Kessler maintains that his agency already has taken steps to streamline its activities. He warned that the congressional proposals, particularly those in the House, would cut holes in America's public health safety net and "end up rolling back 50 years of public protection."

Sen. Edward M. Kennedy (D-Mass.), the leading opponent of the Senate's FDA reform bill, said the proposals are "driven by powerful and well-funded interests to gut the regulatory agency that stands between them and increased profits."

Lobbying over the issue has been fierce. Companies pushing for FDA reform have provided hefty donations to key congressional supporters of reform, a review of Federal Election Commission records shows. The interested companies have dramatically increased the amount of their corporate donations this year to the GOP, whose leaders on Capitol Hill back the initiative.

Pharmaceutical and tobacco companies have donated to conservative think tanks that produce studies and advertisements advocating FDA reform, papers that are used by industry in its effort to bolster the case for FDA overhaul. The Pharmaceutical Research and Manufacturers of America (Pharma) has flown in 140 patients with dire diseases, or their relatives, to urge lawmakers to reform the agency.

Many patient groups that have testified in favor of reforming the FDA receive funding from industry. Six of the nine largest funders of the National Coalition for Cancer Survivorship, which has testified in favor of FDA reform, are pharmaceutical manufacturers and their law firm.

Coalition executive director Ellen Stovall said that less than 30 percent of her organization's money comes from corporate sources. She said it does not influence her organization's positions and points as proof to the coalition's opposition to the current version of the FDA reform proposals. "We are calling for very moderate reforms," Stovall said. "We are not in favor of privatization of the FDA."

Michael Langan, director of public policy for the National Organization for Rare Disorders (NORD), a federation of 140 voluntary health agencies for people with rare diseases, recalled that pharmaceutical companies and Washington think tanks invited NORD and other groups to attend conferences on FDA reform, beginning last year.

"What we quickly realized is that they already had their agenda set out straight in advance," Langan said, "and wanted to push it on us and have us stand side by side." Langan said his group refused, but added that many other of the patients' organizations could scarcely afford to do so.

The pharmaceutical industry has greatly increased donations this year to the Republican Party, whose lawmakers are sponsoring the FDA reform plans.

Eli Lilly & Co., which gave $188,000 in "soft" money (unlimited corporate donations not contributed to specific candidates) to the two major political parties last year, about 70 percent to Republicans, has been far more generous to the GOP in 1996. In the first four months of the year, according to FEC reports, Lilly gave $305,000 to the Republican National Committee. In the first three months of 1996, the only period for which full reports from Democratic committees are available, it gave $32,250 to the Democratic National Committee and its congressional arms.

Likewise, Bristol Myers-Squibb, which gave just under $70,000 in soft money contributions last year, almost all of it to Republicans, donated $275,000 to the RNC in the first four months of 1996. The company gave $15,000 to the Democrats.

Key members of the committees handling the FDA reform legislation have received substantial donations from political action committees sponsored by companies with an interest in the subject.

An analysis by the Center for Responsive Politics of political action committee contributions by pharmaceutical, medical device and biotechnology companies found substantial contributions to members of the House Commerce and Senate Labor and Human Resources committees since 1995; a review of 1996 contributions shows even more in the first quarter of this year.

Rep. Joe Barton (R-Tex.), who sponsored the House bill to reform regulation of medical devices, received $41,000 from the interested industry PACs in 1995 and 1996. Rep. Christopher Cox (R-Calif.), who sparred with Kessler and his aides in a number of recent hearings, received $41,700.

Barton's press secretary, Craig Murphy, said Barton had worked on the issue for years and said the PAC contributions represent "a sigh of relief from people who wanted reform at the FDA."

On the Senate labor committee, Bill Frist (R-Tenn.), who has pushed a provision that would allow drug companies to distribute information about unapproved uses of their products, was the leading recipient of interested industry funds, collecting $58,500 in 1995 and 1996.

Frist's press secretary said that as a physician he had a long-standing interest in the topic and that the PAC funds were unrelated to his involvement with the issue.

Rep. Greenwood said the industry lobbying push has not been as important in building support for the legislation as informal calls to lawmakers from executives of medical companies in their congressional districts and discussions with concerned constituents.

"There is a lot more grass-roots interest in this issue than you might guess," Greenwood said. The idea that "industry is in the driver's seat," he added, "really doesn't hold up."

Staff researchers Nathan Abse, Alice Crites and Barbara J. Saffir contributed to this report.

FOR MORE INFORMATION

For a list of all the drugs and devices approved by the FDA this year, visit The Post's site on the World Wide Web at http://www.washingtonpost.com

BY DENNIS COOK—ASSOCIATED PRESS

Food and Drug Commissioner David A. Kessler and associate commissioner Diane Thompson confer in April during Senate labor committee hearings on legislation to overhaul the FDA.

AIDS Action council

FOR IMMEDIATE RELEASE
July 2, 1996

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AIDS ACTION DENOUNCES SENATE FDA LEGISLATION

Senate Report Confirms Danger of Proposal to American Patients and Consumers

WASHINGTON, D.C. — The U.S. Senate Labor and Human Resources Committee last week filed its report detailing a wide range of dangerous changes to the U.S. Food and Drug Administration that AIDS and patient care advocates fear cede too much of the FDA's safety and efficacy regulatory oversight powers to the pharmaceutical industry. AIDS advocates have long called for the FDA to streamline its drug approval processes and thus speed access to promising drugs for chronic and life-threatening illnesses, including HIV disease. However, they warn that the Senate bill [S. 1477] will inevitably jeopardize public health by increasing the odds that unsafe and ineffective drugs and therapies will reach Americans living with HIV and AIDS.

"Nothing in this bill will in any way speed the ability of American consumers to gain access to new or promising therapies," said Gary Rose, AIDS Action's treatment and research representative. "In fact, many elements of the legislation seem to be intentionally aimed at flooding the market with food and drugs that are unsafe, ineffective, or unproven. Just as important for patients, the bill reduces data requirements for marketing new drugs to such an extent that insurance companies, government programs, and HMOs may be unwilling to provide reimbursement in the present highly restrictive managed care environment."

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Rose explained that what is most disturbing about the Senate bill is that despite the best efforts of the Patient's Coalition — which represents more than 70 patient advocacy organizations — to work with Sen. Nancy Landon Kassebaum (R-Kans.) to craft legislation that would actually solve the problems at the FDA, S. 1477 has become more extreme and less about patient's concerns every step of the way. "It has become patently clear that this process has become an election year gift to industry couched in the rhetoric of 'reform,'" Rose said.

Patient care advocates continue to point to the same major problems in the Senate bill which have, unfortunately, become even more problematic in their articulation in the Senate report.

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- **S. 1477 imposes arbitrary timelines for drug approvals and reviews without providing added resources for their implementation.** The establishment of rigid timelines without appropriate resources will result in either increased denials of new drug applications because the FDA lacks the time or personnel to adequately review applications, or an increased possibility that FDA reviewers will feel compelled to approve drugs based on fewer analyses and less information.

- **S. 1477 limits the FDA's flexibility to develop priorities in its drug review process.** A responsible FDA must have the flexibility to prioritize drug approvals and reviews in a way that addresses and responds to the most significant public health issues. Approval and review of breakthrough drugs for severe, life-threatening diseases such as HIV disease must take priority over approval and review of drugs for treatable conditions such as insomnia, or for drugs that are, with minor changes, identical to already-approved drugs for routine conditions (i.e., sleeping pills). The strict timelines imposed by S. 1477 require the FDA to place priority on meeting time deadlines for the approval of a "me too" drug at the expense of approving or reviewing applications for drugs treating serious health conditions such as AIDS or Alzheimer's.

- **S. 1477 privatizes significant FDA responsibilities and thus undermines the agency's ability to protect the public health and safety.** A number of provisions in the bill allow drug and medical device companies to market products with only *pro-forma* FDA approval if the agency fails to meet the unrealistic review deadlines established in this bill (called marketing approval by default). Under S. 1477, a third party reviewer can be contracted to conduct a review of a drug or medical device. The third party reviewer is not required to have knowledge of the specific drug development process. And, there are no stringent financial disclosure and conflict of interest requirements to protect decision-making from commercial or financial bias (i.e., a company can pay a third party reviewer to have a drug favorably reviewed after which the FDA is required to make an approval decision within 30 days). After receiving approval from private review entities with whom they have privately negotiated a payment schedule, *the FDA will have to prove that the product is harmful to prevent its coming to market.*

- **S. 1477 imposes "hammers", strict timelines that force the FDA to approve a drug with little evidence that the drug is either safe or effective.** The clearest example in the bill provides that if a drug is approved in Europe, it is presumptively approvable in the United States. This provision is extremely problematic in two important ways:

  First, it assumes that a drug or device legally marketed in Europe should be marketed in the United States based on what are often very different drug and medical device regulations and standards. There are numerous frightening cases in which drugs approved in European countries but rejected by the FDA were ultimately pulled from European markets after consumers reported serious injury or premature death associated with their use. Under S. 1477, the FDA would have only 30 days to block automatic approval in the United States of drugs cleared for sale in Europe — eliminating the FDA's reputation as the world's "gold standard" as a watchdog for drug safety and efficacy. Also noteworthy is the fact that

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between 1970 and 1992, the United States withdrew marketing approval for nine drugs for safety reasons while in Europe during the same time period licenses for 56 drugs were revoked because of safety concerns.

Second, these hammers provide immediate disincentives for pharmaceutical companies to conduct research in the United States. It is clear that if the testing of new drugs can be undertaken in Europe where standards for approval are appreciably lower, European trials will be cheaper to conduct. If the data gathered for European approval then becomes the basis by which FDA must make marketing determinations, then it stands to reason that more companies will move more and more clinical trials to the cheaper site. If this bill had been in effect this year, thousands of patients living with HIV would have been deprived of pre-market access to the new protease inhibitors which have proven to be remarkable tools for extending the lives of AIDS patients.

- **S. 1477 lowers safety and efficacy standards for new drugs and for off-label uses of approved drugs.** By requiring only one efficacy study for approval of new drugs, this bill micromanages scientific decisions and discourages thorough clinical research by drug companies. There is no way to predict in advance how many clinical studies might be necessary to determine a drug's safety and usefulness. The FDA must maintain the flexibility to make informed scientific judgements and require the appropriate number of safety and efficacy trials before allowing companies to market drugs for serious diseases such as AIDS and cancer. The threat also remains that S. 1477 will readmit provisions like the Mack-Frist bill that would allow drug companies to market already approved drugs for clinical conditions other than those for which the drug was initially approved. Most troublesome is that this provision would allow companies to market drugs without ever having to demonstrate to the FDA that these drugs are safe and effective to treat the clinical conditions for which they could be sold.

- **S. 1477 limits the FDA's involvement in the production and post-approval review of drugs and medical devices and thus undermines consumer protections.** Drug production problems result in adverse consequences for patients. The FDA must have the ability to inspect, monitor production and protect the American public from poorly made drugs or biologics that are dangerous or of limited usefulness. Current law provides, for example, that when the FDA suspends or revokes a product license because that product poses a threat to public health — when a blood bank ships HIV-contaminated blood, for example — the licensee cannot resume shipments until the problem leading to the threat is satisfactorily resolved. Under S. 1477, if the FDA misses the 30-day reinspection deadline, the blood bank could resume shipping blood regardless of whether it has fixed the problem.

# # #

Founded in 1984, AIDS Action Council is the only national organization devoted solely to advocating on federal AIDS policy and legislation. AIDS Action Council represents more than 1,400 community-based AIDS service organizations throughout the United States.

Consumers Union
Publisher of Consumer Reports

SENATE FDA LEGISLATION HARMS CONSUMERS

BACKGROUND

Since its creation in 1906, the U.S. Food and Drug Administration has been charged with protecting the health of the nation. In 1962, the FDA's mission was expanded to look at efficacy of medical products as well as safety of drugs. In 1976, after the Dalkon shield intrauterine device caused 18 deaths and 66,000 miscarriages, the FDA began regulating medical devices. By the 1980s, the FDA's attention to its mission of public health had led some drug manufacturers and others to believe that the FDA had become too cautious and inefficient in approving food additives, drugs and medical devices for the use of the American public.

Since Dr. Kessler was appointed by President Bush in 1992, he has responded head on to many of the criticisms aimed at the FDA. The FDA took an average of 33 months to approve new drug applications submitted in 1987. For applications submitted in 1992, the average review time was 19 months. In the last year alone, additional progress has been made in reducing approval times. Although the FDA approved approximately 1/3 more new drugs in 1995 than in 1994, the median approval time dropped from 19 months to 16.5 months. Device review times also dropped significantly, from 182 days to 138 days for the class including 98% of medical devices. As part of its streamlining efforts, the FDA has also made it easier for patients to receive experimental therapies, reduced the paperwork burden on regulated industries, and harmonized and expanded opportunities for export of drugs and medical devices to industrialized countries.

In addition to looking at the number of drugs, devices, and biologics approved by the FDA, it is also important to consider what injuries the FDA has prevented by keeping dangerous drugs out of the U.S. market. In the early 1960s, the FDA kept the sleeping pill thalidomide off the U.S. market. In Europe, the drug was approved in several countries, and thousands of children suffered from birth defects as a result of their mothers taking the drug while pregnant. A recent study reported on drugs taken off the market for safety reasons in the U.S., France, U.K. and Germany since 1970. The U.S. approved only 9 of those drugs, compared to 23 in England, 30 in Germany, and 31 in France. Clearly, the FDA has a much better recordkeeping dangerous drugs out of the hands of consumers than its sister agencies in other countries.

PROBLEM

Although the FDA is seeking reform while maintaining the balance between efficiency and safety and effectiveness, some members of Congress are seeking more radical changes to the way in which the FDA does business. In the Senate, these changes are contained in S. 1477, sponsored by Senator Kassebaum. These changes would significantly tip the balance away from consumers, and reduce safety protections that currently prevent numerous injuries and deaths.

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Third Party Review: A Conflict of Interest

The most ill-conceived element of the proposed changes involves the use of third-party, pharmaceutical industry financed review of new devices and indirect food additives. Under this arrangement, private contractors' profits would be dependent on the desire of manufacturers to use them in the future. Clearly, this presents an inherent conflict of interest for reviewers. Although the Senate bill provides a short window in which the FDA could review the results, the time period is insufficient to allow adequate review.

