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001. memo	Denise Ricketson to Elizabeth Drye re: FDA briefing [partial] (1 page)	05/15/1996	b(6)

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FOLDER TITLE:
FDA Reform 1996 [6]

2014-0046-S
rc1404

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
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C. Closed in accordance with restrictions contained in donor's deed of gift.
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b(1) National security classified information [(b)(1) of the FOIA]
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b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
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b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

SPECIAL

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
Washington, D.C. 20503-0001

4/25/96

LEGISLATIVE REFERRAL MEMORANDUM

LRM NO: 4223

FILE NO: 1746

Total Page(s): 57

TO: Legislative Liaison Officer - See Distribution below:

FROM: Janet FORSGREN Janet Forsgren (for) Assistant Director for Legislative Reference

OMB CONTACT: Robert PELLICCI 395-4871 Legislative Assistant's Line: 395-7362
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pellicci_r@a1.eop.gov

SUBJECT: HHS Proposed Report on the House FDA reform bills -- section-by-section analysis

DEADLINE: Monday, April 29,1996

In accordance with OMB Circular A-19, OMB requests the views of your agency on the above subject before advising on its relationship to the program of the President.

Please advise us if this item will affect direct spending or receipts for purposes of the "Pay-As-You-Go" provisions of Title XIII of the Omnibus Budget Reconciliation Act of 1990.

COMMENTS: The attached section-by-section analysis of the three House bills will be transmitted to House Committee staff by HHS as soon as it's cleared.

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RESPONSE TO LEGISLATIVE REFERRAL MEMORANDUM

LRM NO: **4223**

FILE NO: **1746**

If your response to this request for views is short (e.g., concur/no comment), we prefer that you respond by e-mail or by faxing us this response sheet.
If the response is short and you prefer to call, please call the branch-wide line shown below (NOT the analyst's line) to leave a message with a legislative assistant.
You may also respond by:
(1) calling the analyst/attorney's direct line (you will be connected to voice mail if the analyst does not answer); or
(2) sending us a memo or letter
Please include the LRM number shown above, and the subject shown below.

TO: Robert PELLICCI 395-4871
Office of Management and Budget
Fax Number: 395-6148
Branch-Wide Line (to reach legislative assistant): 395-7362

FROM: _____ (Date)

_____ (Name)

_____ (Agency)

_____ (Telephone)

SUBJECT: HHS Proposed Report on the House FDA reform bills -- section-by-section analysis

The following is the response of our agency to your request for views on the above-captioned subject:

_____ Concur

_____ No Objection

_____ No Comment

_____ See proposed edits on pages _____

_____ Other: _____

_____ FAX RETURN of ____ pages, attached to this response sheet

April 19, 1996

DRAFT DRAFT DRAFT

H.R. 3200
"FOOD AMENDMENTS AND THE ANIMAL DRUG AVAILABILITY ACT"[1]

TITLE I – FOOD AMENDMENTS

SEC. 101. FDA MISSION AND ANNUAL REPORT

- Section 2(a), the mission statement establishes prompt and efficient review and approval and global harmonization as primary FDA goals.

  The mission does not include traditional FDA objectives of ensuring that food is wholesome and properly labeled or that consumers are protected from fraud. The mission statement should include protecting the public from products that do not meet the applicable statutory standards because they lack the requisite approval prior to marketing -- i.e., products that are unsafe and ineffective or have not been shown to be safe and effective.

- Section 2(b), requires the Secretary to, simultaneously with the submission of an annual budget, submit to the Commerce Committee in the House and the Committee on Labor and Human Resources in the Senate, an annual report that (1) reviews FDA's performance in meeting its mission and developing policies to implement such mission; (2) reviews FDA's performance in meetings its own performance standards (including meeting statutory deadlines); (3) describes FDA's staffing and lists third parties that have been accredited to perform product reviews; (4) describes FDA's harmonization goals, activities, and accomplishments; and (5) compares FDA's performance with that of the most "successful" agency performing similar functions in other countries and compares the resources used by such agencies.

  The agency does not disagree with the principle that the agency must be held accountable. The concern is that some of the requirements set forth in this provision are not clearly defined and/or possibly not feasible. For example, the requirement that FDA compare its performance with that of the most "successful" agency performing similar functions in other countries is vague and may be difficult, if not impossible, to meet. The term "successful" is not one that provides much guidance. Moreover, it is uncertain whether such data are

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[1] H.R. 3200 includes a number of supportable concepts. The emphasis of this section-by-section analysis, however, is on the problematic provisions in the bill.

available from other countries or whether if such data are available, a comparison is possible.

SEC. 102. ACCESS TO DISEASE PREVENTION INFORMATION

- Section 102 amends the section 403(r)(3) standard for authorizing health claims by adding the sentence: "significant scientific agreement does not require consensus or unanimity."

  This concept is [supportable]. FDA does not interpret significant scientific agreement as requiring consensus or unanimity. FDA clearly stated this in the preamble to its final rule on health claims. If the agency did not follow this view, it could not have approved the eight health claims currently allowed on the food label. In each case, there were scientists that objected to the claims. For example, there was not complete agreement on the relationship between folic acid and neural tube defects, yet the agency has approved this claim for use on the food label.

- Section 102 allows any materials prepared or distributed by a government agency (such as NIH, CDC, or the National Academy of Science) to serve as the basis for a health claim -- i.e., to fulfill the significant scientific agreement requirement.

  This provision fundamentally alters the criteria for health claims that were so carefully worked out in the Nutrition Labeling and Education Act of 1990. Under the bill, there would be no single body to make decisions on health claims, and the result could be inconsistent decisions by different organizations using different standards. Companies would be allowed to pick and choose among government bodies. This provision is likely to result in the type of consumer confusion and misinformation that was abundant before passage of the NLEA.

  In addition, the provision is vague and overly broad. The bill would appear to allow ANY information prepared for whatever reason (i.e., not specifically for the purpose of a diet/disease claim evaluation) to form the basis of a health claim. For example, materials relating to a particular diet disease relationship prepared and distributed as background for a hearing by the NAS or a briefing by NCI could be used as the basis for a health claim. Moreover, information contained in pamphlets written by a private organization and distributed by Federal health agencies or the NAS could form the basis for a health

claim under this provision. Information could be taken out of context.

There appears to be no remedy for FDA is it disagrees about a claim evaluation made by another agency.

SEC. 103. ACCESS TO NUTRIENT DESCRIPTOR INFORMATION

- Section 403 of the Act currently permits foods labeling to include nutrient content claims using descriptors that have been defined by FDA. Section 104 amends that provision to permit synonyms of those defined terms, provided they are not false or misleading.

  The bill provides no mechanism for determining appropriate synonyms. Because there is no standard for companies to meet before using a new descriptor, the burden would be on the agency to prove that a term is not a synonym for a defined term and that the term is false or misleading. The result of this provision would be a large increase in the number of nutrient content descriptors. The uniformity that the NLEA created would be lost. Such a plethora of uncontrolled terms would confuse consumers by diminishing the usefulness of the defined terms. Consumers would be confused as to the nutrient content of a particular food. For instance, is "lots of fiber" a synonym for "excellent source of fiber" or "good source of fiber?"

  FDA's current regulation permit a company to petition for the use of synonyms. In addition, FDA recently proposed to amend its nutrient content claim regulations to permit manufacturers to use synonyms of defined nutrient descriptors as long as such synonyms are not false and misleading and the synonym is "anchored" to the defined term – i.e., the defined term must appear prominently on the label. The agency's proposal properly balances the concern of unbridled uses of synonyms that can lead to consumer confusion with industry's need for greater flexibility to market the healthful aspects of their products.

SEC. 104. SPECIAL LABELING TO PROTECT PUBLIC HEALTH

- Section 104 prohibits FDA from using its misbranding or food additive authority to require food manufacturers to include a description of a method of production or an ingredient other than in the statement of ingredients, unless such disclosure is necessary to protect the public health.

  The effect of this provision will be food labeling that is not complete.

For example, FDA has historically taken the position that if a food production process changes the characteristics of a food, information about that process should be made available to the consumer on the label. The homogenization and Pasteurization notations on milk labels are such examples. This provision might also prohibit FDA from including the olestra statement (which would help consumers connect possible (not medically significant) GI effects with olestra consumption) and irradiation labeling (which is designed to inform consumers that the food has been processed).

In addition, this provision may conflict with other provisions of federal law. For example, section 403(i) requires percent juice labeling to appear on the label. Yet, proposed section 403(t) would prohibit such a disclosure because it is not "necessary to protect the public health." **[DISCUSS]**

SEC. 105. ACCREDITED PERSON REVIEW

- Subsections (a) and (b) of Section 105 authorize the review of health claims petitions by third parties. The third party has 120 days to make a recommendation on the petition and the third party's recommendation shall be deemed the recommendation of the Secretary unless the Secretary finds that it is contrary to the findings required by the Act and provides a detailed explanation for the basis of the finding.

  This provision creates an implicit presumption in favor of a third party's recommendation and expands FDA's burden to deny a petition for a claim subject to third party review in that the agency would need to show why the third party's recommendation was wrong.

- Subsections (c) and (d) of section 105 authorize the review of food additive and color additive petitions by third parties accredited by FDA. In reviewing a food additive petition, the third party shall determine whether there is a reasonable assurance that the food additive may be safely used under the proposed conditions of use. The third party shall submit a report to the Secretary within ___ days. In reviewing a color additive petition, the third party shall decide whether it meets the requirements of the act. The third party shall submit a report to the Secretary within 120 days. With respect to both food and color additives, the third party's recommendation shall be deemed the decision of the Secretary unless FDA finds that there is a reasonable probability that it is not safe and provides a detailed basis of that finding.

This provision changes the food additive standard (for these additives subject to third party review) from a reasonable certainty of no harm to a reasonable assurance that the food additive may be safely used.

This provision shifts the burden of proof from the additive manufacturer to FDA. Under 3200, FDA can only deny approval of a food or color additive that has been reviewed by a third party if it can demonstrate that there is no "reasonable probability" that the additive is "not safe." Since 1958 and 1960, when Congress passed the Food and Color Additive Amendments, it has been the responsibility of additive manufacturers -- those who profit from the additive use -- to demonstrate to the Agency that the additives they propose to add to food are safe. FDA's responsibility has been to review this evidence and either approve the additive if the agency concurs that the additive is safe or refuse to approve the additive it, in the agency's opinion, safety has not been demonstrated. To require the agency to demonstrate that an additive is not safe is to require it to prove a negative.

The deadline provisions in the bill are confusing.

SEC. 106. ACCREDITED PERSONS

- Section 106 addresses the accreditation process. Within 180 days of enactment, the Secretary must promulgate regulations establishing procedures for the accreditation of third parties for purposes of (1) reviewing health claims petitions, food and color additives petitions, new animal drug applications, and (2) conducting GMP inspections to assess conformance with regulations promulgated under section 402.

  This section does not establish how the third parties are to be compensated for services. It lacks clearly defined criteria for establishing the qualifications of third parties. It does not provide sufficient safeguards against conflicts of interest. The provision is vague as to whether FDA can inspect third parties or require third parties to maintain record. It also is unclear as to whether third parties can be given access to privileged information that is in the custody of FDA. In addition, it appears that the intention is not to have the Secretary accredit any particular entity, but rather to have the Secretary designate agencies or organizations who will then perform the accreditation process.

- Section 106 (b) amends the prohibited acts section of the FDC Act to add a new section relating to actions by third parties. Under proposed 301(w), a

third party would violate this section if it submitted a materially false or misleading report, disclosed trade secret confidential commercial information, or accepted a bribe or performed any other corrupt act in connection with its delegated responsibility.

SEC. 107. IMPROVING THE DELANEY CLAUSE

- Section 107 changes the Delaney clause standard from "no risk" to "negligible or de minimis risk." Within 180 days of enactment, FDA must propose regulations establishing criteria for the standard. The proposal will become final unless within 18 months of enactment, FDA issues a final regulation.

[ADD]

SEC. 108. NATIONAL UNIFORMITY

- Section 108(a) prohibits states from establishing any requirements (including prohibitions) for any food, drug, or cosmetic that is of the type authorized or required under the adulteration, misbranding, or new drug provisions of the FDC Act or any regulation implemented thereunder if it is not identical to a requirement imposed under the FDC Act.

  This provision would prohibit state action even in areas where FDA is not very active.

- Subsection (b) prohibits states from imposing any notification requirement for a food, drug, or cosmetic that provides for disclosure of the constituents, source, or method of production or processing such product or for a warning concerning the safety of the product or any component or package thereof unless such requirement is identical to a requirement prescribed under the FDC Act.

  This provision would preclude notifications pursuant to state laws and initiatives, such as California's Proposition 65.

- Section 108 allows the Secretary to provide an exemption under this section of is it justified by compelling and unique local conditions, protects and important public interest that would otherwise be unprotected, would not cause any food, drug, or cosmetic to be in violation of the FDA Act, and would not unduly burden interstate commerce.

SEC. 109. HARMONIZATION

- Section 109 requires the Secretary to regularly and continuously participate in harmonization efforts and to report those efforts to Congress as well as provide 60 day notice to the Committee before executing any agreements with foreign countries. It also requires the Secretary to, within 180 days, make public a plan that establishes a framework for achieving mutual recognition of good manufacturing practices.

SEC. 110. INFORMAL AGENCY STATEMENTS

- Section 110 prohibits the Secretary from relying on policy statements, guidance documents, and similar statements to require any action to satisfy a provision of the FDC Act. It also requires the Secretary to publish a notice of availability of such statements and to make them accessible electronically.

  FDA's position is that guidance documents are not binding on the Agency or the public. FDA recently issued a Federal Register notice that affirms this position and has agreed to take steps to ensure that the agency and the public knows and understands this principle. To the extent that this provision is reaffirming that position it is not problematic. To the extent that it is saying that FDA cannot issue guidance that explains how it believes compliance with the Act may be accomplished, it is problematic -- particularly for the industry. FDA will no longer be able to provide guidance and there is a risk of non-uniformity in the application of the laws and regulations that FDA is tasked with implementing.

SEC. 111. COLORED MARGARINE

- Section 111 repeals section 407 of the Act.

TITLE II -- ANIMAL DRUGS

SEC. 201. EVIDENCE OF EFFECTIVENESS FOR ANIMAL DRUGS

- Section 201(a) amends Section 512(d) of the FDC Act to redefine the "substantial evidence" criteria that currently must be met to establish efficacy. The provision changes the substantial evidence requirement from adequate and well-controlled studies to scientifically sound studies. The requirement that the

studies fairly and reasonably show effectiveness has been changed to a requirement of a reasonable assurance of efficacy. The provision also eliminates the requirement for field investigations unless FDA justifies in writing the need for such investigations to show the effectiveness of animal drugs.

A lower standard for effectiveness is not acceptable. What would be acceptable is a change to current law that clarifies that only one adequate and well controlled study may be necessary and that field investigations be necessary only where appropriate.

- Section 201(c) would eliminate the requirement to show effectiveness of animal drugs intended for uses in minor species or for minor uses.

  Elimination of a requirement to show effectiveness takes us back to 1962. There is no point to having available drugs that cannot be shown to be effective. In fact, the availability of ineffective animal drugs has implications for animal health and creates a significant potential for public health hazards. The use of ineffective animal drugs in minor species or for minor uses can lead to the suffering and death of animals and an increase in the potential for the transmission of zoonotic diseases to humans and the development of antimicrobial resistance.

- Section 201(d) would change the standards for approving combination animal drugs.

  Although the information necessary to establish effectiveness of combination animal drugs could be narrowed in some instances, this provision is written too broadly. It would permit a sponsor to market a combination animal drug containing two or more drugs that are targeted to the same indication without having to show that each drug provides some additional benefit. Moreover, it would not require the sponsor of a animal drug combination to establish the safety of the combination to the animal targeted to receive the combination.

- Section 201(f) includes a provision relating to presubmission conferences. It directs the agency to provide at the request of the sponsor a presubmission conference during which the agency identifies the studies that a sponsor must conduct to show that a drug is safe and effective. The provision further directs that such decisions regarding what studies are needed are binding on the agency unless FDA by order determines that a documented scientific requirement essential to the determination of safety or effectiveness of the animal drug has appeared after the conference.

The concept of presubmission conferences is supportable. The binding nature of decisions regarding studies os problematic. The agency may be unable to determine with certainty what studies are necessary until the results of some preliminary studies are evaluated.

SEC. 202. TIMEFRAME FOR APPROVAL FOR ANIMAL DRUGS

- Section 202 cuts the timeframe for approval of new animal drug applications in half (from 180 days to 90 days).

  The 90 day timeframe is unrealistic.

SEC. 203. DISPUTE RESOLUTION

- Section 203 permits the sponsor of a new animal drug to seek dispute resolution before an advisory committee or a special government employee or a nongovernmental person, acceptable to FDA and the applicant, who is qualified to mediate or arbitrate whenever an "impasse" exists in the review of an application. It requires FDA to refer the dispute to an advisory committee or other third party on receipt of a notification from the applicant that a dispute exists. Within 30 days of receiving the panel or third party recommendation, the Secretary must, in writing, confirm or modify, the panel or third party recommendation providing reasons and reference to data before the committee or third party for any modification.

  It is unclear whether the dispute mechanism is workable for CVM because CVM has only one standing advisory committee to which it refers disputes. In addition, the number of experts on a particular subject may be rather limited.

SEC. 204. LIMITATION ON RESIDUES

- Section 204 amends section 512(d)(1)(F) to permit dose ranges, with endpoints based on human and animal safety, to be used on animal drug labels.

  This would eliminate the requirement that CVM set a tolerance limit based on an optimal dose, the minimum dose at which there is a maximum effect for the particular indication. Thus, CVM can approve a product with dose ranges that allow veterinarians to exercise professional judgment in treating animals. Permitting the use of dose ranges will reduce the potential for public health problems by reducing the risk of developing antimicrobial resistance and allowing effective

treatment of diseases transmitted from animals to man. The provision is supportable.

SEC. 205. VETERINARY FEED DIRECTIVES

- Section 205 adds new section 504, which provides statutory authority for a new class of animal drugs intended for use in animal feed that would be restricted to use in accordance with a "veterinary feed directive."

  This new class is needed because certain animal drugs administered through an animal's feed can only be approved for use under a veterinarian's supervision and thus, cannot be sold over the counter. The regulation of most animal feeds under traditional prescription systems is not practical.

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Add The Following REGO Related Provisions Not Currently in the Bill:

Feed Mill Licensing

Would substitute site licensing for medicated feed applications that currently are required to be submitted by feed mills for individual medicated feeds. The proposal would save both agency and industry resources.

Import Tolerances for Veterinary Drug Residues in Food

Would provide FDA specific legislative authority to establish import tolerances to allow importation of food from animals treated with drugs not approved in the U.S. rather than requiring companies to seek approval of the drug's use in the U.S. The establishment of import tolerances would alleviate the unnecessary burden and cost of obtaining unnecessary new animal drug application approval for drugs that are not manufactured and used in the U.S. without compromising food safety.

April 19, 1996

DRAFT DRAFT DRAFT

H.R. 3201
"MEDICAL DEVICE REFORM ACT OF 1996"[1]

SEC. 1. SHORT TITLE; REFERENCE; TABLE OF CONTENTS

SEC. 2. FDA MISSION AND ANNUAL REPORT

- Section 2(a), the mission statement establishes efficient review and approval and global harmonization as primary FDA goals.

  The agency's core mission is not to approve products, but rather to thoroughly and fairly evaluate them and render impartial decisions about their safety and effectiveness. The mission statement should include protecting the public from products that do not have the requisite approval prior to marketing -- i.e., products that are unsafe and ineffective or have not been shown to be safe and effective.

- Section 2(b) requires the Secretary to, in connection with the submission of an annual budget, submit to the Commerce Committee in the House and the Committee on Labor and Human Resources in the Senate, an annual report that (1) reviews FDA's performance in meeting its mission and developing policies to implement such mission; (2) reviews FDA's performance in meetings its own performance standards (including meeting statutory deadlines); (3) describes FDA's staffing and resources and lists third parties that have been accredited to perform product reviews [drug, rather than device, provisions are listed] and GMP inspections and to conduct investigations; (4) describe FDA's harmonizations goals, activities, and accomplishments; and (5) compares FDA's performance in approving innovative products with that of the most "successful" agency performing similar functions in other countries and compares the resources used by such agencies.

  The agency does not disagree with the principle that the agency must be held accountable. The concern is that some of the requirements set forth in this provision are not clearly defined and/or possibly not feasible. For example, the requirement that FDA compare its performance in approving innovative products with that of the most "successful" agency performing similar functions in other countries is

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[1] H.R. 3201 includes a number of supportable concepts. The emphasis of this section-by-section analysis, however, is on the problematic provisions in the bill.

vague and may be difficult, if not impossible, to meet. The term "successful" is not one that provides much guidance. Moreover, it is uncertain whether such data are available from other countries or if such data are available, whether a comparison is possible. Finally, what devices another country might consider to be innovative could be considered passe (or dangerous) in the U.S. and vice versa.