Rushed Approval and Inadequate Manufacturing Oversight

The problems of third party review would be aggravated by provisions in the FDA legislation proposing a host of new review deadlines for the FDA. These provisions allow the self-interested industry review of more regulated products if these newly imposed deadlines are not met. Inevitably, these artificial deadlines will either result in more mistakes by the FDA that will endanger consumers, or the failure of the FDA to approve drugs, devices, and food additives that further review might indicate are both safe and effective. Under the Senate bill, for example, the FDA would have only 90 days to review some new indirect food additives. Dr. Kessler has testified significant additional resources, not contemplated in either this bill or the latest budget resolution, would be required to meet this ambitious goal. The bill would also require the FDA to accept drugs approved by inferior European approval processes if ambitious time frames were not met.

The legislation also endangers consumers by scaling back FDA approval of manufacturing processes. For example, risky changes in the way blood products are handled, which could decrease the safety of our blood supply, would no longer be subject to FDA approval.

Insufficient Consumer Information

The proposed revamping of the FDA operations endangers the ability of consumers to learn about the regulated substances they use. The bill would eliminate the requirement that drug manufacturers make information regarding the potential dangers of their products available to consumers through the MedGuide program. As a result of an amendment added during the Senate Labor Committee mark up, the bill would weaken the Nutrition Labeling and Education Act by allowing manufacturers to include health claims about a food or food ingredient if such a claim appears in a government document, with no weight given to the validity of that claim or the context in which it appears.

SOLUTION

We have highlighted only a few of the many concerns consumers should have with the radical changes proposed in S. 477 and its House counterparts. We urge Congress to reject these radical proposals, and instead **ENCOURAGE AND INSTITUTIONALIZE FDA'S LONG-RANGE PLANNING OF STRATEGIES TO ENSURE SAFE AND EXPEDIENT APPROVAL OF DRUGS, DEVICES, FOOD, AND BIOLOGICS.**

For further information, contact Adrienne Mitchem at (202) 462-6262

news

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FOR RELEASE: **July 2, 1996**

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APHA Opposes Senate Attacks on the Food and Drug Administration

The American Public Health Association (APHA) is deeply troubled by the intense attacks being lodged against the Food and Drug Administration (FDA) by Senate bill S.1477, the Food and Drug Administration Accountability Act.

APHA strongly believes that passage of this proposed legislation would significantly alter the fundamental role of the FDA. The FDA's mission is to ensure that drugs, biological products and medical devices are safe and effective for the treatment of specific health conditions. The FDA is also charged with monitoring and assuring the safety of all food products available to consumers except meat and poultry products.

"This bill would seriously undermine the FDA's ability to perform vital public health functions," said Dr. Fernando Trevino, Executive Director of APHA.

The legislation, as introduced, would weaken many public health standards and regulatory guidelines which the FDA now enforces. The law would lower drug approval standards by requiring that only one clinical trial be performed on new drugs. Current law protects against ineffective drugs by requiring multiple laboratory tests to protect against drugs which may appear falsely promising in a single trial.

Under this bill, drug manufacturers would be allowed to hire private reviewing companies to evaluate their products. These groups could include individuals who have a financial stake in the outcome of the decision. This type of third-party review will eliminate the FDA's authority to pre-approve drug health claims thereby threatening public health standards currently in practice.

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The proposed legislation would also reduce the FDA's authority to regulate health claims made about food products and new food additives. The bill forces the FDA to demonstrate that a food additive is dangerous instead of requiring industry to prove that a new food additive is safe.

Also under the change, the FDA would be allowed to certify private groups to conduct food safety inspections. The change in policy would allow food companies to hire private inspectors to check for food safety violations and approve new additives. The private inspection panels could be largely composed of scientists who receive funding from parties which have a financial stake in the outcome. This legislation greatly reduces the FDA's policing authority over misleading health claims by privatizing crucial public health decisions. This action could result in an increase in the amount of misleading and inconsistent food health claims.

Controlled clinical trials for health devices will be eliminated by the proposed legislation as well. Manufacturers of medical devices will be allowed to choose a private company, or companies, to conduct third-party reviews of their devices. Consumers will no longer have the guarantee that the medical devices which they use are objectively and governmentally approved. The bill even extends the right of private review to devices classified as high risk such as those used to shunt fluid from the human brain, clear heart patient's veins and hold bones together.

"If approved, this legislation would derail the FDA's progress and allow the food, drug and medical device industries to bypass important public health safety measures," says Trevino.

To ensure the public's access to safe and effective products, APHA urges the Senate not to approve this bill.

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The American Public Health Association, the oldest and largest organization of public health professionals in the world, has been influencing policies and setting priorities in public health for over 120 years and has been in the forefront of numerous efforts to prevent disease and promote health.

CONSUMER GROUPS OPPOSE RADICAL REWRITE OF FOOD, DRUG AND COSMETIC ACT

March 13, 1996

Dear Senator:

We are writing to voice our opposition to S. 1477, Senator Kassebaum's FDA overhaul bill. On behalf of American consumers and patients, we urge you to consider the adverse impact the proposed legislation would have on American citizens' health and safety.

FDA standards have proved to be an effective safeguard of public health and safety. Nonetheless, industry-led proponents of the bill are lobbying to dismantle the FDA, arguing that the agency's tough standards prevent Americans from having greater and quicker access to drugs and medical devices. **The reality is that America's standards -- the highest in the world -- have protected consumers from numerous unsafe, sometimes fatal, medical products.** Thus, from 1970 to 1992, while the U.S. withdrew approval of nine drugs for public safety reasons, the U.K. was forced to withdraw 23, Germany 30, and France 31. For example, the drugs Clometacin, Indomethacin-R and Frenclofenac, approved in Europe as aspirin substitutes, caused hepatitis, fatal internal bleeding, and fatal skin rashes in some consumers. Risking our lives for another headache medicine hardly seems a rational choice.

The Kassebaum bill would allow drug and device manufacturers to promote unapproved uses of their products, exposing consumers to unnecessary and unknown risks. Currently, manufacturers can market products only for the specific uses approved by the FDA. Allowing manufacturers to promote their products for unapproved uses will encourage irresponsible marketing schemes and expose consumers to unknown risks. Consider the cases of flecainide and encainide, two drugs approved for the treatment of specific types of abnormal heartbeats. In the 1980s, based on preliminary studies, physicians began routinely to prescribe these drugs for other heart problems. The FDA later determined that taking either of the two drugs for the other heart problems actually doubled the risk that the patient would die. The proposal, if enacted, would make such stories common.

The Kassebaum bill imposes dangerous penalties for missing unreasonable deadlines. The bill forces the FDA to cut the time it now takes to review new product approval applications by one-third, while providing no additional resources to enable the FDA to accomplish the task. If the agency missed more than five percent of its review deadlines, it would have to abdicate its review functions to private outside reviewers, whether or not such contracting would be cost-effective or time saving. More alarmingly, if the agency missed a deadline for a given product, that product would be deemed eligible for "approval by default" if it had already been approved by a European country.

Moreover, S. 1477 would decimate critical pre-market testing requirements. Clinical trials are vital for determining the safety and effectiveness of medical products for vulnerable populations, such as the very old and the very young. Because of their special needs and sensitivities, medical products that may be used by the elderly and children require testing on additional, not fewer, groups. Reduced testing and data requirements in clinical trials would significantly diminish the FDA's ability to ensure the safety of medical products for all consumers.

As watchdogs of government and its actions, none of us is an uncritical supporter of the FDA. The FDA, like most institutions, can benefit from constructive criticism and change. As spokespeople for America's consumers and patients, however, we believe that the Kassebaum proposal would harm the consumer population at large. We strongly urge you to oppose the Kassebaum proposal in light of these concerns.

Sincerely,

Joan Claybrook
President
Public Citizen

Mary Ellen Fise
General Counsel
Consumer Federation of America

Wenonah Hauter
Environmental Program Director
Citizen Action

Mark Silbergeld
Co-Director, Washington Office
Consumers Union

Children's Defense Fund

March 21, 1996

The Honorable Edward M. Kennedy
United States Senate
315 Russell Senate Office Building
Washington, DC 20510

Dear Senator Kennedy:

I am writing to express the Children's Defense Fund's concerns about S. 1477, the "Food and Drug Administration Performance and Accountability Act of 1995."

Too often, clinical trials on the efficacy and safety of approved drugs for their intended use have been inadequate for children. The lack of pediatric clinical studies means that too few drugs are approved and labeled for pediatric use. Reform of FDA clinical trial requirements should be strengthened to improve the approval and labeling of drugs for children. Instead, S. 1477 relaxes current clinical trial requirements and fails to address the approval needs of children.

Additionally, the lack of approval and labeling of drugs specifically for children means that pediatric providers must all too frequently rely on off-label uses of approved drugs to treat children. Currently, drug companies are allowed to market their products only for FDA-approved uses. S. 1477 would allow drug companies to market their products for off-label uses. This proposal could be a further disincentive for manufacturers to seek approval of drugs for children, compounding the problem of already inadequate labeling of drugs for children. It could also lessen the availability and use of objective and scientific information on off-label treatment usage and consequences. Pediatricians should receive and be able to rely on the most current and objective information available about off-label usage. In addition, manufacturers should be required to report all adverse experiences and reports to the FDA, a requirement which is missing from S. 1477.

Rather than relaxing clinical testing standards and marketing restrictions, Congress should be designing legislation which remedies the current inadequacies in the prescription drug area for children. We urge Congress to proceed cautiously on FDA reform.

Sincerely,

Stan Dorn

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NEWS The National Council on the Aging NCOA

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FOR IMMEDIATE RELEASE

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NCOA: BILLS THREATEN FDA FOOD AND DRUG SAFETY PROTECTIONS

WASHINGTON DC, JULY 2--Dr. James Firman, President and CEO of The National Council on Aging (NCOA) and Co-Chair of the Leadership Council of Aging Organizations, today warned that two bills pending in Congress (S. 1477 and H.R. 3200—The Food and Drug Administration Performance and Accountability Act of 1995) would jeopardize much of the food and drug safety that consumers now enjoy:

> These bills seriously weaken the Nutrition Labeling and Education Act of 1990, which provides consumers with consistent food labeling and the means to resist misleading claims in the marketplace. Such accurate food labeling is fundamental to the survival of many older Americans on restrictive diets. These bills would also weaken the Delaney Clause, which removes from food production the cancer-causing pesticides that concentrate in processed foods. The reintroduction of any of these pesticides would put all Americans at greater risk.
>
> These bills propose to allow third-party contractors, rather than the FDA, to monitor food-processing companies for safety violations. Such new procedures could compromise food safety inspection and present many conflict of interest problems.
>
> Finally, the bills threaten drug safety by restricting the FDA's authority to mandate clinical trials and by authorizing outside agents to conduct third-party reviews. This would reduce the accuracy of FDA-provided information about drug safety and interactions with other drugs. The bills would also limit the FDA's power to prevent the unapproved use of drugs and medical devices.
>
> Americans over 65—about 13 percent of the population— consume 34 percent of all prescription drugs sold. They rely on the safety of food and drugs they buy. These bills would severely jeopardize older consumers' confidence and the health and safety of all our nation's citizens.

The National Council on the Aging, Inc. (NCOA) is a center of leadership, innovation, and nationwide expertise in the issues of aging. A private, nonprofit association of more than 7,500 members (organizations and individuals), NCOA is committed "to promoting the dignity, self-determination, well-being, and contributions of older persons and to enhancing the field of aging through leadership and service, education, and advocacy." Founded in 1950 and headquartered in Washington, DC, NCOA has a diverse national membership of professionals and volunteers, service providers, consumer and labor groups, businesses, government agencies, religious groups, and voluntary organizations.

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The Food and Drug Administration: An American Family Business

The cereal we eat in the morning. The food we give to our babies. The medicines we take and give to our children. The toothpaste and cosmetics in our medicine cabinet. The lifesaving drugs used by the elderly and the sick. The blood supply we depend on. The FDA helps us all by regulating the safety, purity and effectiveness of all of these.

Yet legislation now before Congress will undermine the FDA, lowering standards and stripping the agency of crucial public health responsibilities. That's a prescription for danger that will threaten the health of every American family.

Vote No on Reckless Reform. America Needs a Strong FDA.

Name of Organization • Name of Organization •

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Signers to the Advertisement

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American Foundation for AIDS Research
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American Public Health Association
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Association of Nurses in AIDS Care
Bazelon Center for Mental Health Law
Center for Medical Consumers
Center for Science in the Public Interest
Center for Women Policy Studies
Cities Advocating Emergency AIDS Relief
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Consumers Union
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New York Coalition for Alternatives to Pesticides
NOW Legal Defense and Education Fund
Older Women's League
Public Voice for Food and Health Policy
Rachel Carson Council
Safe Alternatives for our Forest Environment (S.A.F.E)
Service Employees International Union
Society for Progressive Supranuclear Palsy, Inc.
Treatment Action Group
United Church of Christ, Office for Church in Society
United Leukodystrophy Foundation
United Parkinson Foundation [NOTE SPELLING CHANGE]
Wilson's Disease Association

June 17, 1996

The Honorable Nancy L. Kassebaum, Chairman
Committee on Labor and Human Resources
United States Senate
Washington, DC 20510

Dear Senator Kassebaum:

We, the undersigned members of the scientific community, oppose current legislative reform proposals to privatize the Food and Drug Administration (FDA) review and approval functions by permitting industry-financed third parties to review new drugs.

As we understand it, one of the principal concerns underlying the current FDA reform effort is the time and expense required to bring new drugs to consumers. While there may be various ways to streamline the drug review and approval process, relying on third-party reviewers will cause even greater problems. Shifting the responsibility for drug reviews to third parties enhances neither the safety nor the efficacy of new drugs.

On the contrary, proposals to implement third-party reviews introduce new and potentially harmful problems.

One of the most critical features of the current drug review process is the element of independent, unbiased judgment brought to bear on the available data and the recommendations to FDA by its review groups. FDA reviewers are provided with information about, and have extensive knowledge of, all similar approved drugs--something we consider a vital context for consideration of any investigational or new drug application. Less well-informed and experienced reviewers engaged through a third-party contract may lack this important backdrop, as well as the skills necessary to conduct the most thorough review.