SEC. 3. DISPUTE RESOLUTION

- Section 3 provides that whenever an "impasse" exists in the review of an application, device sponsors may seek dispute resolution before an advisory committee or a special government employee or a nongovernmental person who is qualified to mediate or arbitrate and who is acceptable to the Secretary and the applicant. It requires the Secretary to refer the dispute to an advisory committee or third party on receipt of a notification from the applicant that a dispute exists. The panel or third party has 60-90 days to provide the Secretary a report containing recommendations on the matter. Within 30 days of receiving the panel or third party recommendation, the Secretary must, in writing, confirm or modify the panel or third party recommendation providing reasons and reference to data before the committee or third party for any modification. The panel or third party recommendation automatically becomes the Secretary's unless the Secretary acts within 30 days of receipt of the recommendation.

  The section begins by referencing 510(k) submissions and IDE applications (section 520(g)), but it later references PMA's (section 515). It is unclear whether it applies to all three. It also is not completely clear that the provision operates to toll the clock on the review of 510(k), IDE and PMA submissions. (Tolling seems to be contemplated because the bill allows up to 120 days for resolution of a dispute and thus decisions on 510(k)s would be delayed beyond the statutory time period of review.)

  The concept of an effective appeals process is supportable. However, this section would duplicate (and if the sponsor chooses would supersede) existing dispute resolution procedures. It does not appear to require a sponsor to first go up the administrative ladder. Its use is not limited to significant scientific issues. It has the potential for inundating the agency with requests for advisory panel meetings, which have significant resource implications. The advisory committee or third party should have the ability to turn down requests for dispute resolution.

SEC. 4. INVESTIGATIONAL DEVICE EXEMPTIONS

- Section 4 directs FDA to amend its IDE regulations (within 120 days) to permit the use of investigational devices in the diagnosis or treatment of life threatening or irreversibly debilitating conditions by any treating doctor who determines that the risk of not using the device exceeds the probable risk of using it.

  CDRH comments indicated that it already permits use of an investigational device in life-threatening situations pursuant to 21 CFR 812.35(a). This has been interpreted to cover organ threatening and sight threatening situations as well as situations in which patients may suffer irreversible debilitation. **Does this mean that 812.35 has been interpreted to permit the use of investigational devices outside of a protocol. It refers to persons who are "subjects" of the investigation. DISCUSS.**

- New Paragraphs (B) and (C) of section 520(g)(6), added by this provision, require the agency to review, within 30 days, pre-IDE submissions (including protocols). Within the 30 days, the agency must not only review but also explain in writing how a deficient protocol may be corrected.

  CDRH agrees with the concept of pre-IDE conferences. In fact, the provision mirrors current Center policy. However, the bill seems to require IDE sponsors to submit a quasi-formal application and to require that FDA respond to that in writing. It requires FDA to expend significant resources into responding to an informal submission -- i.e. FDA must respond to what a company might do.

- Pursuant to new paragraph (D), submitters may challenge the agency's response by appealing to a classification panel at its next scheduled meeting.

  This provision seems to "elevate" the agency's response to an informal submission. (Note IDE decisions go to an advisory committee or a third party (see section 3); these pre-IDE decisions go to a classification panel.)

- Paragraph (E) on page 8 would require FDA to permit changes to investigational devices without an additional IDE or supplement if there is not a "significant change" in design or basic principles of operation.

  This provision, which is substantially similar to a parallel section in S.1477 (Sec. 303.), gives sponsors wide latitude to make changes to an

investigational device during the course of a clinical trial without prior approval by FDA, a third party, or an IRB. This generally is FDA's practice. **Shouldn't (E) also require that there not be an affect on the validity of the data and patient safety?**

- Paragraph (F) will permit changes to clinical protocols that do not affect the validity of the resulting data and do not alter the risk/benefit relationship for the patient.

  This provision also is substantially similar to a parallel section in S.1477 (Sec. 303.). It gives sponsors wide latitude to make changes to a study protocol during the course of a clinical trial without prior approval by FDA, a third party, or an IRB. The result may be study data that is a mixture of results from the various mid-study changes. This could complicate or undermine FDA's ability to make rational determinations about the safety and effectiveness of the investigational device. Even more problematic is that fact that it would permit sponsors to significantly increase the patient population in a study and thus, because sponsors are permitted to recover developmental costs, would in effect permit sponsors to use the IDE to market their product. Because there would be widespread commercialization, there would be no need for sponsors to come to FDA for approval.

SEC. 5. SPECIAL REVIEW OF CERTAIN DEVICES

- Within 6 months of enactment, FDA must promulgate regulations establishing priority review of breakthrough or other important technologies for life-threatening or irreversibly debilitating conditions. This provision establishes a 60 day comment period and gives the agency 60 days to publish final rules.

  Expedited review of important new devices is a supportable concept. CDRH currently has an expedited review policy in effect (for both 510(k) and PMA devices), which is predicated on essentially the same criteria as in the bill and which is yielding the kind of results apparently contemplated by the provision. The abbreviated schedule for developing and promulgating regulations, as called for in the bill, could detract from current expedited review activities because the people involved in both activities would likely be the same. [Also this must be considered along with the abbreviated promulgation schedules that appear several places in this bill.]

SEC. 6. EXPANDING HUMANITARIAN USE OF DEVICES

- In 1990, Congress passed the humanitarian use device exemption (HUD) to encourage the discovery and use of devices intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect a relatively small number of individuals. The provision exempts HUD manufacturers from the requirement for demonstrating "effectiveness" for devices subject to the PMA and performance standards provisions. Section 6 amends the current provision of the statute by establishing a 30 day time period for agency review of HUD applications, and eliminating any time limit on the HUD exemption (the current law establishes a renewable 18 month term). It also changes the program from a 5 year pilot to a permanent provision and eliminates the requirement for regulations prior to implementation.

  CDRH currently is preparing a regulation implementing the 1990 provision. The regulation would treat these devices as PMA products without the effectiveness requirement. The bill's 30-day review deadline is not realistic. It does not allow enough time to do a credible job of assessing a HUD application. It certainly does not allow enough time to take the issue before an advisory committee. Moreover, it would create an artificially high priority for products that are targeted to benefit a small group of patients who may not have serious diseases or conditions and potentially displace work on products for larger groups of patients with serious diseases or conditions. The elimination of a term for the exemption also is problematic. A use may become widespread -- and at some point no longer meet the definition for a humanitarian use.

SEC. 7. PERFORMANCE STANDARDS

- This section strikes current section 514 of the Act and substitutes a requirement that the Secretary publish notices recognizing standards that can be applied to any approval or compliance determination under the Act. The agency would have to recognize "applicable nationally or internationally recognized consensus standards" through this process and accept certifications that devices conform with these standards. An applicant would be free to use other data to establish safety and effectiveness or compliance with the Act.

  This section differs significantly from the Senate version, which maintains the portions of 514 that permit the agency to promulgate performance standards and which establishes criteria for standard-setting bodies as well as provisions for what should be included in a performance standard. In light of the fact that the agency has never promulgated a performance standard, the deletion of current 514 may

not make a great deal of difference. However, it is not clear how much discretion FDA has in recognizing performance standards. (i.e., the bill says "shall" but leaves open the possibility that the Secretary has discretion to determine what is "applicable," "recognized," and represents "consensus"). Regulations that establish criteria for what standards are acceptable and when recognition of standards may be revoked seem essential.

Nothing in the section appears to prohibit the Secretary from requiring third party certification of conformance with standards. However, that point should be clarified.

SEC.8. EFFECTIVENESS DETERMINATION

- Section 8 changes the current effectiveness standard to include a maximum of one clinical investigation and establishes that no clinical investigation will be required unless the Secretary first consults with a classification panel.

  Although one pivotal trial generally can demonstrate effectiveness, there are times when more than one study is needed. Forcing the agency to consult with advisory panels on a device-by-device basis will introduce substantial administrative burdens. **DISCUSS**

- Section 8 also restricts any clinical trial to controls that are appropriate for labeled uses. **Discuss the implications of this?**

- New section 513(a)(3)(C)(1) prohibits FDA from evaluating clinical data for devices, unless the device is labeled as having a therapeutic effect to the person for whom it is intended.

  This appears to eliminate the agency's ability to require and evaluate clinical data for devices. This emasculates the present system that requires devices be shown to clinically perform as intended and produce useful outcomes for patients. It is a move to the EU system, which looks only at engineering aspects of a device. Without well-designed and well-conducted studies, FDA will be hampered in making well-informed decisions about the clinical efficacy of devices, a situation strongly criticized by the Congress earlier in this decade. This will ultimately impair clinical decision-making by health care providers.

- Add (ii) and (iii) and explain that this is current practice.

- New section 513(a)(3)(C)(iv) also provides that the review of a device application cannot include the evaluation of any use not included in the labeling.

  This appears to prohibit FDA from including, in the labeling, warnings about indications for which a product is dangerous or known not to be effective.

SEC. 9. PRE-MARKET NOTIFICATION

- Subsection (a)(1) exempts all Class I devices from the requirement of submitting a premarket (section 510(k)) notification. Subsection (a)(3) requires FDA to publish a list of exempt Class II devices within 30 days. It gives anyone the right to petition for other Class II devices to be exempt, and provides 120 days for the Secretary to review such petitions.

  Re: Class I devices: FDA has already exempted 572 class I devices from premarket notification. Many of the devices that FDA has not exempted, were not exempted for public health reasons. For example:

  1. FDA needs to review tests on the technical performance of hearing aids to ensure that they function as intended.

  2. Rebreathing devices are used as components within certain anesthesia machines, volume ventilators and resuscitation devices. Certain rebreathing devices have been directly related to death, serious injury, and serious illness resulting from complications caused by their design, performance, etc.

  3. Patient examination gloves have a significant history of defects such as hole not readily detected by the user. This is unacceptable for a device that is important in the prevention of HIV and other blood borne diseases.

  The Senate bill gives FDA 15 days from the date of enactment to publish in the Federal register a list of Class I devices that FDA determines require a 510(k) to protect the public health. A similar provision should be added to the House bill.

  Re: Class II, the provision is almost identical to S. 1477, Sec. 702 (a). There is no opportunity for public comment ont eh exemptions. Moreover, under the House version, however, a petition for a Class II exemption is deemed granted if the Secretary does not respond within

120 days.

- Subsection (a)(2) permits device sponsors to submit 510 (k) notifications to third parties.

- Subsection (b)(1) (initial classification) is essentially identical to the Senate version (Sec. 702 (b) of S. 1477), except that a panel recommendation automatically becomes a final order if the Secretary does not make a determination within 10 days.

  The same concerns that were raised with respect to the Senate version apply to this section: i.e., it is not desirable from a scientific or resource perspective to have every NSE decision go to a panel; the time frames are unreasonable.

- Subsection (b)(2) authorizes third parties to review 510(k) submissions for Class II devices. The third party's determination that a device is Class II shall be considered an order of the Secretary initially classifying the device. If the third party determines that the device should be classified as Class III, such person must refer the report to the Secretary.

  The bill authorizes manufacturers of class II devices to obtain market clearance from third parties, whose decisions are binding and devoid of any FDA review and concurrence. This sets up the possibility that a high risk device that should be in class III may be found by a third party to be "classifiable" in class II and the decision of the third party would be implemented without any input from FDA, its advisory panel, or the public.

- Subsection (b)(2) also provides for third party review of Class III devices. It gives third parties 60 days to review 510(k) submissions for Class III devices and submit a recommendation regarding initial classification to the Secretary and to the submitter. The third party's recommendation becomes a final order unless the Secretary determines that the device is NSE and issues an order within 30 days of receiving the recommendation. Such order must provide a detailed explanation and justification for the basis of the Secretary's disagreement with the third party. If the Secretary does nothing, the recommendation of the third party becomes a final order 90 days following the Secretary's receipt of the third party report. [It is unclear how this 90 day time period relates to the 30 days in which the Secretary must act.]

- Subsection (b)(2) also prohibits the Secretary from withholding a substantial equivalence determination because of failure to comply with GMPs.

This is similar to provision in Sec. 702 (a) of Senate bill. It prevents FDA from ascertaining GMP compliance prior to market clearance and to thereby have a reasonable assurance that a device is substantially equivalent or that the firm can reliably and consistently produce high quality devices.

- Subsection (c) -- device modification-- eliminates the requirement that a manufacturer file a 510(k) for any modification other than a major change in intended use if the modification is supported by appropriate data and can be shown not to adversely affect the safety and effectiveness of the device. Records of data supporting the change must be kept for commercial life of device.

  Under the bill, unless the manufacturer's own data shows that the safety and effectiveness were to diminish, FDA could not require data on the modified product. This would eliminate FDA's role in assuring that modifications made to a product do not adversely affect its safety and effectiveness. Thus, changes to biomaterial, power sources, and control mechanisms would be permitted and FDA would not see data. This provision creates an enormous loophole to the 510(k) requirement.

  This is a lower standard than the modified Senate version. Unlike the House version, the Senate provision on device modification (sec. 702 (d)) includes the following as 510 (k) triggers: significant change in operating principles; significant change or modification in design; significant change in manufacture (assuming the word "manufacture" was accepted by the Senate committee). In addition, the Senate version requires the manufacturer's supporting data to include information demonstrating compliance with GMPs and to maintain supporting data for a least 2 years.

- Subsection (c) -- the substantial equivalence provision -- would specify that each use included within a general use for a predicate device be deemed a legally marketed use for purposes of premarket notification.

  This would allow a device originally marketed for one clinical indication to later be marketed for other indications, even high risk ones. **Add example**

  This is similar to the Senate provision on general use/specific use (S. 1477, Sec. 702 (c)), with the significant omission of language similar to that of the Kennedy amendment, which was intended to clarify that it is up to the Secretary to determine whether a specific use is "reasonably" included within a general use. The Senate version is also more explicit

about the fact that the requirement to submit a 510 (k) still pertains.

- Subsection (c) also changes the substantial equivalence provision by providing that data required to show substantial equivalence may be either "scientific" or "clinical" and changes the term "efficacy" to "effectiveness."

SEC. 10. CLASSIFICATION PANELS

- Section 10 requires the Secretary to schedule 6 meetings a year for each classification panel and scientific advisory panel. This section establishes equal access for all persons to panel members and equal participation in meetings. This section also establishes a 30 day time frame for FDA review of a panel recommendation.

  The requirement for advisory panels to meet six times per year is unrealistic. CDRH manages over 20 different panels. Even if half of the meetings could be accomplished electronically, the logistics of pre-panel preparation and scheduling would be formidable. The time demands imposed by the bill on advisory panels could have a negative affect on the willingness of existing panels to continue to serve in their present capacities and have a chilling affect on FDA's ability to recruit future panel members. The 60 day timeframes are unrealistic. It is one half that required by S. 1477.

  The provision assumes that all matters presented to advisory committees are susceptible to "final" determination. This is not always true. A better approach would be to require FDA to make a determination within __ days or to notify the affected persons of the reason why a decision has not been made and the timetable by which a decision will be made.

- Section 10 provides sponsors direct contact with classification panel members.

  This provision would allow sponsors to lobby classification panel members.

SEC. 11. PREMARKET APPROVAL

- Subsection (a) of this section establishes the scope of third party authority for premarket approval. Third parties will handle the receipt, filing, and review of the PMA, as well as classification panel presentations and evaluations of classification panel recommendations. The third party must make a

recommendation to the Secretary within 30 days following receipt of a classification panel recommendation. The third party's recommendation about a PMA, i.e., whether it should be approved or denied, is considered an order of the Secretary unless the Secretary finds that there is a "reasonable probability that the device is not safe or effective," and provides a detailed explanation of the basis of the finding.

This standard requires the Secretary to establish a negative instead of finding that the application does not provide reasonable assurance of safety and effectiveness. This provision implicitly negates the bases set forth in current 515 (d)(2) as grounds for disapproval by the Secretary when a PMA is reviewed by a third party.

- Subsection (b) establishes interim deadlines for the Secretary to meet to ensure that a PMA is reviewed within 180 days. It provides that the 180 day timeframe shall not be enlarged by any amendment to the application.

  This is substantially similar to Sec. 707 (a) of the Senate bill, with additional provisions for situations in which a PMA is reviewed by a third party. It requires numerous meetings and includes unrealistic timeframes. For example, by requiring FDA to meet with companies within 90 days and to present a description of deficiencies in the application and "what information is required to bring the application into a form that would require approval," the bill actually requires FDA to do a comprehensive review in one half the current statutory timeframe.

  The prohibition against enlargement of time poses a special concern in cases when major deficiencies are discovered or unsolicited major amendments (e.g., new intended uses) are submitted. Under the bill the review clock cannot be reset.

- Subsection (b) also requires a report to the Commissioner and Secretary every time an interim deadline is not met. The report is due within 10 days of the missed deadline and it must fully explain the reason that the timeframe was not met. Within 10 days of receipt of the report, the Commissioner must provide an explanation to the applicant of the reasons for the failure to meet the deadlines and set forth the date for satisfying the scheduled review times. The Secretary must submit an annual report to Congress that summarized each time a requirement was not met, explains the reasons for the failure, and provides proposals to ensure that deadlines will be met.

  An administrative nightmare.

- Subsection (c) requires FDA to promulgate regulations to amend 21 CFR Part 814 to conform to this section of the bill and to eliminate the need for PMA supplements for changes that "do not actually affect device safety or effectiveness."

  This language is looser than the similar Senate provision, which links the exemption from supplement filing to a demonstration through data that changes will not adversely affect safety or effectiveness. The House version requires regulations to be promulgated on an expedited schedule.

  This provision, for all practical purposes, eliminates the requirement relating to PMA supplements for manufacturing changes and other changes that do not actually affect product safety and effectiveness. In effect, this relieves manufacturers from seeking FDA approval despite changes in manufacturing processes, sites of manufacture, sterilization procedures, etc.

  It is worth noting that this change is in contradiction to EU's medical device directive, which requires manufacturers to inform notified bodies of the kind of changes described above and to submit to assessments by the notified bodies for the purpose of verifying that the changes do not affect the firm's compliance standing. Thus, this provision can actually undermine harmonization efforts.

SEC. 12. ACCREDITATION OF THIRD PARTIES

- Subsection (a) requires the Secretary to promulgate regulations to establish procedures for accrediting third parties to review PMAs and perform GMP inspections. It establishes certain criteria for accreditation of third parties relating to conflict of interest, competency, and protection of information. It also requires the Secretary to provide for accreditation through government or qualified non-government entities.

  This section does not establish how the third parties are to be compensated for services. It lacks clearly defined criteria for establishing the qualifications of third parties. It does not provide sufficient safeguards against conflicts of interest. The provision is vague as to whether FDA can inspect third parties or require third parties to maintain records. It also is unclear as to whether third parties can be given access to privileged information that is in the custody of FDA. In addition, it appears that the intention is not to have the Secretary accredit any particular entity, but rather to have the

Secretary designate agencies or organizations who will then perform the accreditation process.

- Subsection (b) amends the prohibited acts section of the FDC Act to add a new section relating to actions by third parties. Under proposed 301 (w), a third party would violate this section if it submitted a materially false or misleading report, disclosed trade secret confidential commercial information, or accepted a bribe or performed any other corrupt act in connection with its delegated responsibility.

SEC. 13. RECLASSIFICATION OF PREAMENDMENT DEVICES

- Section 13 sets an 18 month deadline for the agency to complete the reclassification of Class III pre-amendment devices. At the end of that time period, this provision requires the Secretary to reclassify these devices into Class II if they have not been the subject of a 513 (i) (2) rule down-classifying or retaining the device in Class III.

The provision mandates completion of a resource-intensive activity without consideration as to priority, benefit, or workload. It would be virtually impossible for CDRH to evaluate and act on incoming data for over 30 devices that are presently considered to be candidates for reclassification. The net result would be that a high percentage of these would be retained in class III.

SEC. 14. DEVICE TRACKING

- Section 14 amends the device tracking provision to require a regulation for imposing a tracking requirement, limits tracking to class II and III devices, changes the criteria for a tracking requirement, and eliminates FDA's discretion to apply the provision to "any other device."

Section 14 parallels Sec. 704 of the Senate bill but makes it more difficult to designate a device for tracking. Instead of requiring a potential device failure to be "reasonable likely" to be life-threatening or have "serious adverse health consequences," the House version requires the failure to be life-threatening or have permanently debilitating effects. The provision eliminates the "discretionary" category, which now includes infusion pumps, breast implants, and other silicone related devices. The Senate language is preferable, but it could be improved by changing the "permanently implantable" language to "implanted for more than 30 days."

SEC. 15. POSTMARKET SURVEILLANCE

- Section 15 eliminates the old discretionary category and makes the old mandatory category discretionary. If also further limits the type of device that can be the subject of postmarket surveillance

  Section 15 parallels Sec. 705 of S.1477, but further limits the type of device that can be the subject of postmarket surveillance. The House version eliminates the catch-all category in the Senate bill for devices that potentially present a serious risk to human health or create public health concerns that justify surveillance.

  Another problem with the provision is that it only permits FDA to require postmarket surveillance for devices "first introduced or delivered into interstate commerce after January 1, 1991." The date restriction would exclude Shiley heart valves, breast implants, and Landmark catheters. This cut off was eliminated from the Senate bill.

- Paragraph (b) limits the scope of the surveillance to information "necessary to determine the occurrence of unforseen events" and limits surveillance to 18 months

  This is narrower than the current standard ("data or other information necessary to protect the public health and to provide safety and effectiveness data"), which is in S. 1477. Certain devices (e.g., implantable hips) have long latency periods and the frequency of adverse events cannot always be detected within this 18 month timeframe.