Privatization will dramatically increase the potential for abuse and potential conflict of interest. Individuals who are stringent in their demands for clear and convincing data are unlikely to be engaged regularly for reviews when the drug sponsor's interest is squarely on the side of approval. Clearly, only careful and unbiased oversight, as provided by FDA, reduces the possibility of abuse and/or conflict of interest.

These bills impose significantly increased burdens on the FDA without additional resources. These bills also impose substantial burdens on Scientific Advisory Panels by requiring six annual meetings regardless of whether there is anything to review. The bills require detailed written responses to sponsors on virtually any issue that may arise during the review process.

Additionally, the bills subject any FDA decision about drugs to judicial review potentially threatening to paralyze the Agency with unnecessary litigation.

In summary, proposals to establish a third-party review mechanism will not enhance the scientific community's ability to bring new drug treatments to market nor will they enhance our ability to provide safe and effective treatments to the public. In fact, these proposals will increase the likelihood that ineffective, unsafe and possibly dangerous compounds will come to the marketplace.

We urge you to reject attempts to privatize the FDA.

Sincerely,
(list of signers to follow)

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Boston University School of Medicine

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National Minority AIDS Council

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The Reverend Ted Karpf
Executive Director
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United States Senate

COMMITTEE ON LABOR AND
HUMAN RESOURCES

WASHINGTON, DC 20510-6300

May 22, 1996

Dear Colleague,

We are writing to share important testimony on the subject of FDA reform delivered on Wednesday, May 8, by Dr. David Kessler, Commissioner of the FDA. We also want to let you know of pending efforts to rewrite the Federal Food, Drug, and Cosmetic Act and reform the role of the FDA. Dr. Kessler's testimony is specifically directed at legislation introduced in the House, but much of it is relevant for legislation before the Senate, as well.

The Senate Labor and Human Resources Committee recently voted to report S. 1477, "The Food and Drug Administration Performance and Accountability Act of 1996." This legislation has constructive elements, but unfortunately it also would seriously compromise the FDA's ability to protect American consumers, and could actually slow the development of priority new products. House Republicans have introduced even more unsatisfactory proposals, but no bill has been reported yet.

FDA is the nation's premier consumer protection agency. It ensures the safety and effectiveness of products ranging from food, blood plasma, and childhood vaccines to prescription drugs and medical devices. Consumers rely on FDA to guarantee the safety of products making up one-quarter of our total economy. FDA approval of medical products is recognized as the gold standard for the world.

But recently FDA has been the target of an intense, industry-sponsored campaign to privatize its core functions and reduce its ability to protect the public.

The anti-FDA campaign centers on allegations that patients are suffering because of agency delays that deny access to needed drugs already approved in foreign countries. In fact, FDA cut drug review times 40 percent between 1987 and 1993. By 1994, FDA was approving drugs as fast as or faster than Great Britain and other foreign countries, according to the General Accounting Office.

Since GAO completed its study, FDA review times have dropped even farther. Unlike foreign approval authorities, FDA has combined speed with safety. FDA's record of approving drugs that were subsequently withdrawn due to unacceptable injuries is far better than its foreign counterparts.

The bill will impose so many new bureaucratic requirements and burdens on the agency that it will be unable to perform its priority functions in a timely and effective way.

Because of these concerns, a broad coalition of patient advocacy and consumer groups--including the National Organization for Rare Disorders, the National Breast Cancer Coalition, the American Foundation for AIDS Research, Consumer's Union, and the National Council of Senior Citizens -- has urged that S. 1477 be modified or rejected. Editorials in the Washington Post, New York Times, and other journals have criticized the legislation and urged caution.

We hope to work with the proponents of S. 1477, so that the unacceptable elements of the current bill can be eliminated. We encourage you to support our efforts to seek bipartisan, constructive reforms which strengthen, not weaken, public health protections and enhance the FDA's productivity. While the FDA is not perfect, the pending congressional proposals for "reforming" FDA would undermine essential standards and undercut public confidence.

We are enclosing Dr. Kessler's testimony, a summary of S.1477, a more detailed explanation of our concerns, and additional materials we hope you will find informative. If you would like further information, please call David Nexon on Senator Kennedy's staff (47675) or Paul Kim on Senator Pryor's staff (4-5364).

Sincerely,

Edward M. Kennedy

David Pryor

Enclosures

This exemplary record does not mean that FDA cannot be improved. The Agency is now implementing significant reforms to expedite the approval process, reduce unnecessary regulatory burdens on industry, and address specific trouble spots, such as excessive delays in approval of devices and food additives. Bipartisan provisions in the FY 1996 Omnibus Appropriations Act recently signed into law by the President will improve America's unduly restrictive drug export policy and create a more level playing field with foreign competitors. Clearly, there is a role for constructive reform, but changes that weaken FDA's ability to protect American consumers are unacceptable.

Provisions in S.1477 that will contribute to constructive reforms include steps to encourage earlier and more frequent cooperation between FDA and industry to reduce total development time. The bill also codifies some of the reforms that FDA has already undertaken and provides authority for other reforms that the agency and industry have agreed upon.

Nevertheless, numerous provisions of S.1477 will create an unacceptable risk to public health and safety. If enacted, they will weaken FDA and turn over key functions to private industry. Specifically:

The bill will eliminate FDA authority to require prior review and approval of <u>any</u> manufacturing changes, even those that could result in contamination of the blood supply by HIV, or release of polio vaccines that cause polio rather than prevent it.

The bill will turn over review of medical devices to private companies selected and paid by the regulated industry, even high risk devices such as heart valves and pacemakers. The inherent conflict of interest is obvious.

The bill will establish unrealistic time-frames for product review, without providing additional resources for the agency. If FDA fails to meet these time-frames, it would be forced to contract out review functions to private organizations. This change will make it more difficult for FDA to protect the public against specific products that are not safe and effective. It will also drain resources from the agency and ultimately cripple it as an effective regulatory body.

The bill will create a priority for products first approved in Europe. The agency will be expected to review these products more quickly than competing American products, even if the American products are more significant for public health. In addition to distorting review priorities, this provision will encourage American companies to shift research abroad.

The bill will weaken the agency's ability to require appropriate labeling on prescription drugs, even though Medicare alone spends $20 billion annually on hospitalizations resulting from improper use of prescription drugs.

The Washington Post

AN INDEPENDENT NEWSPAPER

The House and the FDA

A CERTAIN disconnect persists between the goals expressed by proponents of Food and Drug Administration reform legislation—currently beginning its trek through the House after hearings last week—and the more sweeping, problematic and sometimes downright dangerous measures that are actually being proposed. Much of the testimony at the hearings consisted of wrangles over whether the House-sponsored measures on drugs and device review would, as FDA analysts testified, irresponsibly preempt a wide range of safety regulations at the state level. More general and urgent is the concern over whether the Republican-backed strategy of farming out significant chunks of the safety review process for even the riskiest medical devices and drugs—what some would call "privatizing" the main FDA functions—would effectively remove any government ability to enforce a standard on which consumers could rely.

Unhappily, the answers to both these questions appear to be yes, though the proponents of the bills keep reiterating that their only aim is to streamline the FDA's functions, ease the burdens on U.S. drug and device manufacturers and help the agency do its job better. But if the FDA for many years loomed over the medical approval process like some sort of terrible bureaucratic demon, with small companies telling horror stories about rooms full of documents and endless, unexplained delays, that isn't the ground over which the current legislative battle is being fought. You rarely hear in these criticisms any account taken of the several-years push to speed up those processes under FDA Administrator David Kessler—with the result that the United States now approves most new drugs as quickly as the British and European approval systems. The Senate finished a similar process two weeks ago, bringing out of the Labor and Human Resources Committee a bill that had gone in with elaborate safeguards for the few pilot programs that would allow contracting out—but that emerged from the committee with those pilot programs suddenly and inadvisably expanded to full-fledged changes of approach and philosophy.

Would it be easier and better for drug and device companies to bring out new products if, as many device manufacturers want, the FDA were simply to rule that a drug cleared in Europe could be marketed here without further testing? Would yet more simplification of the safety testing and outright removal of the standard for "efficacy"—a drug or device must actually do something, not just avoid harm—increase the flow of possibly therapeutic new medical products? Maybe—in a world where all devices and drugs *could* be assumed to be safe and no peddler of an experimental treatment had ever been known to cut a safety corner or miss a possible danger. That's not the world as it is, though. Streamlining beyond a reasonable point carries costs—costs that are being too little acknowledged by the proponents of these reforms.

Edward M. Kennedy

Prescription for Disaster

Republican legislation in Congress to "reform" the Food and Drug Administration would dramatically weaken the FDA's ability to protect the public health. The t on the FDA is particularly serious, because the agency is responsible for the safety of a quarter of all the products in the American economy—especially the food we eat and the prescription drugs we take.

The Republican bills would water down requirements that guarantee these products are safe and effective. They would turn over of the FDA's most important functions to private industry, with built-in conflicts of interest. They would give preference to products approved in Europe and other foreign countries, where the public is less well protected. And they would saddle the agency with so many new bureaucratic requirements and so much red tape that it would be unable to do its job. If the Republican proposals are enacted, Americans can expect many more drug disasters like thalidomide and DES, medical device failures like the Dalkon shield, lethal vaccines like the Cutter polio vaccine, threats to the blood supply and even threats to the food supply, such as the "mad cow disease," which has rocked the British beef industry.

The Republican proposals, by eliminating essential FDA oversight of the production of medical products, threaten the safety of drugs, medical devices, blood and vaccines. A minor manufacturing change that alters the solvent to kill viruses in blood products can result in ineffective sterilization of the blood, risking the transmission of AIDS or hepatitis. A change in the filters used to produce vaccines can turn a protective vaccine into a killer. A change in filters used to produce the Cutter polio vaccine resulted in 200 cases of polio in the 1950s, before the FDA required more rigorous standards. Under the Republican bills, the agency would no longer be permitted to review such manufacturing changes in advance to ensure that the public is protected.

The House Republican bill eliminates existing requirements for the FDA to approve certain products that can be dangerous to public health—such as leaky surgical gloves or faulty diagnostic tests. In recent weeks, it was revealed that a defective new AIDS test kit was distributed to 2 million patients abroad. American consumers, however, were spared exposure to this dangerous product.

The Senate bill gives the FDA only 90 days to review certain new food additives, even though these additives can result in the involuntary exposure of millions of Americans to potentially harmful substances.

The Dalkon shield, used to prevent pregnancy, injured 90,000 women because of a design flaw. This tragedy led to legislation strengthening FDA oversight of medical devices. The Shiley heart valve proved vulnerable to breakage, killing the patients. Before the valve was withdrawn, the manufacturer proposed a new version six times more dangerous than the original. The FDA rejected it, but 4,000 patients received it in Europe. Under the Republican bills, the FDA's ability to prevent such tragedies would be seriously compromised.

The House bill would reduce standards for approving a new use for a drug already approved for another purpose. The lower standard would restore the pre-1962 requirements that brought us DES. In recent years, drugs approved for life-threatening heart arrhythmias were widely prescribed for mild arrhythmias. This "off-label" use of the drug has been estimated to have caused as many as 50,000 deaths.

Both the Senate and the House bills contain an inherent and outrageous conflict of interest. They are designed to shift responsibility for product approval from the independent experts at the FDA to private businesses. The profitability of these firms would depend on the fees they attracted from the very companies whose products they review. The Senate bill pretends to give the FDA final approval of the decisions of these private reviewers, but the time frames for action are so short and the rules for oversight so limited that the agency would be reduced to little more than a rubber stamp. The House bill is even more extreme, removing the FDA from certain product approvals altogether.

As hard as it may be to believe, another provision in the bills would prohibit the FDA from requiring companies to make information available to patients on possible dangers of prescription drugs. At a time when hospitalizations from improper use of prescription drugs by senior citizens cost Medicare $20 billion a year, it is foolish to deny patients information they need to monitor their use of medications.

The Republican bills also contain provisions to micromanage the agency. The strategy of the Republicans and their special interest constituency is clear: Set up procedures that make it impossible for regulatory agencies to protect the public, and then use their failures as an excuse to dismantle them.

The assault on the FDA is fueled by a well-funded campaign alleging that patients are suffering because foot-dragging by the agency is denying them needed drugs already approved in foreign countries. Much of the funding for this campaign comes from tobacco companies, who have their own reasons to discredit the FDA. In fact, FDA drug review time was cut by 40 percent between 1987 and 1993. According to the nonpartisan congressional General Accounting Office, by 1993 the United States was reviewing drugs as fast as, or faster than, Great Britain and other foreign countries. Review times in the United States have dropped even farther since.

And unlike foreign approval authorities, the FDA has combined speed with safety. Between 1970 and 1992, 56 drugs were introduced in France, Germany, Great Britain and the United States that subsequently had to be withdrawn because they were unsafe. Only nine had been approved in this country, compared with 31 in France, 30 in Germany and 23 in Great Britain.

The FDA is not perfect, but it is still renowned as one of the most effective regulatory agencies in the world. There is always room for improvement, but the Republican proposal is a blueprint for demolition, not modernization, and Congress should reject it.

The writer is a Democratic senator from Massachusetts

The Washington Post

AN INDEPENDENT NEWSPAPER

Prodding the FDA

IF YOU'VE heard the ideological fervor with which anti-regulatory types habitually attack the Food and Drug Administration, you might be surprised at the sorts of issues that are occupying the warring sides on FDA "reform" legislation in the Senate. The bill, sponsored by Sen. Nancy Kassebaum (R-Kan.), has little in common with the plans that came out of Speaker Newt Gingrich's Progress and Freedom Foundation or the Heritage Foundation last year. Those groups regard the FDA as a particularly noxious and burdensome example of regulatory excess, and their visions include stripping or privatizing the FDA's enforcement powers or eliminating the requirement that a drug be "efficacious" as well as "safe" in order to go on the market.

None of these approaches got the support of the mainstream pharmaceutical industry, which relies on the FDA and gleans both legal and marketing advantages from its stamp of approval both here and abroad. What the drug companies, the medical-device companies and the young biotechnology industry wanted was to prod the agency out of longstanding habits of bureaucratic backlog, foot-dragging and unnecessary paperwork. The Kassebaum bill does this by a complicated system of deadlines, structural changes and "hammers"—points in the development process at which the FDA would have to approve or disapprove a drug or explain why it hadn't acted. As it happens, these are areas where the FDA has itself made strides, with agency head David Kessler instituting reforms to reduce backlogs and bottlenecks.