SEC. 16. HARMONIZATION

- Paragraph (a) adds a requirement that GMP regulations conform "to the extent practicable" with international standards.

- Paragraph (b) requires the Secretary to meet with other countries to discuss methods and approaches to reduce regulatory burdens, harmonize regulatory requirements, and seek appropriate reciprocal arrangements. Within 180 days of enactment, the Secretary must make public a plan that establishes a framework for achieving mutual recognition of GMPs. The Secretary also must provide 60 day notice to the Committee before executing any agreements with foreign countries.

SEC 17. GOOD MANUFACTURING PRACTICE INSPECTIONS

- Subsection (a) amends section 704 of the FDC Act to permit third parties to conduct gmp inspections. It also amends the section to require a 10 day waiting period after any inspection (whether by a third party or FDA?) to give the subject an opportunity to respond to any observations. The agency may not take any regulatory action following an inspection until it has reviewed a timely response from the subject of the inspection, unless there is a reasonable probability that a device would cause serious, adverse health consequence or death or that any regulated article could present and unreasonable and substantial risk. The Secretary must also provide a detailed assessment of the response submitted by the subject of the inspection within 30 days.

  In general, requiring a 10 day waiting period, a review of the manufacturer's response, and a detailed response in 30 days may have a significant impact on agency workload (for the inspections the agency would continue to do). Because a warning letter is considered regulatory action, this provision would stop FDA from issuing one until this process is complete. This may not significantly slow down current time frames for issuing warning letters, but it has the potential to hamper agency action.

- A third party performing a GMP inspection does not submit a copy of its observations to the Secretary. However, if the findings indicate a serious problem, the third party must immediately notify the Secretary unless the person subject to the inspection immediately ceases distribution, notifies health professionals and device user facilities, and undertakes all corrections identified by the third party. When such compliance is completed, the third party provides a certification of compliance, a copy of which is provided to t the Secretary. The Secretary may not perform another gmp inspections for 2 years after the date of the certification unless justified by good cause.

  As it is drafted, the agency never becomes involved in compliance matters when a third party has undertaken the original inspection. The third party oversees corrections and certifies to the Secretary that the company is in compliance. The Secretary may not conduct a GMP inspection for 2 years after the date of this certification, "unless justified by good cause."

SEC. 18. USE OF SCIENTIFIC AND MEDICAL INFORMATION

- Section 18 amends 502(f) to make it legal to disseminate medical texts, journal articles, and government information, and to make presentations at medical and scientific meetings about off-label uses. These activities would not constitute misbranding and would not trigger the need to file a 510 (k) or

PMA unless the person "in addition" encourages the unapproved use of a legally marketed device through labeling, advertising,or other means of promotion. The provision also establishes that knowledge of an off-label use would not trigger any obligation for the manufacturer to change the labeling or amend a marketing application. The section also makes it permissible for sponsors of IDEs and their agent to disseminate materials, make presentations, and display investigational devices at trade shows so long as the sponsor or agent does not "encourage the use of the device".

This section assumes that the various activities it permits are not promotion and do not encourage off-label uses or uses of investigational products. The provision will make it possible for sponsors to promote off label uses and investigational products without filing marketing applications or IDEs. The provision eliminates incentives for manufacturers to conduct studies needed to demonstrate the safety and effectiveness of new uses and to go through the regulatory process at all for off-label uses.

SEC. 19. REPORTS

- Section 19 (a) eliminates reporting requirements for distributors.

  Eliminating distributor reporting is not objectionable.

- Section 19 (b) eliminates reports of malfunctions when the available information clearly shows (presumably to the satisfaction of the manufacturer or importer) that the failure was caused by improper servicing or maintenance as determined by review of the device labeling.

  Eliminating this reporting requirement would have a crippling effect on FDA's ability to identify and insure correction of serious device problems.

- Subsection (d) eliminates user reporting requirements and requirements relating to annual certification and reports of removals and corrections.

  The elimination of user facility reporting is problematic. The certification requirements and reports of removals and corrections also serve important oversight functions and they hold manufacturers accountable for compliance with the law.

SEC. 20. G.M.P. AND DEVICE REPORTS

- Section 20 eliminates civil penalty liability for misbranding a device by failing to make required reports or for adulterating a device by failing to comply with GMPs if the person acted in good faith, had no reason to believe the law was being violated, and had no prior notice from the Secretary that the acts constituted violations.

  The reference to 301(g)(1)(B) does not make sense.

SEC. 21. CIVIL PENALTIES

- Paragraph (1) gives the Secretary discretion to direct a person subject to civil money penalties to apply the amount to the correction of violations, as verified by an independent auditor.

  The intent of this provision is unclear. Is the idea to allow violative companies to benefit? Doesn't this then create an incentive to violate the law? Would the money be used to compensate persons injured by the device?

- Paragraph (2) adds the right to discovery for particular violations concerning the distribution of growth hormones to minors.

  What is this intended to accomplish and why is it in the device reform bill?

SEC. 22. INFORMATION SYSTEM

- Section 22 requires FDA to establish a system to track the status and progress of each application. The system must permit access by the applicant.

  This section raises concerns re: protecting the confidentiality of applicant information. In addition, there are resource implications re: set-up and maintenance.

SEC. 23. ENVIRONMENTAL IMPACT REVIEW

- Section 23 eliminates the requirement to prepare an environmental analysis unless the Secretary demonstrates that because of extraordinary circumstances, the action will have a significant effect on the human environment and the consideration of such significant effect will directly affect the Secretary's decision on the action.

  This is similar to Sec. 406 of the Senate bill, but the House version

makes it harder to require an environmental impact review because it requires the Secretary to demonstrate that the action "will have a significant effect on the human environment."

SEC. 24. INFORMAL AGENCY STATEMENTS

- This section prohibits the Secretary from relying on policy statements, guidance documents, and similar statements to require any action to satisfy a provision of the FDC Act. It also requires the Secretary to publish notice of availability of such statements and to make them accessible electronically.

  FDA's position is that guidance documents are not binding on the Agency or the public. FDA recently issued a Federal Register notice that affirms this position and has agreed to take steps to ensure that the agency and the public know and understand this principle. To the extent that this provision is reaffirming that position it is not problematic. To the extent that it is saying that FDA cannot issue guidance that explains how it believes compliance with the Act may be accomplished, it is problematic -- particularly for the industry. FDA will no longer be able to provide guidance and there is a risk of non-uniformity in the application of the laws and regulations that FDA is tasked with implementing.

SEC. 25. RESEARCH AND EDUCATION; PRACTICE OF MEDICINE

- New section 908(a) requires FDA to train and educate its employees.

  FDA currently does this through staff colleges etc.

- New section 908(b) limits FDA's research activities to research directly related to the implementation of the FDC Act.

- New section 909 states that nothing in the FDA Act shall limit or interfere with a health care practitioner's authority to prescribe or administer legally marketed drugs or devices.

SEC. 26. PUBLICATION OF NOTICE DEVIATION

- Section 26 prevents FDA from making public any information regarding a notice that informs a regulated person of a purported deviation from a requirement of the Act until after the Secretary has completed the investigation

of such deviation.

This provision calls into question the agency's long-standing practice of making 483s, warning letters, and correspondence with regulated industry available to the public. Such a radical change in FDA's public information procedures and regulations could hamper the agency's ability to carry out its public health mission effectively. The difficulty the agency currently has with respect to prohibitions on public disclosure of information contained in marketing applications would extend to disclosure of information about observed violations and enforcement initiatives.

April 22, 1996

DRAFT DRAFT DRAFT

H.R. 3199
"DRUG AND BIOLOGIC PRODUCTS REFORM ACT OF 1996"[1]

SEC. 1 SHORT TITLE, REFERENCE, AND TABLE OF CONTENTS

SEC. 2 FDA MISSION AND ANNUAL REPORT

- Section 2(a), the mission statement establishes efficient review and approval and global harmonization as primary FDA goals.

  The agency's core mission is not to "approve" products, but rather to thoroughly and fairly evaluate them and render impartial decisions about their safety and effectiveness. The mission statement should include protecting the public from products that do not have the requisite approval prior to marketing -- i.e., products that have not been shown to be safe and effective.

- Section 2(b) requires FDA to, simultaneously with the submission of an annual budget, submit to the Commerce Committee in the House and the Committee on Labor and Human Resources in the Senate, an annual report that (1) reviews its performance in meeting its mission and developing policies to meets its mission; (2) reviews its performance in meetings its own performance standards (including meeting statutory deadlines); (3) describes its staffing and lists third parties that have been accredited to perform product reviews and GMP inspections and to conduct investigations; (4) describes its harmonization activities and accomplishments; and (5) compares FDA's performance in approving innovative products with that of the most "successful" agency performing similar functions in other countries and compares the resources used by such agencies.

  The agency does not disagree with the principle that the agency must be held accountable. The concern is that some of the requirements set forth in this provision are not clearly defined and/or possibly not feasible. For example, the requirement that FDA compare its performance with that of the most "successful" agency performing

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[1] H.R. 3199 includes a number of supportable concepts. The emphasis of this section-by-section analysis, however, is on the problematic provisions in the bill.

similar functions in other countries is vague and may be difficult, if not impossible, to meet. The term "successful" is not one that provides much guidance. Moreover, it is uncertain whether such data are available from other countries or if such data are available, whether a comparison is possible.

SEC.3 STREAMLINING CLINICAL RESEARCH ON DRUGS AND BIOLOGICAL PRODUCTS

- Section 3 provides that a clinical investigation of a new drug may begin 21 days after the Secretary has received a submission that contains adequate reports of basic information necessary to assess the drug's safety and adequate information on the chemistry, manufacturing, controls, and primary data tabulations for the drug from animal or human studies, except that for phase I or II clinical investigations, detailed information shall not be required unless the office director makes a written request within 21 days.

  The effect of section 3 is to reduce (from 30 days to 21 days) the amount of time FDA has to place a clinical hold before the investigation of a new drug begins. The shortened timeframe is even more difficult to meet because, as set forth below, it does not permit a telephone call. (Moreover, the written notification that is required must set forth the reasons for the clinical hold.) CDER alone received 1972 INDs in FY 1995. CBER received an additional 457. The problem is that studies may be allowed to proceed without FDA being able to assess the risk. The reduced time frame in the bill shaves LITTLE time from the total drug development process, but a LARGE fraction of the time available to FDA for the protection of human subjects. Patients enrolled in these clinical trials will suffer the consequences of FDA being unable to meet the timeframes.

  This provision does not seem to require the sponsor to submit information on the study design. If this is the intent of the provision, that is problematic.

  The provision exempts Phase I and II studies from requiring the inclusion of detailed information on chemistry, manufacturing, controlled, and data tabulations unless the office director makes a written request within 21 days. Because this is the stage of the clinical investigation where FDA is deciding whether to allow a drug to be administered to human subjects, this is the stage where FDA needs certain detailed information. [If a request for detailed information is made, can the investigation proceed or does the agency have to couple

the written request for detailed information with a clinical hold?]

- FDA cannot place a trial on clinical hold unless the Secretary demonstrates "based on specific information available to the Secretary" that the drug presents an unreasonable risk to the safety of the subjects taking into account the trial design, the conditions for which the drug will be studied and the health status of the subjects. The clinical hold must be in writing and must specify the basis for the clinical hold. The Secretary may issue a clinical hold upon a demonstration that the drug to be investigated represents an unreasonable risk to the safety of the persons who are the subject of the clinical investigation, taking into account the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved. If the sponsor requests that the hold be removed, the Secretary must provide a decision in writing within 15 days or the clinical hold shall be deemed withdrawn.

  Because the notification may not have to include the design of the trial or the health status of the subject, FDA may not have the information necessary to make the requisite finding. Moreover, even if FDA had the requisite information, it would not have enough time to make the finding.

  The provision restricts FDA's ability to place a trial on clinical hold to instances when the drug to be investigated represents an unreasonable risk to the safety of the persons who are the subject of the clinical investigation, taking into account the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved. Under current law, FDA can place a trial on clinical hold for a number of other reasons. For example, a Phase I, II, or II clinical trial can be placed on hold if the clinical investigators are not qualified to conduct the investigation; the information the sponsor has given to the investigators about the drug and its pharmacological and toxicological effects, and what is known about the safety and effectiveness of the drug in humans is misleading, erroneous, or materially incomplete; or the IND does not contain sufficient information to assess the risks to subjects. A Phase III trial can also be placed on hold if the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. See 21 CFR 312.42(a); see also 21 CFR 312.55, 312.23(a)(5).

  The provision requires review of a response to a clinical hold within 15 days. This is unrealistic. Pursuant to REGO, FDA has proposed to complete such a response within 30 days.

- As an alternative procedure, a Phase I or Phase II clinical investigation may begin after an accredited institution has approved the investigation and the Secretary has been notified by the sponsor. The notification need only set forth the name and address of the sponsor and the uses of the drug that the sponsor intends to investigate.

  This provision is problematic re: Phase II clinical investigations because for certain drugs, such as AIDs drugs, the investigation does not proceed beyond phase II trials. This provision would permit sponsors to begin the studies without submitting data to FDA. FDA would have a difficult time issuing a clinical hold because it would not have access to the detailed information about the study. (It is not clear that the notification requirements set forth above apply -- and even if they do, Phase I and II are exempt from submitting detailed information.)

  It would be very difficult for local IRBs to include among their members or consultants all of the expertise needed to assess the risks to patients with various diseases. The scheme set forth in the bill increases the possibility that patients would exposed to an unreasonable risk.

- Section 3 also gives FDA exclusive jurisdiction over the regulation of new drugs in clinical investigations.

  This eliminates duplication by NIH (i.e., for drugs (including biotechnology drugs) being study under HHS-funded research.

SEC.4 THE CONTENT AND REVIEW OF A NEW DRUG APPLICATION

- Section 4 permits sponsors of new drug application to submit summary data. Primary data may be requested by the office director. Such request must be in writing and must specify the reasons for the request for a particular application.

  This provision will compromise the credibility of FDA's review process. Summary reports sometimes contain errors that can be discovered only by reviewing primary data. Moreover, summary data has been screened, processed and interpreted by the sponsor. Companies often just do not see the shortcomings of their drugs. Someone other than a company official should be taking a hard look at the underlying data. Primary data are essential to verify the interpretation of summary data. Problems associated with a drug may be visible through an examination of the raw data that are not visible

from a summary. For example, deaths and discontinuations of study subjects may be attributed to causes other than the drug but review of the raw data may show adverse reactions associated with the drug itself. The submission of primary data is essential to discovering and discouraging the submission of fraudulent data.

Even hints of information found in patient reports can reveal or lead to critical information. For example, then a CDER reviewer reviewed the patient data for xxx, she (not the company) noticed that three of the subjects suffered from xxx while on the experimental drug. Based on her knowledge of this class of drugs, and the fact that no other drugs of this type caused this type of side effect, she decided to look further. She consulted with the company, which took a look at data available from the other countries where the drug had already been approved. The company found not merely xxx, but also deaths due to the drug. Based on this careful observation by an FDA reviewer, the drug was not approved in the United States, and it was removed from the market in xx, xx, and xx. The House proposes to eliminate FDA's ability to find the next case of xxx.

- Section 4 also requires FDA to meet with product sponsors within 30 days of a request for a meeting. FDA advice provided in writing and made a part of the administrative record cannot be changed after testing begins unless the sponsor agrees or the office director determines, after an informal hearing, that such a change is needed to protect the public health.

  FDA makes every effort to hold meetings promptly in response to any reasonable request. It may not always be possible to do it within 30 days. In addition, there often are times when knowledge of a disease or product will evolve, and the agency should be able to require appropriate data as needed to assure that a product is safe and effective.

- Written review decisions on scientific and medical matters on a new drug will be binding on field and compliance staff.

- Action on an application cannot be delayed because of the unavailability of information from or action by field personnel.

  This provision would require the agency to approve products before allegations of fraud, misconduct in a clinical trial, manufacturing problems etc. could be investigated. This could allow an unscrupulous sponsor to deliberately delay an inspection so that information would not be available from the field personnel, and the approval decision would have to proceed without this information.

SEC.5 EFFECTIVENESS DETERMINATION

- Section 5 provides that "one or more" clinical investigations may be needed to show effectiveness. It also provides that a well-controlled investigation "shall include only methods of control that are appropriate to the disease or condition for which a drug is intended as prescribed, recommended, or suggested in its labeling."

  The addition of "one or more" before "clinical investigations" is problematic only if it would not permit the agency to require more than one clinical investigation where appropriate. [There are differences of opinion within FDA as to whether the bill language might so this.]

  [what does this mean?]

- Section 5 also provides that an application for a new drug for a serious or life-threatening condition shall be considered to have substantial evidence if it could fairly and responsibly be concluded by experts that there is a reasonable likelihood that the drug will be effective in a significant number of patients and that the risk from the disease is no greater than the risk from the condition.

  This provision, which allows approval of a new product without adequate and well-controlled trials, undercuts the efficacy standard and shifts the risk analysis away from risk/benefit.

- Section 5 also would permit the approval of a new use of a previously approved drug on the basis of a demonstration that the new use is common among clinicians experienced in the field and represents reasonable clinical practice based upon reliable clinical experience and confirmatory information.

  This would establish a new process for approving new uses of existing drugs and devices that would significantly lower approval standards. It would establish a procedure for recognizing new uses based on clinical practice.

  A drug may come into common use for a condition because current theory, and experience understood in light of that theory, suggests that the drug would be reasonably expected to have the desired effect, but testing such a hypothesis against data in a controlled trial can expose new aspects of the system and may demonstrate that the drug is not acting as it had been predicted to act. Clinical experience cannot be depended upon to bring such new findings to light because it contains too many uncontrolled differences among cases and observers.

This provision moves us away from the accepted scientific standard of evidence and could perpetuate inappropriate, unproven, and ultimately unprovable medical practices.

- Section 5 provides that the determination of effectiveness cannot include the evaluation of relative effectiveness unless the effectiveness of the drug is explicitly compared in the labeling to that of another drug.

  There are public health implications if FDA is not allowed to consider relative effectiveness for products that involve serious or life-threatening illness or which involve public health transmittal risks. For example, FDA requires a 95 percent efficacy rate for gonococcal eradication for products intended to treat GC. This is an efficacy rate products can meet today. It would not be in the public interest to have products available that are less effective in treating a public health epidemic. The same is true for illnesses that are life-threatening. Lesser efficacy than that which other products have established represents a threat to public health.

  In addition, there are instances when the testing of a new product involves testing versus another treatment rather than versus a placebo. Use of a placebo would be unethical. Here relative effectiveness is the only thing that can be considered.

- Section 5 also provides that the determination of effectiveness cannot include the evaluation of any use not explicitly included in the labeling.

  This appears to prohibit FDA from including, in the labeling, warnings about indications for which a product is dangerous or known not to be effective.

- Section 5 provides that the determination of effectiveness cannot include the evaluation of cost effectiveness, unless the labeling references such.

  This is FDA's current practice.

SEC.6 SCIENTIFIC ADVISORY PANELS

- Section 6 requires advisory committees to include non-voting industry and public representatives.

  Is there a problem with non-voting members attending closed meetings and or receiving confidential information?

- Section 6 provides sponsors direct contact with advisory committee members.

  This provision would allow sponsors to lobby advisory committee members.

- Section 6 requires advisory committees to meet at least 6 times a year -- three of those meeting must be face to face.

  Current advisory committee members already have problems with time commitments.

- Section 6 requires FDA to make a final determination within 30 days of an advisory committee recommendation.

  The timeframe for action on a panel recommendation is one half that required by S. 1477. Moreover, the provision assumes that all matters presented to advisory committees are susceptible to "final" determination. This is not always true. A better approach would be to require FDA to make a determination within __ days or to notify the affected persons of the reason why a decision has not been made and the timetable by which a decision will be made.

SEC.7 MARKETING APPROVAL

- Section 7 provides for third party review of new drug applications. It defines the scope of review responsibilities of accredited persons to include the review of applications to determine whether there is a "reasonable assurance" that a drug is safe and effective. Prior to 60 days before the end of the review period, the third party shall submit a report to FDA of its review and recommendation as to whether the application should be approved or denied. The recommendation of the accredited person shall be deemed to be approved by the Secretary unless the Secretary finds that there is a reasonable probability that the drug is not safe or effective. [What if the third party finds that the product application should be denied?] The Secretary shall evaluate the recommendation within 60 days of receipt and in the event that the Secretary makes a finding that the drug is not safe or effective, the Secretary shall provide a detailed basis of the difference.

  FDA has no authority to decide whether third party review is appropriate under the circumstances. Even the most complicated types of reviews could go to third parties if the sponsor so chooses. The third party's lack of experience and institutional knowledge in a given area (i.e., a new technology) will not prevent it from performing the review. Unsafe and or ineffective products could therefore reach the

market.

The provision is confusing re: the approval standard. It indicates that reviews shall be conducted under the standards and requirements of the Act, but it also appears to suggest a somewhat different approval standard for accredited reviews -- i.e., a "reasonable assurance" of safety and effectiveness. In addition, it is shifting the burden to FDA. It is requiring FDA to show a scientific "negative" -- this is a difficult burden for the agency to meet and would not adequately protect the public from potential harm.