The Hill fight turns out to be mostly about whether this is happening fast enough, how much further and faster it can safely be pushed and who—FDA or Congress—should have final say over its shape. Parts of the bill are designed to speed up the progress of big drug trials and reduce the time needed to file certain kinds of applications. The questions here are simple scientific ones: What is the optimum setup for a big drug trial involving 4,000 college students? Can that number be safely cut to 1,500 students?

It may very well be, as the drug companies complain, that years of FDA caution have "barnacled" the process till a push like this was needed to get things moving faster. But aside from the motivational qualities of the threat of legislation, you've got to wonder whether these are questions best settled by a legislative body containing, on the Senate side at least, exactly one doctor.

The Washington Post

Next Round on the FDA

A DRUMBEAT continues for what's being called "reform" of the Food and Drug Administration. Sen. Nancy Kassebaum (R-Kan.) introduced a bill in December that would push the FDA toward what her spokesman characterizes as "creating a collaborative process" with drug companies and device manufacturers and tightening the deadlines on the process by which the agency certifies drugs as safe and effective. A group called Citizens for a Sound Economy released a spatter of radio ads. Characters representing the worried families of sick people engaged in mournful dialogues about how the FDA still hasn't approved "that new treatment" and how maybe "Congress needs to shake them up, too."

Though the players are new, this is yet another round of a long-running oscillation between the two dangers any government confronts in regulating drug safety: being too careful and not being careful enough. The most famous public health disaster from not-careful-enough drug regulation was, of course, thalidomide. It was followed by years of increasing caution and eventually a fair amount of bureaucratic slowdown at the FDA. This brought the agency under attack from AIDS activists in the 1980s and the vice presidential government-reinvention initiative in the 1990s.

Between them, these two attacks have caused the pendulum to swing a considerable way back. The former sought and eventually got fast tracks for experimental drugs that, though they might be dangerous, offered hope to the dying. A General Accounting Office report last month certified that the FDA had all but eliminated its backlog and cut approval times by as much as half, in large measure because of a 1992 law that charged drug companies "user fees" to put more analysts on the case.

The restructuring bill seeks to push this process farther and faster and, in some cases, to remove the safeguards that make such speeded-up approval feasible. The Kassebaum bill proposes among other things to cut approval times sharply by bringing drug companies into the process, not merely of doing the experiments (they already do this) but of clearing and evaluating the results that are submitted to the agency for review. It also would lift restrictions on advertising for "off-label" or unapproved uses of drugs. Under current law, a doctor can prescribe a drug for any purpose, whether or not it's the purpose the FDA has tested and cleared, but the drug makers can advertise only where there is some evidence of effectiveness.

You can't do too much of this without careful attention to the safeguards that public health demands. Those weighing FDA "reform" should look carefully at the steps already taken before deciding whether to go farther down the path.

The New York Times

NEW YORK, TUESDAY, MARCH 12, 1996

Go Slow on F.D.A. Reforms

Americans who remember the thalidomide disaster in England 35 years ago, when many mothers who had taken the drug had babies with serious birth defects, were grateful that the Food and Drug Administration kept it off the market in this country. But now the F.D.A. has come under fire for taking too long to approve drugs and medical devices. Congress is considering legislation that is designed to speed things up, but that may go too far in loosening regulatory safeguards.

The F.D.A. aims to insure that drugs and medical devices are safe and effective and that food additives are safe. Companies applying for approval of new drugs and devices submit their research data to the F.D.A., which assembles expert advisory committees to help determine whether the safety and efficacy standard has been met.

But over the years there have been complaints that the agency's regulatory machinery grinds far too slowly. Many companies that manufacture drugs and medical devices complain that the process often takes years. Some patients with serious or terminal diseases like cancer or AIDS have been frustrated by agency rules that prevent them from trying experimental drugs.

Senator Nancy Kassebaum, Republican of Kansas, recently introduced legislation designed to ease the rules. Her proposal would set a deadline of four months for the review of breakthrough drugs, down from the present six months. It would cut approval time for all other drugs from 12 to 6 months. In addition, the proposed bill would allow approval of medical devices on the basis of less rigorous research than is now required.

If the agency fails to meet the specific review times, a company could still market its product on the basis of approval by the European Union. That's a return to the days before the agency was required by a 1962 law to make an affirmative finding of safety and not just rely on the testing of others

Dr. David Kessler, the F.D.A. Commissioner, insists that internal management reforms have already brought good results. Approval time for new drug applications was reduced from an average of 33 months in 1987 to 19 months in 1992. In 1994, 96 percent of new drug applications were acted on within the allotted 12 months. With the F.D.A already making good progress, Congress should be wary of pressing it to move too fast in approving new drugs. Haste could prove hazardous.

Our perspective

Risky reform

Go slow in making FDA changes

In 1955, while preparing a new anti-polio vaccine, Cutter Laboratories of Berkeley, Calif., accidentally introduced live polio viruses into what was supposed to be a dead-virus serum. More than 100 patients contracted the disease and 11 died before the tainted vaccine could be pulled from distribution. Congress responded by greatly expanding the authority of federal regulators to scrutinize every step of a drug's development and manufacture.

Those powers are among dozens that would be curtailed by a far-reaching Republican proposal to streamline — indeed to weaken — the federal Food and Drug Administration. The agency approves new drugs, medical devices and food additives.

The legislation goes way too far, way too fast.

A package of bills, moving separately through both houses of Congress, would tighten FDA deadlines, ease the paperwork burden on medical manufacturers, sweep aside state regulations that exceed federal standards, greatly expand the use of private laboratories to test new drugs and medical devices, and reduce the FDA's powers in a variety of ways.

The reforms are propelled in part by a legitimate concern: that FDA paperwork may keep promising drugs off the market and hamper American manufacturers in the race for cutting-edge technology. But these bills rely on untested techniques and remove too many of the safeguards that keep risky products off the market. Making modest changes, in the direction the FDA is already heading, is the way to go.

If the problem is a bottleneck in new-product approvals, for example, why not give the FDA more staff or the power to employ outside laboratories? These bills allow manufacturers to hire private labs directly, then submit their results to the FDA. If private labs come to depend on repeat business from manufacturers, the potential for conflict of interest is simply too great.

If the goal is merely to expedite FDA review, why do the bills allow manufacturers to shield basic test results unless the FDA specifically asks for them? Currently, this "primary" clinical data is part of the routine application. Separating that data only adds an extra step to the review process and invites the suspicion that companies have something to hide.

And if the legislation's authors don't mean to dilute FDA standards, why do they shift the burden of proof — from the manufacturer who must now prove a product safe before bringing it to market, to the FDA, which would have to prove that a product is dangerous before blocking its introduction?

The bills' sponsors say these measures are necessary because the FDA is incapable of reforming itself. But that is demonstrably false. Since 1987, the FDA has cut approval time for new drugs by half, to 16.5 months, and has cut the review time for most new medical devices by more than one-fourth. A recent study by the General Accounting Office found that in 1994, the FDA approved new drugs faster than its counterparts in Great Britain, Germany, France and Japan.

This is not to say that FDA reform is unnecessary. The review process for new medical devices remains tortuous and overlong. Manufacturers such as Minnesota-based Medtronic deserve a more "transparent" FDA so they can track their applications through the regulatory pipeline. And, as Rep. Jim Ramstad, R-Minn., has pointed out, third-party review has been used successfully by other agencies and could be expanded at FDA with proper safeguards.

Under some pressure from Congress and industry, the FDA has started pilot projects to expedite medical-device approval and use outside labs for new-drug applications. Those pilot projects should be expanded and accelerated. But it's too soon to say that the risk of good drugs kept off the market outweighs the risk of bad drugs unleashed on it. Since the subject is science, the FDA deserves to be tested by scientific method, not reformed by untested methods.

EDITORIALS

Sniping at the FDA

REPUBLICANS have gotten themselves into such a snit about the excessive amount of time the Food and Drug Administration spends reviewing new drugs that they are in danger of losing sight of the big picture.

Namely, the agency has tackled the problem itself, done a lot to streamline the review process and continues to move in the right direction.

GOP critics say patients and businesses are hurt because the FDA takes too much time to approve drugs and medical devices. No one disputes that in the past the agency has moved slowly. However, some GOP spin doctors overlook the fact that the median approval time for new drug applications has been cut in half. Today some drugs are approved in just six months.

Furthermore, the agency has an excellent track record for safety. Its regulators are very careful, but their thoroughness pays off in quality and patient confidence. Drugs approved by government regulators in Great Britain, Germany and France have had to be withdrawn far more often those that have won the FDA's stamp of approval.

Also to their credit, officials of the FDA are making special efforts to speed up federal approval of cancer drugs — aiming to knock a year off the process. And they're doing more to make cancer drugs that have been declared safe abroad available here.

Even so, frenzied House and Senate Republicans press ahead with demands to overhaul the FDA as though none of this were going on. Particularly troubling is the insistence on requiring faster reviews and permitting some parts of the drug-approval process to be contracted out to private vendors.

Certainly these accomplishments need to be understood. It's hard to believe that congressional Republicans could try to undercut such efforts — unless their goal is political gain rather than the health of America's people.

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General Manager | Mark A. Brown

Tuesday, *May 7, 1996*

HOW WE SEE IT

Keep watchdogs on job

Imagine going to court against a powerful manufacturer only to learn that the judge had been selected and paid by your opponent with promises that if he handled the case appropriately he'd likely be hired again. Does that sound like justice? Does it sound fair? Of course not. But that would be the result of three bills currently under consideration by the U.S. House of Representatives to privatize the Food and Drug Administration's review functions.

Pity the chickens: If the measures pass, the safety of drugs, medical devices and foods would be controlled not by the public's watchdogs at the FDA but by industry-retained reviewers. The foxes themselves wouldn't be watching the henhouses, but they would be writing the guards' job descriptions and paying for their work. Meanwhile, all of us chickens would become fair game.

The contention among pharmaceutical companies, medical device manufacturers and certain food producers is that it takes too long to receive approval for new products, and they've pumped thousands of dollars into the political campaigns of many legislators to influence their votes.

On the other side are the FDA and many consumer groups who fear what could happen to public health if monied special interests determine which products could go on the market and when.

Fastest approvals: According to the General Accounting Office, in 1987 the average approval time for new drugs was 33 months. In 1995, approval time had been reduced to a median of 16.5 months. For the 15 highest priority drugs, the median approval time was six months. Studies both by the GAO and the British-based Centre for Medicines Research all demonstrate that American patients have access to therapeutically important new drugs that have been proved safe and effective sooner than the citizens of any other nation.

While the three bills under consideration are called "reform" bills, none of the so-called reforms does anything to improve public health or safety. Currently, FDA reviews are conducted by scientists, engineers and medical researchers who work for the public. They comply with stringent financial disclosure and conflict-of-interest requirements designed to protect the decision-making process against bias.

A reviewer paid by a drug company to decide the future of that company's products can hardly be unbiased. We don't think the public good is served by such an arrangement.

Make sure new drugs are safe

Don't sacrifice FDA safeguards for speed and profit

THE FEDERAL Food and Drug Administration has made considerable progress in loosening its regulatory strings to approve new products faster to the potential benefit of patients and consumers.

Changes in the process used to approve cancer drugs and to provide quicker access to drugs already approved in other countries are among sensible reforms already implemented at minimal risk to the public.

However, changes being pushed now in Congress go too far, too fast. They risk the public's health in a mad rush to deregulate without due regard for the consequences.

The FDA's historic mission has been to protect the public from dangerous drugs, medical devices and food additives. Proposals in the House to shift much of that duty to the private sector — the same sector that profits from new products — are akin to having the fox guard the medical hen house.

One, for instance, would shift the burden of proof for new food additives. Instead of manufacturers having to prove that products are reasonably safe, the FDA would be saddled with having to show that additives are unsafe. That's a nearly impossible standard to meet for products on which not enough studies had yet been done.

Another proposal would take the impartial FDA out of the business of doing safety reviews for new products. Instead, the reviews would be done by an FDA-approved contractor to be picked by the very company seeking the approval.

It doesn't take much imagination to see the potential for chicanery and conflict of interest there. But even assuming the private sector is strictly scrupulous, FDA Commissioner David Kessler is persuasive when citing another shortcoming.

Kessler notes that FDA workers who review data about various products have a broad base of knowledge to draw on when assessing a new item's claim. For example, he said, an FDA reviewer a few years ago uncovered fraudulent data being used to push a skin cream designed to protect U.S. soldiers from chemical attack. The FDA specialist was able to spot the phony data only because they were out of line with results from other products he had reviewed.

That kind of safeguard would be lost with the congressional proposal to let independent contractors take over the task. When high-risk products are involved, the results could be deadly.

The FDA already is further streamlining its operations. It has begun work on pilot projects to involve third parties in reviewing low- and moderate-risk products. New, less rigorous standards for testing and using cancer drugs were announced a few weeks ago. And approval time for drugs has been significantly reduced.

Republican prodding and anti-regulatory fervor no doubt played a part in many of those improvements, and most make sense.

But reform can go too far. These do, and so do some of the other efforts being pushed by a House subcommittee on health. Congress should heed Kessler's warnings and let the FDA keep putting safety first

The Boston Globe

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The FDA and Shannon McDermott

Janet McDermott is waging a valiant struggle to get medication that will prevent the seizures suffered by her daughter Shannon. But Shannon's plight should not encourage support for a bill in Congress that would force the Food and Drug Administration to speed up the approval process for new drugs.

The McDermotts, who live in Marshfield, have tried every treatment recommended by Shannon's doctors to relieve the seizures. The latest drug prescribed for the 8-year-old is Sabril, not yet approved in the United States. Shannon's mother must go to Canada for it.

Mrs. McDermott has also traveled to Washington, at the expense of a pharmaceutical trade group, to lobby on behalf of a bill that would shift the balance of regulatory power at the FDA. This measure would apply to every experimental medicine, from cancer treatment to baldness cure, and to medical devices like heart valves or prostheses.