The provision appears to be saying that if a third party recommends approval of an application, it is deemed approved unless FDA finds that there is a reasonable probability that the drug is not safe or effective. It further says that FDA has 60 days to make this finding and, if it does, it must provide a detailed basis for it. Sixty days is little time for the agency to thoroughly and thoughtfully review a recommendation.

SEC.8 ACCREDITATION OF THIRD PARTIES

- Subsection (a) requires the Secretary to promulgate regulations to establish procedures for accrediting third parties to review new drug applications and perform GMP inspections.

  This section does not establish how the third parties are compensated for services.

  Contracting out may slow rather than speed approval times -- for example, it will take time to train the third party reviewers; third parties do not now have the institutional knowledge needed to adequately review applications.

  Third party review raises safety issues. Because third parties lack institutional knowledge they will not be able to spot the problems that an experienced reviewer might see; FDA's in-house expertise will be lost. The end result may be unsafe or ineffective products on the market.

  See p. 12

  Other issues: what about tort liability? Will third parties still be in business?

- Subsection (a) further requires the Secretary to provide for accreditation through government or qualified non-government entities. This paragraph also establishes certain criteria for accreditation of third parties relating to conflict of interest, competency, and protection of information.

  From this section, it appears that the intention is not to have the Secretary accredit any particular entity, but rather to have the Secretary designate agencies or organizations who will then perform the accreditation process. It would help if FDA could add qualifications.

  The provision does not sufficiently address conflict of interest issues. What employment restriction will be imposed regarding future/past employment with a sponsor or a sponsor's competitor? Lack of clarity on conflict of interest issues could result in questionable reviews.

- Subsection (b) amends the prohibited acts section of the FDC Act to add a new section relating to actions by accredited third parties. Under proposed 301(w), a third party would violate this section if it submitted a materially false or misleading report, disclosed trade secret confidential commercial information, or accepted a bribe or performed any other corrupt act in connection with its delegated responsibility.

SEC.9 DISPUTE RESOLUTION

- Section 9 permits drug sponsors to seek dispute resolution before an advisory committee or a special government employee or a nongovernmental person who is qualified to mediate or arbitrate and who is acceptable to FDA and the applicant whenever an "impasse" exists in the review of an application with respect to any specific issue. It requires FDA to refer the dispute to an advisory committee or third party on receipt of a notification from the applicant that a dispute exists. Within 30 days of receiving the panel or third party recommendation, the Secretary must, in writing, confirm or modify the panel or third party recommendation providing reasons and reference to data before the committee or third party for any modification. The panel or third party recommendation automatically becomes FDA's unless FDA acts within 30 days of receipt of the recommendation.

  The section duplicates existing dispute resolution procedures. It has the potential for inundating the agency with requests for advisory panel meetings, which have significant resource implications.

SEC.10 GOOD MANUFACTURING PRACTICE INSPECTIONS

- Paragraph (a) amends section 704 of the FDC Act to permit third parties to conduct GMP inspections. It also amends the section to require a 10 day waiting period after any inspection (whether by a third party or FDA ?) to give the subject an opportunity to respond to any observations. The agency may not take any regulatory action following an inspection until it has reviewed a timely response from the subject of the inspection, unless there is a reasonable probability that a drug would cause serious, adverse health consequences or death or could present an unreasonable and substantial risk of injury or illness to the public health. The Secretary must also provide a detailed assessment of the response submitted by the subject of the inspection within 30 days.

  In general, requiring a 10 waiting day period, a review of the manufacturer's response, and a detailed response in 30 days may have a significant impact on agency workload. Because a warning letter is considered regulatory action, this provision would stop FDA from issuing one until this process is complete. This may not significantly slow down current time frames for issuing warning letters, but it has the potential to hamper agency action.

- A third party performing a GMP inspection does not submit a copy of its observations to the Secretary. However, if the findings indicate a serious problem, the third party must immediately notify the Secretary unless the person subject to the inspection immediately ceases distribution, notifies health professionals and drug user facilities, and undertakes all corrections identified by the third party. When such compliance is completed, the third party provides a certification of compliance, a copy of which is provided to the Secretary. The Secretary may not perform another gmp inspection for 2 years after the date of the certification unless justified by good cause.

  As it is drafted, the agency never becomes involved in compliance matters when a third party has undertaken the original inspection. The third party oversees corrections and certifies to the Secretary that the company is in compliance. The Secretary may not conduct a GMP inspection for 2 years after the date of this certification, "unless justified by good cause."

  The two year prohibition poses additional problems. Conditions can change: a change in ownership or internal management may change manufacturing conditions, or personnel may simply drift into bad habits. This is more likely if companies know that FDA may not reinspect for two years. Awareness that FDA can inspect at any time

reinforces vigilance.

SEC.11 GOOD MANUFACTURING PRACTICES

- Section 11 states that all chemistry, manufacturing, and controls that comply with an approved NDA or with the opinion of an appropriate FDA official responsible for review of chemistry, manufacturing, or controls and which is reduced to writing and made part of the record shall be deemed to comply with GMPs.

  If field inspectors find problems, we should not be prevented from taking action.

- Section 11 further states that FDA cannot take action to delay or prevent the manufacture or marketing of a drug for failure to conform to gmps unless there is a reasonable probability of actual harm to public health or the Secretary determines in writing after a formal hearing that the drug is not bioequivalent, deviates from drug specifications, lacks adequate assurance that it will meet represented sterility, or has been rendered unsafe or ineffective.

  Drugs not made under GMPs may have safety and efficacy problems that will not be apparent to either the manufacturer or FDA.

SEC.12 PILOT AND SMALL SCALE MANUFACTURE

- Section 12 provides that a new drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the product and to obtain approval prior to scaling up to a larger facility unless FDA demonstrates in writing specifying in detail the reasons, after an informal hearing, that a full scale production facility is necessary to assure safety and effectiveness.

  For most drugs, this is currently permitted by CDER and, in fact, is explicitly defined/allowed in a guideline that has been harmonized in the US, EU and Japan in the ICH process. However, it is not acceptable if it pertains to sterile drug products. Adequate sterility assurance is built into a drug or product during the manufacturing process. End-product testing (i.e., compendial sterility tests) and specifications cannot adequately provide sterility assurance. Change from a pilot plant to a larger facility often involves changes in the processes and monitoring systems used to control microbial contamination, changes in the methods and controls used to sterilize

equipment, and, in some cases, changes in the processes and controls used to render the product itself sterile. Non-sterility of an injectable drug product, for example, can have severe adverse consequences for patients, including death.

For biologics, under REGO, FDA has issued guidance to clarify its policy on licensing small-scale and pilot facilities.

SEC.13 MANUFACTURING CHANGES

- Section 13 permits manufacturers of drugs and most biologics to make changes in manufacturing without prior approval as long as there is not a resulting change in formulation or release specifications and the changes are validated and records are made available to FDA during inspections.

  Changes that do not affect formulations or release specifications, however, can still change the safety and effectiveness of a product. For example,

  (1) In the infamous "Cutter" incident with Salk polio vaccine, the company simply changed the type of filter used during manufacturing of the vaccine. No change in formulation or release specifications resulted, but the change in filter led to live virus in the product. Eleven people died and about two hundred more got polio.

  (2) A change of the method of growing cells that a biotech heart drug is made from resulted in a change in the fine structure of the drug molecule that resulted in an ineffective dose not detectable by final product testing.

  (3) Without submitting a supplement, a firm substituted an unapproved source of bulk drug for an approved source of carbamazepine, a seizure medication. The drug from the unapproved source caused the tablets to dissolve more slowly than did the product made from the approved source. The slower dissolution could result in patients absorbing the drug more slowly and thus getting smaller doses. FDA received reports of problems that may have been related to this unapproved change.

  There are additional examples of changes that the bill would allow to be made without FDA review that could raise significant safety

concerns. For example, under the bill, a company could change the strain of a virus used for a vaccine such as oral polio vaccine, which could result in increased number of cases of vaccine associated polio. Similarly, a manufacturer could change the method of viral inactivation in a blood product used to treat hemophilia, which could result in a product that could transmit hepatitis or HIV.

FDA already has undertaken to reduce the number of manufacturing changes that require pre-approval.

CDER is working diligently with industry to delineate a series of science-based recommendations for the tests and filing requirements when change occurs in the manufacture of an approved new drug. The first of this series is a guidance termed SUPAC-IR, which is intended to provide guidance for immediate release (IR) solid oral dosage forms. Further guidance documents are planned for other types of new drug dosage forms, including extended release solid oral dosage forms, liquids and semisolids, and certain biotechnology products.

CBER has created a reporting process tailored to the severity and complexity of manufacturing changes. Less stringent reporting requirements will apply when changes do not pose a substantial risk of adverse effects on product purity, potency, or safety.

CVM is taking steps towards revising its regulations to ease the process of submitting and reviewing manufacturing changes by better categorizing the types of manufacturing changes, better characterizing the procedures for handling changes, and more appropriately correlating submission and review procedures with the particular categories of changes.

SEC.14 INSULIN AND ANTIBIOTICS

- Section 14 repeals requirements for lot and batch verification.

  This is consistent with REGO.

SEC.15 NONPRESCRIPTION DRUGS

- Section 15 provides that all applications for Rx to OTC switches shall be reviewed by a single office in CDER. That office is to report directly to the Center Director.

The result of this provision will be that reviewers who have worked on the product's NDA and have expertise in the area will not be responsible for reviewing the switch applications.

SEC.16 INFORMATION SYSTEMS

- Section 16 requires FDA to establish a system to track the status and progress of each application. The system must permit access by the applicant.

  This section raises concerns re: protecting the confidentiality of applicant information. In addition, there are resource implications re: set-up and maintenance.

SEC.17 ENVIRONMENTAL IMPACT REVIEW

- Section 17 eliminates the requirement to prepare an environmental analyses unless the Secretary demonstrates that because of extraordinary circumstances, the action will have a significant effect on the human environment and the consideration of such significant effect will directly affect the Secretary's decision and on the action.

  This is similar to Sec. 406 of the Senate bill, but the House version makes it harder to require an environmental impact review because it requires the Secretary to demonstrate that the action "will have a significant effect on the human environment."

SEC.18 APPLICATION OF STATE AND FEDERAL LAW TO THE PRACTICE OF PHARMACY COMPOUNDING

- Section 18 (1) exempts drugs that are compounded by pharmacists on the order of a licensed physician from the drug and device provisions of the Act, and (2) exempts bulk drug products or other drugs intended for use by pharmacists for compounding from all of the Act's provisions, except those that relate directly to identity, purity, or quality.

  The exemption has no constraints on the volume of compounding. This is likely to encourage large-scale manufacturing under the guise of pharmacy compounding.