Under present law, the FDA is exceedingly careful about which drugs it qualifies for use. Before an application can be accepted, medicines must undergo animal tests and at least two clinical trials on people. Approval for Sabril was delayed when the first use on animals showed that it might cause holes in the brain. Subsequent tests showed that this condition did not apply to humans.

It is reassuring that federal law demands rigorous testing. The legislation, which just cleared the Senate Labor Committee over the objections of Sen. Edward Kennedy, would change the emphasis of the FDA from review to approval. In the most extreme case, the FDA would have to accept a drug cleared by the European Union unless it can state in writing why approval for the medicine should be withheld.

Only four years ago, Congress imposed a user fee on the drug industry. The money is being spent to hire 600 additional reviewers, and approval times have been reduced to 16 months, compared with 33 months in the late 1980s.

In response to public pressure, the FDA has already expedited approval of drugs that fight AIDS and cancer. Other improvements in the process may well be in order, but these are best recommended by an unbiased group before being considered by Congress. An independent review of FDA procedures should be undertaken only when the impact of the user fee can be assessed.

As for Sabril, an FDA spokesman, James O'Hara, says the drug could be offered to Shannon McDermott on a special, individual testing basis. Hoechst-Marion-Roussell, the manufacturer, demurs, saying that it would rather devote resources to testing the drugs on large groups. Shannon would not qualify for such group trials.

That decision is well within the company's rights as a maker of medicine. Julie O'Dell, a company spokeswoman, says the Sabrin work should be completed by the end of the year and the drug available for widespread use in 1997. That's a long time in the life of an 8-year-old, but in matters of drug safety, caution is better than haste.

WEDNESDAY, APRIL 10, 1996 THE WASHINGTON POST

The FDA Legislation

UNTIL RECENTLY, the Senate bill to streamline some drug and device approval procedures for the Food and Drug Administration was moving forward cautiously. The bill that emerged from committee, though, is incautious—loaded with last-minute changes that destroy any claim to judiciousness.

An amendment by Sen. Dan Coats (R-Ind.) seizes on and vastly expands what would have been an FDA pilot program—an experiment allowing companies to opt for a private third-party route that might speed up the more onerous parts of the approval process, whose results the FDA would then look at before giving the final sign-off. The Coats amendment turns this into a procedure in which any manufacturer could request the third-party review for any device, could itself choose the private company or companies to perform the review and could decide how much to pay for it—a process that gives huge and obvious incentives to third-party review companies to be as fast and undemanding as possible. And under this scheme, the chosen outside reviewers, not the FDA, would effectively have the final say. (The FDA would have to prove harm in order to prevent a device's coming to market, rather than, as now, the manufacturer's having to prove safety.)

The idea of prodding the FDA to offer third-party review as a road to efficiency, without recklessly dismantling safeguards, was at least consistent with the stated argument from "reform" proponents that the purpose is not to weaken safety protections but merely to serve industries' and patients' interests better by bringing the long, drawn-out approval process to conclusion more quickly. Accordingly, the pilot program would have limited the experiment to devices classed low or moderate risk already, limiting the chances of danger in case the untested system proved too porous. The Senate committee, though, changed that, extending eligibility for the third-party system to all devices—including the ones classed as high risk.

These risks aren't exactly abstractions. Medical devices get embedded in the human body, hold people's bones together, are carried in the body for years. Does anyone seriously think for a moment that there is a public outcry for the removal of incentives to double-check the safety of things that shunt fluids from the human brain, clear heart patients' veins, are buried in the skin of people's arms? Or, for that matter, for the removal of an independent check on the safety of drugs and the food supply?

Arguments over efficiency and how best to get the job done are legitimate, but the public interest in having the FDA ride herd effectively on the safety of these miraculous medical devices and incredibly powerful drugs remains high. The Senate committee add-ons don't sufficiently recognize or respect that fact.

New York Times, Saturday, April 6, 1996

Streamlining the F.D.A., Safely

The Clinton Administration is making it easier for cancer patients to get promising drugs that have not been fully tested. By loosening some of the Food and Drug Administration's rules to accelerate access to experimental drugs, the White House may defuse more sweeping and dangerous reforms under consideration by Congress.

The F.D.A.'s job is to insure that drugs and medical devices are safe and effective and that food additives are risk-free. The agency gives approval only after lengthy clinical trials by the manufacturer. But many companies complain that the F.D.A. is slow to respond, escalating costs. In addition, some groups representing AIDS and cancer patients say that its bureaucracy denies them faster access to promising remedies.

Congress, the companies and the agency are now struggling to get drugs and medical devices to needy patients as quickly as possible without jeopardizing public health or sacrificing the standards of safety and efficacy that give consumers confidence in F.D.A.-approved products.

The Clinton Administration proposes faster approval for cancer-fighting drugs. Previously, the F.D.A. asked for proof that an experimental drug would help a patient's chances for survival or improve that patient's quality of life. Under the new rules, a drug can be approved based on a "partial" positive response, like shrinkage of a tumor. In addition, companies making experimental drugs that have already been approved overseas can seek permission to distribute those drugs to American cancer patients even before the F.D.A. has given final approval. These measures, which need no further approval, will take effect immediately and could apply to about 100 drugs under study.

The new initiatives are welcome but unlikely to appease Congress, which is pressing for more sweeping F.D.A. reform. Last month the Senate Labor and Human Resources Committee approved a bill sponsored by Nancy Kassebaum, Republican of Kansas, that calls on the agency to expedite clinical investigations of new drugs, devices and biological products as well as breakthrough drugs for life-threatening diseases. If the agency fails to review most applications within six months, the product sponsors could force it to contract with outside experts to complete the process.

Similarly, a bill being pushed on behalf of the House G.O.P. by James Greenwood of Pennsylvania sets tight approval deadlines and would turn over some F.D.A. review authority to third parties.

The F.D.A. would retain a supervisory role. But the outside experts and "third parties" envisioned in both the Senate and House bills could, under the guise of regulatory reform, lead to the privatization of many of the F.D.A.'s functions and undermine its role as an independent government protector of public health.

The drive to reform the F.D.A. comes at a time when the agency has been improving its performance. In 1994, 96 percent of new drug applications were approved within the 12 months allotted under current law, and the agency has been streamlining many of its internal procedures. Important life-enhancing drugs and medical devices should obviously get to consumers as quickly as possible. That is what the Administration's new cancer drug initiative aims to do. But safety and effectiveness should not be sacrificed for efficiency. At the moment, the Administration seems more mindful of that than Congress.

SUNDAY, MARCH 3, 1996 The Washington Post

OUTLOOK

Commentary and Opinion

Sugar-Coating a Bitter Pill

Sweet Talk Aside, the GOP and the Pharmaceutical Industry Want to Cripple Safety Testing

By Thomas J. Moore

THE DRUG industry and its allies call it "streamlining the Food and Drug Administration." Patients are promised they will get new drugs more quickly. Hidden behind this slick sales pitch is the most frightening effort to roll back drug safety and efficacy laws since federal regulation began in 1906.

With Senate Republicans promising floor action as early as next month, this legislative blitz may succeed before a broader public realizes what's at risk. On Wednesday the Senate Labor Committee meets to mark up its bill. While described in some press accounts as "moderate," it would achieve an unprecedented cutback in drug testing requirements. The House Commerce Committee—whose chairman is highly critical of the FDA—has promised to get a bill to the floor promptly. The Pharmaceutical Research and Manufacturers Association and its allies already have a major lobbying campaign in high gear. It features ads attacking the FDA, a letter-writing effort and the usual generous campaign contributions. Industry lobbyists are even rounding up patients dying of serious diseases or their relatives and flying them to Washington to plead with key members of Congress.

BY JOHN MACDONALD FOR THE WASHINGTON POST

Indeed, why do we insist on a powerful FDA that requires elaborate clinical testing of each new drug that can take 10 years to complete and a year to evaluate? Why not let medical researchers, doctors and patients make the judgments about drugs with minimum government interference? We test because prescription drugs regularly cause the most painful injuries imaginable—hideous birth defects, irreversible brain damage, life-long addiction and thousands of preventable deaths.

Other damage is less severe but more widespread. For example, 20 of the 200 most commonly prescribed drugs cause sexual disfunction. Two of the most widely used

See FDA, C4, Col. 1

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classes of c —beta-blockers and benzodiazepine tranquilizers—impair judgment and the ability to think clearly. Painkillers, including aspirin, cause thousands of hospitalizations each year for perforated ulcers or internal bleeding.

Having recently studied the toll of death and injury from prescription drugs under existing law, I shudder at proposals to weaken an already inadequate system. Based on my research, I estimate that each year prescription drugs injure about 5 million Americans enough to require medical treatment. Another 1 million are injured so severely they require hospitalization. Deaths could be 100,000 or more. Overall, you are 10 times more likely to be severely injured by a prescribed drug than in an automobile accident.

These figures have to be approximations because there is no systematic monitoring of the adverse effects of drugs. In most states, you must report an auto accident with a few hundred dollars damage. But when a prescription drug is suspected of causing death or serious injury, neither doctors nor hospitals have any legal obligation to report it. In one famous study of Rhode Island doctors, only 55 of 27,000 significant adverse drug reactions believed to have occurred in one year were ever reported. Injuries occur when anything goes wrong in the complex system that requires thorough clinical testing, intensive FDA review, effective post-market surveillance, alert physicians and knowledgeable patients. But without adequate clinical testing the whole system is crippled from the start.

Thousands of lives are also at risk when drugs that the FDA-approved for one medical condition become widely prescribed for another. This is called "off-label" use, and two Senate bills being championed by the industry would encourage still more of this practice. Such off-label use helped create the nation's worst drug disaster.

A family of drugs that were FDA approved for life-threatening heart rhythm distu s were widely prescribed for patients with mild irregular heart beats. In 1989, a government-sponsored clinical trial proved conclusively that two of these drugs killed 6 percent of the heart patients who took them in just one year's time. That would mean an estimated 50,000 deaths among similar patients taking all brands of these drugs in just a few year's time—a death toll comparable to U.S. losses in the Vietnam War.

Another loophole in existing law allows drugs to be sold for long-term use without long-term clinical testing. The most frequently prescribed drug today is conjugated estrogen, a hormone that women take after menopause. Last year a large—but not definitive—epidemiological study showed that taking estrogen increased the risk of breast cancer. On the other hand, another study—also not definitive—suggested estrogen may cut the risk of death from heart disease. Here is a drug on sale for decades to millions of people and generating hundreds of millions of dollars in revenue every year. But because even now we haven't done the proper clinical studies—costing a fraction of those sales—we don't know whether it is harmful or beneficial over the long term.

Even more lives are at stake in new questions about the safety of calcium channel bloc —a family of heart drugs taken ower blood p re and prevent chest pains. They are taken daily by 7 million Americans. Last year three studies appeared in peer-reviewed medical journals suggesting that some—or possibly all—of these agents may cause heart attacks instead of preventing them. The evidence persuaded an expert panel at the National Institutes of Health to issue an unusual warning, saying the safety of all calcium channel blockers was "unclear" and urging doctors to avoid one of them, short-acting nifedipine (sold as Procardia and Adalat). It doesn't do us any good to get new drugs quickly if we can't tell their effects.

The experience with Prozac, Paxil and other anti-depressants shows that even when a drug proves beneficial, we also need to take a careful measure of its adverse effects. Talk to patients who are taking these popular drugs and you will often get passionate testimonials about the benefits. But you will also hear the sorrow of those who say they've lost their interest in sex. At last official count, there were 242 different adverse effects of Prozac, including 39 separate problems related to genital or urinary systems. About 1 in 5 people who take Prozac experience an adverse effect.

All this explains why clinical testing is so essential, but not why it is so expensive or needs to take so long. Despite its aura of high-tech wizardry, drug research remains a hit-or-miss game where researchers grope in the dark, wrestling with immensely complex biological systems that no one yet understands. This is one reason why 90 percent of drugs that enter human testing fail to win FDA approval. "Drug development is like watching people who learned how to make a transistor but don't yet know how a radio works," notes experimental pathologist Christian Haudenschild. Biological ignorance is an argument for more drug testing not for less.

Escalating costs of drug development is often used to justify less testing. A Tufts University study estimated it costs $291 million to bring a new drug to market—and the industry claims it costs even more. But the amount spent on the actual human and long-term animal tests is less than $16 million. Where did the rest go? To test the other nine drugs that didn't make it, to ongoing research and to the interest costs of the money over the full period.

BY JOHN MACDONALD FOR THE WASHINGTON POST

Costs are also driven up by drug companies scrambling to copy someone else's winner. There are currently in development 127 drugs that work on the same mechanisms as Prozac or Elavil. Most will never make it to market, but they will help run up the research bill. And finally, testing is so expensive because the effects of many popular drugs are so small that it takes observing thousands of people for several years to detect any measurable effect. Cholesterol-lowering drugs are the classic example. Look at the evidence from the clinical trial of Pravacol, one of the most effective: Among the 3,302 people who took it for five years, there were 74 fewer heart attacks and deaths. Those promoting the drug can say correctly that it reduces the risk of death or heart attack by 31 percent. But o ry 1,000 persons who take Prava for one year, 995 get no benefit. To produce just this evidence involved screening 81,000 patients, took more than five years and cost millions.

With the health of millions of people at stake, certifying that a drug is safe and effective is one of the most difficult and complex scientific judgments i in our society. Not only do we nee rigorous clinical studies, we also nee an expert and impartial FDA to judge them. If the final tests of a drug show tell-tale signs that it might be danger ous, I want an agency smart toug enough to stand up to a powerful pharmaceutical giant with millions alread invested.

In the User Fee Act of 1992, Congress showed that we can indee speed drugs to patients without cuttin corners on safety and clinical testing Using fees collected from industry, th FDA has hired more experts to revie drugs—which are now being approve in about half the time it took in 1987 But much still remains to be d e.

We need a coherent program to re duce the hundreds of thousands of pre ventable deaths and severe injurie from drugs. The whole system need an impartial oversight agency modele on the National Transportation Safet Board. We need expert panels to ide tify the drug studies that are too e pensive—or not potentially profitabl enough—for a drug company to unde take. We need to fix the informatio system that buries doctors under a avalanche of often biased and unnece sarily complicated data while depriv patients of basic facts about the dru they take. Prescription drugs rema the biggest commercial source of acc dental injury and death for which the is little or no hope of compensation.

Congress is now heading in th wrong direction. We should encourag drug companies to do more testing a less marketing, not enact a law th would achieve the reverse.

Houston Chronicle March 23, 1996

Don't let Congress cripple the FDA

By JOE GRAEDON
and TERESA GRAEDON

People's Pharmacy

Americans are an impatient people. We have grown accustomed to instant coffee, one-hour photo processing, fast food and faxes.

Delay is frustrating. If you don't believe us, just try stepping into the express checkout lane with more than 13 items.

Obsessed with speed, we tend to forget there can be risks to rushing. We see every innovation as progress and rarely pause to examine its potential problems.

This may explain why the current legislative proposals to "streamline" the Food and Drug Administration seem so appealing. Everyone wants a quick cure for cancer, AIDS, Alzheimer's disease and arthritis. In its haste to hurry the FDA's approval process, Congress may well hamstring this critical agency.

We are not big fans of the FDA. We often criticize this bureaucracy for its insensitivity and inflexibility. But without this watchdog, Americans would be at far greater risk of injury and illness.

Even under the current system, there are flaws. A General Accounting Office study revealed that more than half of the new drugs approved by the FDA are later found to have serious or even life-threatening consequences that did not show up in the original data.

It is estimated that more than 100,000 Americans die each year as a result of prescription drug problems. That's the equivalent of a 727 going down every day. If that many people were dying in plane crashes, there would be an outcry for the Federal Aviation Administration to crack down.

Prescription drug companies are aggressively promoting their products directly to consumers in magazines, newspapers and TV. In addition, many drugs that were once available only by prescription are now sold over the counter. Instead of cutting back on the FDA's oversight, this country needs better protection of the public health.

Millions of women are worried about the unresolved question of whether female hormones promote breast cancer. Reports that Ritalin and a common ingredient in laxatives cause cancer in animals has consumers concerned. And some people are frightened about the possibility that certain blood pressure pills may increase the risk of heart attacks.

Whether Congress cuts the FDA's authority, consumers are more vulnerable today than ever before. Doctors, overwhelmed with paperwork, have a hard time staying current on powerful new drugs. Pharmacists are being stretched to their limits, and managed care is affecting everyone.

As eager as we all are to have new and better treatments, cutting back on drug testing and speeding FDA review may not improve health overall.

Q: My husband has been on Mevacor for years to lower his cholesterol. We read that this drug causes cancer in animals. Is there any danger?

A: We wish we knew. An article in the Journal of the American Medical Association (vol. 275, p. 55-60) noted that lovastatin (Mevacor) and related drugs produce tumors in rodents. Whether this is a problem for humans remains controversial. The FDA does not have a good system for evaluating such long-term risks.

Joe Graedon is a pharmacologist. Teresa Graedon holds a doctorate in medical anthropology and is a nutrition expert. *The People's Pharmacy* with Joe and Teresa Graedon is a call-in show syndicated to many public radio stations.

Allison M. Zieve
And Sidney M. Wolfe

Don't Weaken The FDA Laws

In his Feb. 1 op-ed piece, "Keeping Doctors Up to Date on Drugs," Sen. Bill Frist tries to sell the public on a dangerous idea. He wants to remove the 34-year-old ban that ensures that drug companies do proper testing before they promote a drug or medical device for a particular medical use. The proposal touted by Frist—that drug and medical-device companies be permitted to promote their products for uses never approved by the FDA—strikes at the heart of the processes used to ensure that drugs and medical devices are safe and effective. Not surprisingly, the drug and medical device industries have been pushing this idea for some time.

Referring to "FDA-approved products," Frist misunderstands the federal drug- and device-approval systems. The approval processes do not evaluate the safety and effectiveness of a product in general, but only for a specified use. The FDA weighs the benefits of that use against the risks to determine if, on balance, doctors should be prescribing it for that particular purpose. Manufacturers are permitted to promote and advertise their products only for approved uses—those uses that have been evaluated for safety and effectiveness.

Experimenting with an unapproved (off-label) use exposes patients to unknown risks, usually without their consent or knowledge. A few years ago, thousands of physicians prescribed Tambocor and Enkaid to treat patients with mild irregular heartbeats—an off-label use of a drug intended for life-threatening heart conditions. The doctors and drug companies hoped these drugs would prevent cardiac arrest. They were proven tragically wrong when a study funded by the National Institutes of Health discovered that the drugs frequently caused cardiac arrest in recent heart attack survivors. The death toll—measured in thousands—would have been even higher if the companies had been free to promote the drugs even more aggressively for this off-label use, as Frist advocates.

Taking Exception

Frist also errs in suggesting that prohibiting sponsors from disseminating information about unapproved uses suppresses discussion or publication in journals of studies concerning off-label uses. In fact, the FDA's policy ensures that such discussion is objective and honest, untainted by the economic self-interest of a manufacturer seeking to expand its product's market. Under the FDA's recent draft policy statement, physicians are free to attend seminars on off-label uses and to publish and read articles on such uses. The product's manufacturer, however, cannot be involved in preparing, financing the dissemination of, or disseminating the material.

To permit written promotion of unapproved—including specifically disapproved—uses would be to pay mere lip-service to existing product-approval requirements and the clear intent of previous Congresses to protect the public from dangerous and unproven drugs and devices. Adoption of Frist's proposal would quickly halt much of the expensive clinical testing of unapproved uses needed to ensure safety. What corporation would invest millions of dollars in safety testing that might detect serious problems with its product when promotion for unapproved uses offers a faster, cheaper route to increased sales?

Finally, Frist states that a busy physician may not have time to seek out the latest information on all drug uses, apparently referring to unapproved drug uses. Yet he wants to relax the restrictions on off-label promotion because, he says, physicians should be trusted "to sort out" the information on unapproved uses. Senator, you cannot have it both ways. If physicians do not have time to seek out the latest information and are dependent on manufacturers sending them material on unapproved uses, manufacturers are likely to monopolize the information flow to physicians. Thus, these busy doctors will not see the complete story on the new use but only the information hand-picked by the manufacturers to increase their products' sales.

In short, the purpose of the approval processes is to prevent doctors and their patients from being misled by unproven health claims. No system of after-the-fact enforcement would be adequate to that task. When an unproven assertion of safety and effectiveness is made and relied on, the resulting injury is often irreparable. Our strong pre-market approval system is essential to protect our health and safety. The proposal Frist advocates threatens that system.

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THE LANCET

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EDITORIAL

In defence of the FDA

The US Food and Drug Administration (FDA) has a massive remit and is a huge organisation. It regulates 25 cents of every dollar spent by the American consumer, or about $1 trillion worth of goods and services annually. To do that FDA employs over 9000 people and has a budget of $1 billion. The agency's regulatory and enforcement successes are too much for the anti-government minions. For example, the speaker of the US House of Representatives, Newt Gingrich, has accused the FDA of "Stalinist" tactics and has called its commissioner, David Kessler, "a thug and a bully". Wrong.

Kessler has managed to speed a government bureaucracy in the right direction. The perennial complaint that new-drug approval takes too long is now outdated. Since passage of the Prescription Drug User Free Act of 1992, median approval time for new drug applications has fallen from 27 months in 1992 to 19 months in 1994. Alendronate was approved in 6 months (see p 1028). For applications handled through the user fees process (not all are), the 1994 median was 13½ months. A backlog of nearly 700 drugs awaiting FDA action in 1992 has been cut to zero, right on schedule. And the improved performance extends to generic drugs, biological agents, and medical devices. An automated cervical-screening system was approved in just 7 months (see p 1029).

Not content with or perhaps frustrated by this impressive record, FDA critics have stooped to irresponsibility. One Congressman recently announced that "2888 Americans have died needlessly because the FDA took too long to approve the coronary stent". A conservative lobby group has bought newspaper space to proclaim "If a murderer kills you, it's homicide. If a drunk driver kills you, it's manslaughter. If the FDA kills you, it's just being cautious". The advertisement continues: "during the seven years it took to approve tacrine, thousands of Alzheimer's patients gradually lost their memories . . . 14 000 heart-attack victims so far have died who could have been saved by the cardiac-pump during the two years the FDA has delayed approval". *Lancet* readers will not have tacrine was a wonder drug, or that the pump was such a marvellous invention. And readers will have seen enough drug tragedies to have learned the need for caution. 56 drugs were withdrawn from US, UK, German, and French markets in 1970–92; only 9 were US withdrawals.

The FDA has also been accused of slowing the pace of drug development in the USA by prolonging the pre-approval stages of pharmaceutical research. However, everywhere such development is taking more time. World wide, the lag from synthesis to marketing of a new drug increased from an average of 8 years in the 1970s to at least 12 by 1990. Of the 44 new drugs approved by the FDA in 1993/94, 17 were marketed first in the USA. Among the other 27 were 13 whose applications were not even filed with the FDA until an average of 7 years after they were introduced in another country. Indeed, the greener grass claimed to be growing in Europe seems less fertile to those who do business there. European pharmaceutical and biotechnology companies are pouring money into the USA.

Perhaps FDA critics would be silenced if other public health agencies—such as the Centers for Disease Control and Prevention—took up the slack of enforcement. The reforms that the FDA is making are streamlining drug development and approval; some of the more punitive measures that the industry finds burdensome are being lifted; and restrictions on minor drug manufacturing changes that pose no threat to public health are being eased. An additional goal is to speed device approvals by implementing user fees. And the FDA's stand against allowing drug companies to promote "off label" use of their products—surely an invitation to dangerous drug marketing—is welcome too. Much work remains to be done. For example, the acceptance of placebo-controlled evidence in preference to comparator drug trial data is a serious flaw in the regulatory process. Yet the absurd proposal that FDA functions be privatised needs fierce resistance, lest public debate over what is prescribed for patients be governed in private by the profit-makers.

Gingrich & Co.'s attack on the FDA can make anybody sick

Tom Bigler

One of the more preposterous and yet revealing proposals to surface in the still-evolving Gingrich manifesto is one that would greatly alter if not eliminate the federal Food and Drug Administration (FDA).

The FDA, among many other duties, has the responsibility of assuring the safety and effectiveness of the vast array of prescription drugs used in the United States. To ensure, for example, that there will not be an incidence in this country of the terrible experience in Europe that resulted from use of Thalidomide, the FDA requires exhaustive laboratory and animal studies before any new drug may enter the U.S. market.

This insistence on rigorous research consumes time — to which many pharmaceutical firms and patients object. The drug houses say that because of the delay they are losing money, while patients fear they are losing a cure.

It was the kind of complaint from a constituent which first got Rep. Newt Gingrich interested in challenging the FDA. As spelled out in two separate reports by two separate reporters for the Wall Street Journal in late January, his involvement says much about its inspiration.

In the summer of 1993, according to these reports, Gingrich introduced legislation designed to suspend duties on several drug components imported by Solvey Pharmaceuticals, Inc., which is headquartered in Gingrich's home district. Shortly thereafter, the company was approached by the president of the Progress and Freedom Foundation for a contribution. About six months later, Solvey gave $30,000 to the Foundation.

The Foundation president had been executive director of Gingrich's political action committee, Gopac. The Foundation is described as a conservative think tank created by Gingrich associates; its major functions are sponsorship of his nationally televised classroom lectures and the separate National Empowerment Television talk show.

The Wall Street Journal reports claim that a consequence of the Solvey contribution, and a host of similar contributions from other major pharmaceutical firms, is that the Foundation now also has the large task of preparing proposals to revamp or replace the FDA.

Gingrich's early explanation of why the FDA should be eliminated or radically changed was that its work should be taken away from "bureaucrats" who were wasting time and put into the hands of industry, which knew how to get things done.

What that proposal chooses to ignore is that once upon a time the responsibility belonged wholly to the private entrepreneur. Government stepped in only when it became evident that those creating products for profit, too easily measured their product only in terms of profit and not in terms of safety or effectiveness for the consumer. Too many worthless, even harmful products were marketed. Although business prospered, consumers suffered.

Moreover, human nature being what it is, there is every reason to expect that if nearly a century of protection by the FDA was terminated, the old practices would be quickly resumed. In just the last decade, a leading American manufacturer of baby food discovered a production error and was only narrowly prevented from marketing bottles labeled "apple juice," but which contained only sugared water. Some in the company protested that "It wouldn't hurt anyone," but would cost the firm millions to correct.

In this era when the bottom line has become the sole measurement of the success of a business administration — and a cost-benefit limitation would be placed on regulation — consumer protection would vanish virtually overnight.

This prospect fits neatly into columnist George Will's defense of "Engine" Charlie Wilson's declaration of forty years ago that "What's good for General Motors, is good for the country." Under that definition, the business came first while the country and its people became an after-thought — a "trickle-down" relationship. The sole criteria for any program's worth would be the volume of profit it allows.

While it may be revealing to some how rewarding it can be to "take care" of a constituent in this "new" Washington scene, most people will realize they've heard this song before.

Most people are consumers — and even his most indiscriminate supporters must wonder if they really want to lose their protections just so Gingrich & Co. can enjoy those "rewards."

No creation of man is perfect, and all of them can profit from honest periodic reexamination. If done in this case, it seems a sure bet that more would be found in the Food and Drug Administration to praise than to change.

In this case, however, the agency is damned in advance.

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THE

"USA TODAY hopes to serve as a forum for better understanding and unity to help make the USA truly one nation."
—Allen H. Neuharth
Founder, Sept. 15, 1982

THE NATION'S NEWSPAPER
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Today's debate: REGULATING DRUGS

Rx for disaster: Peddling drugs for unapproved uses

OUR VIEW **Easing regulation of prescription drugs isn't the lifesaver the drug merchants claim.**

Hot on the heels of legislation recently introduced in Congress, the nation's $55.5-billion pharmaceutical industry is angling behind every closed door it can find to ease controls on the marketing of prescription drugs. If it succeeds, more Americans will be mismedicated; more will suffer unforeseen side effects; and more will die.

Briefly, drug makers want the right to tell doctors about studies that support "off-label" use of their products — uses not approved by the Food and Drug Administration. Experience says such studies can be flawed. And such uses can be dangerous:

▶ Flecainide and encainide, two drugs approved for specific types of abnormal heartbeats, were routinely prescribed for other heart problems in the late 1980s — until follow-on research indicated that such use more than doubled the risk of death.

▶ Centoxin, a drug engineered to fight septic infection, had to be yanked off the market in Europe. The FDA decided that the first clinical trials were insufficient, and a second set found many more patient deaths than predicted.

▶ Clonidine, an adult high blood pressure medicine, was prescribed off-label more than 200,000 times in 1994 to treat children with attention deficit disorders. Now, research has uncovered severe side effects and a handful of deaths.

Why risk more of the same?

Physicians are already free to prescribe for off-label uses; half the 2.1 billion prescriptions written each year are such. Within existing limits, most doctors can judge the benefits and risks of off-label uses.

But giving drug makers carte blanche to market their products for unapproved uses will swamp doctors with inadequate studies. Who should the public depend upon: the FDA and its objective mission to evaluate new drugs, or the companies that have wagered millions developing those drugs?

If drug companies can sell drugs based on studies of their choice, they have no reason to seek FDA approval for any use except the narrowest, easiest ones. That done, it would be simple to market the drug for another, more dangerous use.

Drug industry briefing papers say that "pharmaceutical companies ... are in the best position to provide current, scientifically accurate information about (their) products." Maybe, but that's a handy prescription itself — for conflict of interest.

The industry also says that seeking FDA approval for every use is time-consuming and costly. Reforms are in order, but off-label marketing doesn't repair the FDA; it just destroys the agency's quality controls.

There are many reasons why this idea, now in the formative stages in Congress, should be snuffed out. It undermines drug safety and endangers consumers. It also means lower costs for makers, who would spend less on trials and studies. But who do you think will pay *that* price?

Don't Jeopardize Food Safety NYT 5/26

With "mad cow" disease barely faded in the headlines, it seems an odd time for Congress to consider weakening America's food safety laws. Yet that is the threat of a package of proposals intended to "reform" the Food and Drug Administration.

The F.D.A. is responsible for insuring food safety and truth in food labeling. Among other things, the agency approves food additives, inspects food processing plants and insures that health claims on food labels are supported by "significant" scientific agreement.

In recent months, the agency has come under fire in Congress for moving too slowly. Reform proposals are making their way through the House and Senate, with the House version set for consideration by the commerce committee soon.

One of the most controversial parts of the House bill, sponsored by Representative Scott Klug, Republican of Wisconsin, would weaken the 38-year-old Delaney Clause, which absolutely prohibits manufacturers from putting cancer-causing additives in processed food. The House proposal would allow "negligible or insignificant" cancer risks in food and color additives, and drugs given to food-producing animals.

In 1993, the Clinton Administration agreed to loosen the Delaney Clause's no-risk standard relating to pesticide residues in processed foods — but only in exchange for a uniform standard that would be much tougher in limiting pesticide residues on fresh foods, where the clause does not apply. Congress, however, never took action. Now the House proposal would adopt a similar standard for food additives that are deliberately applied to foods.

The Administration, however, sensibly wants to keep Delaney in place for processed foods. It draws a distinction between directly added substances, like preservatives and food coloring, which do not need to be in the food at all, and indirectly added substances, like pesticides, which may inadvertently enter the food supply. Moreover, the Delaney Clause is a powerful regulatory club that should not lightly be given away except for some clear gain in overall safety.

In another section aimed at providing national uniformity, the House bill would pre-empt many state safety and labeling laws that are more stringent than the Federal law or that simply make sense locally. The bill could thus nullify warning labels on shellfish in states like Florida and California, date-stamping to prove freshness as required in Ohio and labeling of kosher foods in New York and other states.

The bill also sacrifices sensible uniformity on food labels achieved in the 1990 Nutrition Labeling and Education Act. That law tried to minimize false and misleading food labels by setting clear guidelines for terms like "low" or "reduced" fat. Now, Mr. Klug's bill would allow use of synonyms devised by manufacturers, like "not much" fat, that could be misconstrued.

Both the House bill, and a bill heading to the Senate floor, would privatize some F.D.A. functions by allowing third-party approvals of food additives and inspections of food plants.

The United States has a pretty good track record in keeping its food supply safe. But that record will be jeopardized unless the current Congressional proposals are significantly revised.

WARNING: Cutting the FDA Could Be Hazardous to Your Health

The right-wing's attack is mostly bunk. But the agency could be improved

BY JOSHUA WOLF SHENK

It was the first time Don Vasbinder had seen a body in a bag of cocoa beans. In late 1993, inspectors from the Food and Drug Administration (FDA) sniffed something wrong in a shipment of beans from Brazil. Inside, they found a rotting corpse. "That was a first for me," says Vasbinder, the director of imports for the Baltimore district office of the FDA. "But the old-time food inspectors say that's not uncommon. In fact, they found another body shortly thereafter in Philadelphia."

If Vasbinder, a slight man with big block glasses and a Ph.D. in chemistry, is unfazed by this story, it's because in his 20 years with the FDA he has seen just about everything. Rusted surgical knives. Rotted mud fish from Singapore. Condoms with holes in them. And those are just the imports. Including the multi-billion dollar domestic market in pharmaceuticals, medical devices, and food, the FDA regulates products that account for 25 cents of every dollar spent in this country. A tour of FDA facilities in Baltimore, where scores of inspectors and scientists are only a small part of the 9,000-person, $980 million agency, yields a quick understanding of the FDA's importance: In the pesticide group, chemists have found dangerous levels of DDT in grain intended for breakfast cereal. In the drug lab, chemists have caught at-home tests for pregnancy and glucose that do not work as claimed. Stories of impure food and drugs—laced with unsafe chemicals, insect parts, rusted metal, even cigarette butts—are common.

Of course, as inspector Dean Cook points out while we walk through a spice plant filled to the roof with sacks of cola nuts, black pepper, and oregano, the vast majority of the goods he checks are safe. Reviewers of drugs and medical devices at FDA headquarters in Rockville, Maryland also attest that most manufacturers want to make money by producing good products, not by scamming the system. But it is equally obvious that bad apples (so to speak) abound, both in this country and abroad. Keeping the food supply clean and the marketplace of drugs and medical devices safe and effective often takes more than a strong sense of smell. With chemical compounds and complicated medical devices, it takes years of careful study.

It is this studiousness and circumspection that rankle the agency's critics. In Congress, the same coalition that slashed the budget of the Environmental Protection Agency and pushed a moratorium on all new federal regulations is setting its sights on the FDA. It's a matter of jobs, Newt Gingrich explains, arguing that FDA overregulation is squelching industry and stifling economic growth. Shortly after his inauguration as speaker, Gingrich called the FDA the country's "leading job killer." And in a recent speech before health insurers, he said that in "phase three" of his revolution, "Maybe we'll take out FDA."

At Gingrich's flank is a cadre of conservative activists in Washington. The Washington Legal Foundation is running ads in major newspapers proclaiming "If a murderer kills you, it's homicide.... If FDA kills you, it's merely being cautious." The Progress and Freedom Foundation is proposing that drug and device approval be farmed out to private research groups or universities. Sam Kazman of the Competitive Enterprise Institute would remove the FDA's "monopoly," meaning that the agency would continue to operate but couldn't keep goods off the market. These groups happen to receive generous donations from the

pharmaceutical and medical device industry as well as tobacco companies frightened of the FDA's proposal to regulate cigarette marketing to children.

The FDA has always been controversial. Industry lobbied hard against the original Food and Drug Act in 1906, and the agency has been granted more power only when scandals shocked Congress into action. In 1996, though, the agency's waters are particularly choppy. Besides Republican hostility, the FDA also faces pressure to move more quickly from liberals in Congress such as Representative Ron Wyden and Senator Barbara Mikulski.

With the FDA's very existence called into question, you might expect the Washington press corps, congressional auditors, and the executive branch to be scrambling to evaluate the agency. In what way are the critics correct? What are the FDA's strong suits? What is the agency trying to do—and what is it actually doing where the rubber meets the road (or where the tablet meets the mouth)?

In a town often scandalously blithe about matters vital to the lives of Americans, the FDA has gotten no such treatment. The watchdogs are napping. If they woke up, they'd find an agency with a clear mission, dedicated staff and leadership, and the best safety record and reputation of any health agency in the world—an agency that is often wrongly maligned. The FDA isn't perfect, and its imperfections aren't pretty. But only through tough, fair scrutiny and analysis, of which this piece is a modest effort, can it be improved.

Drugstore Cowboys

The purpose of a business is simple: to provide a desired good or service and make a profit. In government, purpose is sometimes more difficult to discern. What is an agency's mission? In what way does it improve citizens' lives?

FDA Commissioner David Kessler sums up the FDA's mission in three words: "safeguarding America's health." More specifically, the FDA ensures the safety of the nation's supply of food, drugs, medical devices, and other health-related material, such as cosmetics, devices that emit radiation (like TVs and microwaves), and the blood supply. With drugs and devices, the FDA goes one step further and checks to make sure products work for the purpose claimed by the manufacturer. The logic is simple: While protections against egregious fraud are important in any industry, ineffective health-care products pose a particular risk. If a lamp doesn't work, you can take it back to the store and buy another one. But a pacemaker that doesn't work could kill you.

The clear sense of mission—the knowledge that their work can literally be the difference between life and death—infuses the agency with energy. "The FDA has way more than its share of bright, dedicated, competent people," says William Vodra, who worked for the agency's general counsel in the 1970s. "We would have discussions all the time, and ultimately someone would ask: 'Okay, what's in the public interest here?' On Capitol Hill, you never hear issues framed that way." Even critics, like Richard Samp of the Washington Legal Foundation, praise FDA staffers. "I'm generally impressed by their intelligence and public spiritedness," Samp says. "These people don't sit around dawdling in their offices, turning around paperwork all day."

In addition to the widespread acclaim for FDA employees, the agency's basic mission is affirmed by supporters and critics alike. Gingrich's blustering aside, there is widespread agreement that the FDA should remain, in Samp's words, "a centralized government bureaucracy providing an official stamp of approval that a product is certified as safe, based on the best available technology."

The issue with the FDA, then, is not what it should do—the question is how it does what it does. Like all regulatory agencies, the FDA faces the challenge of protecting the public without suffocating commerce. With drugs and medical devices, it faces an additional, more delicate, task: The FDA must protect the public from hazards without holding up useful treatments—keeping a life-saving drug off the market can be as lethal as allowing a flawed drug to go forward.

The famous case of Dr. Frances Kelsey illustrates the tricky business of regulating health products. Between 1959 and 1961, thousands of babies in 20 countries were born with grievous deformities because their mothers had taken a new sedative called thalidomide during pregnancy. In the United States, the drug had never been marketed because Kelsey, the medical officer in charge of the application, had held it up.

Clearly, Kelsey made a huge save. And conscientious work like hers has made FDA approval the worldwide "gold-standard" for medical product

According to a study by Dr. Sidney Wolfe at the Health Research Group of Public Citizen, this country only had to recall 9 drugs between 1970 and 1992. Over that same period in France there were 31 recalls; in Germany, 30; in Britain, 23.

But Kelsey's legacy has another side: According to close watchers of the FDA, she was known for being slow and ponderous—sometimes to excess. We know about the tragedy she stopped. But could she have caused a tragedy by scuttling beneficial new therapies? That question cuts to the heart of the FDA.

Among critics, it is an article of faith that the FDA is slow and getting slower. A commonly-cited Tufts University study shows that the average time required to bring new medicines to market in this country has increased from about eight to 15 years since the early 1960s. It's true that the FDA can be guilty of excessive caution, particularly when keeping a product off the market because they're not 100 percent sure it works. Reviewers have an incentive to err on the side of caution: If they let a bad drug get through, they face a rain of humiliation. If a good drug is stopped or unduly delayed, the only complaints come from industry.

Still, in context, the data cited by critics do not indicate an agency in crisis. Every decade or so, a defective medical product slaps Americans in the face and reminds this country of the necessity of thorough reviews. In 1962, it was thalidomide —which, along with earlier scandals, led Congress to require the FDA to check for the efficacy as well as the safety of drugs. In 1976, it was the Dalkon Shield—an intrauterine device that caused 18 deaths and 66,000 miscarriages and led to FDA regulation of medical devices. In the late eighties came another series of scandals involving heart valves, jaw implants, and breast implants, among others. The resulting clampdown on devices led to a backlog in the early 1990s.

The Tufts study is not inaccurate; it does take longer to develop a drug now than in 1960. But the FDA rightfully is being more cautious than it was in 1960. It is also crucial when assessing the FDA's speed to distinguish between drugs and devices that truly improve on existing therapies, and those that replicate other products or add the chemical or engineering equivalent of a new bell or whistle. "If you're a drug company," explains Sidney Wolfe, "and you see a lucrative $4 billion market for a drug that treats arthritis and it's nothing really new, but you can repackage it as something radically new, then you're going to go for it." According to the London journal *SCRIP*, of 47 new chemical entities introduced in the world between January 1 and December 8, 1994, only two were breakthroughs. Both were first approved and marketed in the United States. Remember the drugs recalled in Europe but never introduced here? Not one had shown a significant advance over existing therapies. In other words, it's not safe to assume that holding up a drug or medical device means lost lives.

But some FDA-regulated products *are* breakthroughs. The challenge for the agency, then, is to maximize its speed without sacrificing its standards. And according to a recent GAO report, the agency actually has made great strides in its review speed. In 1987, the average review time for a New Drug Application—submitted after a drug has been fully tested in human subjects—took an average of 33 months; in 1992, the average was 19 months. This study also found the FDA to be quicker than the British Medicines Control Agency, to which critics often unfavorably compare the FDA.

When it comes to reviewing products that are, in fact, significant advances, the FDA has a good history; it has even improved in recent years. The agency correctly employs triage—assigning priority to products depending on the seriousness of the illness to be treated and the availability of other therapies. AZT, one of the few drugs available to fight AIDS and HIV, was approved in just a few months. Much of the improvement in review times is due to the institution of user fees for drug applications. Just as college applicants pay a fee to have their applications reviewed, drug companies now pay to have their data analyzed and methods reviewed. The FDA uses the funds to augment its staff, which leads to a quicker turnaround time.

Certainly the FDA could improve. It has, for example, a lackluster history with generic drugs, which are radically less expensive than patented drugs and can save consumers thousands of dollars in drug costs. With exploding health-care costs, it makes sense to push generics through as fast as possible. But for years, the pharmaceutical industry pressured the FDA to preserve the industry's competitive edge by holding up generics. The agency obliged, insisting, for example, that a generic undergo the same testing as a new drug, even though it might be identical to a drug already on the mar-

The Washington Monthly

JOURNALISM AWARD

OCTOBER 1995

George C. Wilson & Peter Carlson
The Washington Post Magazine

Wilson and Carlson scrupulously document the tarnished history of the U.S. Navy's A-12 Avenger, a state-of-the-art stealth bomber that was at least a billion dollars over budget and a year behind schedule when then-Secretary of Defense Dick Cheney scrapped it in 1991. The project, along with the ensuing legal battle between the contractors and the government, may ultimately cost taxpayers $5 billion.

Jorge Oclander
Chicago Sun Times

In a revealing two-part exposé, Oclander looks at the infiltration of the Chicago Police Department by local gangs, whose loyalty is not to the community but to their respective organizations. Constitutional rights protecting freedom of association are undercutting efforts to combat this problem.

Katherine Boo
The Washington Post

In a meticulously reported and movingly written story, Boo follows D.C. social worker Darryl Wilson, part of a D.C. government "family preservation" team, as he heroically tries to keep one dispirited family whole without allowing the children within it to be destroyed.

The Monthly Journalism Award is presented each month to one or more newspaper, magazine, radio, or television stories (or series of stories) that demonstrate a commitment to the public interest. We are particularly interested in reporting that explains the successes and failures of government agencies at all levels and of other institutions such as the media, corporations, unions, and foundations that contribute to the existence or solution of public problems. Please send nominations (including two copies of the article or broadcast text) to Monthly Journalism Award, 1611 Connecticut Ave. NW, Washington, DC 20009. Nominations for stories run in January are due February 10.

ket. That practice was changed in 1985, when generics accounted for only 14 percent of prescriptions written. Today, they account for 45 percent, and the FDA now allows generics on the market the day a patent expires. But Congress hasn't granted the agency the authority to charge user fees to test generic drugs, and so it has insufficient resources to review them; that means useful and more affordable generics aren't making it onto the market. Whether through user fees or standard appropriation, the FDA's budget needs to match its responsibilities.

And unlike its stellar record on safety, the FDA's record regulating product efficacy—something it's been doing only since 1962—is spotty. Too often, the agency takes an all-or-nothing approach: A drug is either fully approved for safety and efficacy, or it is kept out of patients' hands entirely. Once a breakthrough drug has been proven safe, there's no reason why people shouldn't be able to use it—assuming they're fully informed that the FDA has yet to certify the drug's effectiveness. Along these same lines, compassionate use—exemption from FDA rules due to a clear and pressing need—should also be expanded. Denying dying patients a drug because it might hurt them is clearly a fool's bargain.

On the whole, though, the FDA's record on drug reviews is good. The story with medical devices is somewhat more complicated. Rhetorical fireworks from agency critics have largely centered around devices, in part due to the fact that, unlike drugs, devices tend to be made by small entrepreneurs. A "no" from the FDA—or a delay in approval—can mean the end of a company.

Some of the critics' claims have legitimacy, but many do not. The Sensor Pad, intended to help women detect breast cancer, is an example of critics gone awry. FDA "ineptness," the Washington Legal Foundation claimed in ads run in *USA Today* and *Roll Call*, "is *still* killing thousands of women ... The FDA has obstructed approval—for nine years—of the Sensor Pad.... In Canada, the product was approved in less than 60 days."

In fact, the best evidence indicates that the Sensor Pad is no more helpful in detecting lumps in breasts than bare hands and soapy water. The device was once marketed in Canada but ordered withdrawn by officials who echoed the concerns of the FDA: that the product could actually be less effective than traditional methods and might lull

women at risk into a sense of complacency. To blame the FDA for thousands of breast cancer deaths, then, is the height of irresponsibility.

But the critics have a point about another device featured in Washington Legal Foundation ads and used by Gingrich as a prop to attack the agency: the CardioPump. An aid for paramedics conducting CPR on victims of cardiac arrest, the pump is sold legally in a dozen countries, including Japan and Germany; in Austria, it is standard equipment on ambulances. Even though many health professionals are convinced that the CardioPump is a valuable, life-saving tool, the FDA has kept the product off-market. The agency defends its decision by pointing to studies showing that, while patients treated with CardioPump do in fact reach the hospital in greater numbers than a control group, they do not *survive* at a higher rate. Unlike the Sensor Pad, however, there is absolutely no evidence that people will suffer from the Cardio-Pump's use. Given that the pump certainly isn't harmful, why not leave the decision to paramedics and hospitals after warning them that the FDA is not convinced of its efficacy?

But if less regulation is required with some devices, other areas show a need for more regulation, specifically the thousands of products that were "grandfathered" into approval. That means they went on the market before the FDA began regulating devices in 1976 and were subsequently granted a reprieve until the agency could get around to checking them. In many cases, they still haven't gotten around to it, and consumer advocates rightly complain about the slow pace. Some types of pacemakers grandfathered into approval, for example, have a 25 percent failure rate. It's a glaring loophole in an otherwise tough regulatory scheme.

The Food We Eat

Early last February, the makers of Similac infant formula were flooded with calls from frantic parents in Southern California. The formula had produced rashes, stomach aches, and seizures in 54 infants. The FDA staked out warehouses, searched dumpsters, and eventually caught two men selling fake Similac to supermarkets. Within weeks, the fake formula was confiscated.

Such heroic FDA stories are not uncommon, and it's not just consumers who benefit. Just ask Pepsi Co. In 1993, when the FDA exposed as a

The Washington Monthly

Money & Politics Journalism Award

George Bauer and Steven Rosenfeld
Monitor Radio

Over the past year, the *Monthly* has taken occasional looks at how money drives the political process; we've also tried to keep an eye out for colleagues doing the same. The good news is that while the influence of money certainly isn't diminishing, press attention to it is increasing. Publications from *The New York Times*, which has been regularly examining how lobbyists affect legislation, to *Sojourners* magazine, which recently devoted an entire issue to money in politics, have provided models for how to raise public awareness on this issue. This radio series, which began in September and continues through the 1996 election, is among the best we've found. Bauer and Rosenfeld have been criss-crossing the country to produce vivid, informative pieces on how a "money-hungry political system" is corrupting integrity in local, state, and national elections—and in government. They've looked at how Willie Brown parlayed favors from his tenure as Speaker of the California House to feed his race for San Francisco mayor. They've gone to Mississippi to explore how Washington political consultants are transforming even rural races and upping the money it takes to run them. And they took listeners to New York, where a city councilman has brought suit claiming that the amount of money required to run for Congress is an unconstitutional barrier to electoral participation.

hoax claims that syringes had been slipped into Pepsi, the company saved the millions it would have cost to recall and dispose of its product.

Yet much of the FDA's work is rarely noticed, let alone shone on by the klieg lights of press conferences. That's partly because their lifesaving work is so prosaic in appearance: At the FDA district office in Baltimore, I watched inspectors matter-of-factly sniff black tiger shrimp from Thailand —that's "organoleptic testing"—and scientists quietly testing baby corn and crab meat for botulism.

But while much of the FDA's work is admirable and underappreciated, the federal regulation of the food supply does need improvement. Spread across three agencies, it is often poorly coordinated. The FDA splits food regulation with the Department of Agriculture, which regulates meat, poultry, and some types of dairy products. The Environmental Protection Agency sets the rules for pesticides, and the FDA enforces them. The Department of Transportation even gets in on the act, setting standards for refrigerated vehicles.

With the resources it has, the FDA does a good job. But the resources are inadequate—and the jury-rigged nature of food regulation is a prime culprit. Take the recently-announced FDA rules on seafood inspection. One hundred and fourteen thousand Americans are poisoned by seafood each year; yet seafood regulations have changed little since the turn of the century. So it is a welcome sign that the FDA has finally overcome pressure from the seafood industry and imposed a new system of lab checks and computer monitoring.

But, believe it or not, the system will actually bring a decrease in inspections. That's because the new system is so complicated that it will double the average inspection time, but the FDA doesn't plan to put any new inspectors on the job.

And the shortage of inspectors isn't confined to seafood. FDA food inspections dropped precipitously from 20,528 in 1981 to 5,741 in 1994. The consequences are alarming: Raw oysters kill at least a dozen people each year, but the FDA has not responded to the problem. Last year in Florida, the Norwalk virus in oysters caused 121 illnesses, but there was no FDA recall. "The reality is," says Caroline Smith DeWaal, director of food safety for the Center for Science in the Public Interest, "they don't have inspectors, and they don't have a program adequate to meet the problem. With the pressure to approve drugs faster, it's only getting worse."

Why would pressure to approve drugs more quickly mean less regulation of food? Because the FDA has to do both jobs with only a limited fund pool. While Congress has piled on mandates for the FDA in monitoring drugs and devices, the blood supply, and medical procedures, lawmakers have made far fewer demands with respect to food safety. And so, with a total budget that is now stagnating in real terms—the agency received no increase for inflation in 1996 appropriations—the FDA has been forced to shift resources away from food. The $220 million the FDA spends on food regulation is only 40 percent of what the Agriculture Department spends on meat and poultry regulation alone.

Even with its comparatively enormous budget, of course, the Agriculture Department does not inspire confidence that it can keep tainted beef out of Americans' mouths. But the FDA shouldn't have to reduce resources on food inspections in order to increase resources on medical products—nor would taxpayers want it to. One sensible solution is to separate the regulation of food and drugs and devices into different agencies. If the FDA does keep all its jobs, Congress needs to make sure the agency is adequately funded for all its responsibilities.

Questions Still Unanswered

One magazine article can hardly cover all the important ground at the FDA. Consider the early testing of drugs on humans. Before a drug or device is even submitted to the FDA for approval, the "sponsor" has to go through a long series of tests. This is where most of the expense and delay in getting drugs from the laboratory to the pharmacist's shelf happens. How can these tests be done more quickly and at lower cost, and what can the FDA do to streamline the process?

The agency's actions in areas outside its traditional role of regulating food and medical products also need evaluation. Take cigarettes, for example. David Kessler is a hero for facing up to the tobacco companies. But is his agency the most sensible place to conduct such regulation? It seems more appropriate for the agencies responsible for fighting drug abuse—who now deal almost exclusively with illegal drugs—to spend some of their $14 billion annual appropriation curbing the abuse and youth-oriented marketing of cigarettes and alcohol.

Then there's an issue thrust into the limelight by Gingrich. Is the FDA hurting job growth in this

country? Since his office would not provide evidence to back up his claim that the FDA was a "job killer," it seems the speaker may be on shakier ground than he might wish the public to believe.

Drug companies allege that the FDA has gotten slower and more bureaucratic since the thalidomide scandal of the early sixties—hurting their bottom line. So why is the stock of industry giant Merck & Co. 113 times more valuable now than it was in 1962 (in figures not adjusted for inflation)? Investors in drug stocks haven't just done well, they've done *very* well. Consider the story of Anne Scheiber, reported recently in *The Washington Post*. She bought $10,000 worth of shares in Schering-Plough Corp. in 1950. Today, that investment is worth $7.5 million. The industry as a whole has also done quite nicely. In 1980, non-generic drug firms had $12 billion in U.S. sales—a figure that exploded in the next 15 years to $57 billion.

Conservatives claim that the FDA hurts business. Then why is Merck's stock now worth 113 times what it was in 1962?

Yes, American pharmaceutical and biotech companies are opening some operations overseas, but it is difficult to tell to what extent, if any, FDA regulations are to blame. Fruit of the Loom is moving overseas, too, but not because of excessive underwear regulation. And it isn't just the drug industry that's booming. A recent report in *The Wall Street Journal* showed that Swiss firms are rushing to invest billions of dollars in American biotechnology. "It is in the U.S.," Ralph King reports, "where the biotechnology industry began and, for the most part, remains."

Some other criticisms are as dubious as the notion that the FDA drives American industry overseas. "The problem with health care in America today is the FDA," the Washington Legal Foundation claims in its ads. If the FDA is *the* problem, one wonders if the tally of 41 million uninsured Americans makes the group's top five? Other critics don't seem to share the basic values that undergird the FDA's existence. Henry Miller, a former FDA official, recently blasted the agency in a *National Review* article as slow and politically-motivated. But when I asked him about the study showing France and Britain with triple the number of drug recalls as the U.S., Miller replied that he wouldn't mind more recalls if it meant getting drugs through more quickly. Considering the devastation that a bad drug can cause—Clometacin was withdrawn in France after 130 reports of hepatitis, including nine deaths; Indomethacin-R was withdrawn in Britain after 717 adverse reactions and 36 deaths—this is hardly a trade-off most of us would like to make.

This is not to demonize the agency's critics. The FDA's job is important enough—and the balance between getting good drugs on the market while keeping bad ones off is delicate enough—that vigorous criticism of the agency should be welcomed, not dismissed out of hand. Still, it hardly benefits the public to have the conversation dominated, and too often distorted, by a right-wing fringe. When confusion reigns, groups in the know, such as the regulated industry and big-money donors to Congress, benefit. And the public suffers.

Enhancing public understanding of the FDA should be a top priority of government auditors, the press, and the FDA itself. As it is, the only way a major review can get started is for a high official to pressure the GAO or the inspector general at the Department of Health and Human Services. Such reviews are rare. More common is the confusion that characterizes debates over the CardioPump and Sensor Pad. Critics accuse the agency of stonewalling; the FDA responds that it's doing a good job. The truth is hard to discern.

What's needed at the FDA is a strong, generously funded inspections office, which at the request of industry or Congress or interested citizens could review the handling of a particular case, produce an explanation in clear language as to what happened, and recommend future action. This would both educate the public and inject a sense of accountability into the FDA's review process. And since government reports can get buried, the press is an even more important engine for honest and constructive evaluations of the agency.

In this heated political climate, tough, fair scrutiny of the FDA is more necessary than ever. Think about it: When you brush your teeth in the morning, you know your gums won't turn black. When you take pain medicine at night, you can be confident that you won't get hurt—and that you haven't been ripped off. You can eat your meals without worrying about salmonella or a surprise serving of rat droppings. We take all these things for granted. We can't afford to do the same with the agency that makes that possible. □