  The exemption would allow bulk drug suppliers or drug manufacturers to circumvent the approval requirements of the Act by shipping bulk

drug substances to pharmacies for reconstituting or other processing. A shadow industry of unapproved generic drugs will develop.

Some might argue that the gmp requirements do not apply because they do not relate directly to the purity, quality, or identity of the drug substance. FDA would disagree.

The exemption would allow potentially dangerous compounding. For example, sterile drugs could be compounded (even on a large scale) without regard to CGMPs for sterile products. Improperly compounded sterile products could result in serious adverse effects, including death.

SEC.19 HARMONIZATION

- Provides that the Secretary shall participate in meetings with other countries to discuss methods and approaches to reduce the burden of regulation, to harmonize regulatory requirements, and to seek appropriate reciprocal arrangements. Within 180 days of enactment the Secretary must make public a plan that establishes a framework for achieving mutual recognition of gmps. The Secretary must provide 60 day notice to the Committee before executing any agreements with foreign countries.

SEC.20 USE OF SCIENTIFIC AND MEDICAL INFORMATION

- This section amends 502 (f) to make it legal to disseminate medical texts, journal articles, and government information, and to make presentation at medical and scientific meetings about off-label uses. These activities would not constitute misbranding and would not trigger the need to file a new drug application unless the person "in addition" encourages the unapproved use of a legally marketed device through labeling, advertising,or other means of promotion. The provision also establishes that knowledge of an off-label use would not trigger any obligation for the manufacturer to change the labeling or amend a marketing application. The section also makes it permissible for sponsors of INDs and their agent to disseminate materials, make presentations, and display investigational devices at trade shows so long as the sponsor or agent does not "encourage the use of the drug".

  This section assumes that the various activities it permits are not promotion and do not encourage off-label uses or uses of investigational products. The provision will make it possible for sponsors to promote off-label uses and investigational products without filing marketing

applications or INDs. The provision affirmatively eliminates incentives for manufacturers to conduct studies needed to demonstrate the safety and effectiveness of new uses and to go through the regulatory process to have off-label uses reviewed.

SEC.21 INFORMAL AGENCY STATEMENTS

- This section prohibits the Secretary from relying on policy statements, guidance documents, and similar statements to require any action to satisfy a provision of the FDC Act. It also requires the Secretary to publish notice of availability of such statements and to make them accessible electronically.

  FDA's position is that guidance documents are not binding on the agency or the public. FDA recently issued a Federal Register notice that affirms this position and has agreed to take steps to ensure that the agency and the public know and understand this principle. To the extent that this provision is reaffirming that position it is not problematic. To the extent that it is saying that FDA cannot issue guidance that explains how it believes compliance with the Act may be accomplished, it is problematic – particularly for the industry. FDA will no longer be able to provide guidance and there is a risk of non-uniformity in the application of the laws and regulations that FDA is tasked with implementing.

SEC.22 RESEARCH AND EDUCATION; PRACTICE OF MEDICINE

- New section 908(a) requires FDA to train and educate its employees.

  FDA currently does this through staff colleges etc.

- New section 908(b) limits FDA's research activities to research directly related to the implementation of the FDC Act.

  This may prevent FDA from continuing research that is vital to maintaining and protecting the public health.

- New section 909 states that nothing in the FDC Act shall limit or interfere with a health care practitioner's authority to prescribe or administer legally marketed drugs or devices.

  Although generally FDA does not wish to interfere with the "practice of medicine," there have been instances in which the agency has taken

action against physicians (e.g., where there was a concern for patients' safety, approved products were being promoted by the physicians for unapproved uses, failure to comply with the requirements for conducting clinical investigations). New section 909 could hamper FDA's ability to act in these circumstances.

SEC.23 DELEGATION OF AUTHORITY

- Section 23 provides that the authority granted under the provisions relating to the request for primary data, changes to testing protocols, IND submission requirements, and establishment of advisory panels may not be delegated.

SEC.24. JUDICIAL REVIEW

- Section 24 provides for judicial review of any written decision respecting any aspect of an investigational new drug or any written decision respecting any aspect of an application, petition, or notification for marketing review or approval for a drug.

  This provision could paralyze the agency. Current section 505(h) limits judicial review to decisions refusing to approve or withdrawing application approvals after notice to the applicant and an opportunity for a hearing. It is unclear whether this provision eliminates or retains the requirements for final agency action/exhaustion of administrative remedies – i.e., new section 505(h)(1) appears to permit virtually unfettered judicial review but new section 505(h)(3) appears to limit the court's jurisdiction in accordance with Title 5, Chapter 7 of the U.S. Code (Judicial Review -- final agency action, exhaustion of administrative remedies, etc.)

SEC. 25 PUBLICATION OF NOTICE OF DEVIATION

- Section 25 prevents the Secretary from making public or communicating to any person outside of FDA any information regarding a notice that informs a regulated person of a purported deviation from a requirement of the Act until after the Secretary has completed the investigation of such deviation.

  It is unclear what is meant by "after the Secretary has completed the investigation of the deviation." Does it mean after FDA completes a particular inspection and issues a 483? If so, the provision changes nothing in the way FDA currently does business.

If, however the intent is that there be no disclosure until after FDA determines that further regulatory action is not indicated or until FDA closes the matter out, this is a problem. It could interfere with FDA enforcement actions because FDA would be unable to disclose, to DOJ or a court, the inspectional observations. Moreover, it would call into question the agency's long-standing practice of making 483s, warning letters, and correspondence with regulated industry available to the public. Such a radical change in FDA's public information procedures and regulations could hamper the agency's ability to carry out its public health mission effectively. The difficulty the agency currently has with respect to prohibitions on public disclosure of information contained in marketing applications would extend to disclosure of information about observed violations and enforcement initiatives.

SEC.26 BIOLOGICAL PRODUCTS

- Section 26 establishes distinct product categories for (1) biological products, (2) blood and blood components, and (3) tissue. Each is discussed separately.

Biological Products

- Section 26(a) adds a definition of "biological product" to the FDC Act. The definition excludes blood, blood components, organs, eyes, milk, or human tissue. (It includes a derivative or blood and blood components.) A biological product is a drug within the meaning of paragraph (g) but is not a new drug within the meaning of paragraph (p)

  The definition uses the FDC Act language "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease . . . in man" instead of the PHS Act language "applicable to the prevention, treatment, or cure of diseases or injuries." It also adds "or physiologic condition" after the word "disease."

  The provision would prohibit the regulation of immune milk as a biologic product.

  Because a biologic is not a "new drug" within the meaning of 201(p), the new drug provisions of the FDC Act (primarily section 505) do not automatically apply. However, section 26(b) (discussed below) sets forth a premarket approval scheme that incorporates many of the section 505 provisions.

- Section 26(b) adds new section 506, entitled "Biological Products." New

section 506 provides that biological products cannot be introduced or delivered for introduction into interstate commerce unless an approved product license application is effective. The section 505 new drug procedures (except for those relating to patents, generics, and the release of safety and effectiveness data) apply. Section 506(b) requires the Secretary to harmonize PLA regulations with the NDA and GMP regulations within 2 years.

By taking the regulation of biologics out of the PHS Act, the bill is eliminating the flexibility that FDA now has to tailor the information in an application to new and emerging technologies. Elimination of the potency standard (which was in the PHS Act) may be problematic for some products. DISCUSS

There is no apparent justification for barring generic competition for this class of products.

The provision also prevents FDA from getting establishment information on vaccines.

New section 506(b)(5) provides that in the case of a derivative of blood and blood components, a product license will apply to all facilities of the applicant that are licensed under subsection (c).

New section 506(c), however, applies to blood and blood components, which by definition are not biologics. It provides that blood and blood components may be obtained and processed only in licensed facilities. The meaning of this section is therefore unclear. It may mean that blood derivative products can only be manufactured from blood source material that is obtained and processed in appropriately licensed facilities, as specified in the blood derivative product license application. This is what FDA currently requires. If this is the intent of the provision, then it should be clarified. Alternatively, it may mean that a product license for a derivative cannot be limited to products made from source materials obtained or processed only at facilities specified in the product license – i.e., the product may be obtained or processed at any facility that is licensed. The problem with this approach is that just because a facility is licensed for blood or blood components does not mean that those blood or blood component products are appropriate for purposes of manufacturing blood derivatives – i.e., not all plasma is an appropriate source for blood derivatives. FDA needs to know that the source material for a blood derivatives is appropriate – otherwise the dependability of blood derivatives

(such as Factor VIII for hemophiliacs) cannot be guaranteed.

Blood and Blood Components

- New section 506(c)(1) provides that blood and blood components that are introduced or delivered for introduction into interstate commerce require approval of a product license application. Blood and blood components intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease or physiologic condition in man are subject to (A) performance standards for safety, purity, and where applicable, potency, (B) gmps, and (C) labeling established by regulation and shall be obtained and processed only in facilities licensed by the Secretary.

  It appears that both product and establishment licenses are required for blood and blood components when interstate commerce is involved, Apparently without interstate commerce, only a facility license is required.

  [Note, the regulation of blood and blood components [and tissue] is under a provision entitled "Biological Products" -- even though the definition of biological products does not include blood or blood components [or tissue].

- New section 506(c)(2) provides that licensed establishments are subject to FDA inspection, which may be conducted by nonprofit membership organizations that meet the requirements that the Secretary establishes for the accreditation of third parties.

  This provision may restrict third party inspections of blood establishments to "nonprofit" organizations. This is somewhat narrower than the broader eligibility requirements for other organizations under section 712. The provision may be read to mean that, unlike members of other industries, members of the blood industry may be inspected by the organizations that they themselves constitute -- a situation that would otherwise be read to be inherently impermissible under the terms of section 712 (because they have an organizational affiliation with the inspected entity under section 712(b)(3)). It also seems to rule out third party inspections of blood facilities by for-profit organizations, which would be permitted for other industries.

- New section 506(c)(3) directs the Secretary to establish licensing requirements for blood and blood component facilities and an application for such a license must be granted or denied within 90 days.

This time period is much shorter than the PDUFA timeframes for drugs and biologics. It would be difficult to meet.

- New section 506(c)(3)(C) permits the Secretary to immediately suspend a license, with an informal hearing to follow, if the identified deficiencies constitute an immediate danger of serious adverse health consequences or death.

  The standard for suspension is raised from the current "danger to health" standard.

- Before revoking a license, the Secretary must provide a written list of deficiencies and provide 30 days for a written response and for correction of the deficiencies. If the facility fails to provide an adequate response or makes corrections, the Secretary shall provide an opportunity for an informal hearing (within 30 days of receipt of the written response).

  The requirement for a hearing within 30 days of receipt of a written response is much shorter than that for any other FDA-regulated product category.

- The revocation or suspension of a license shall not prevent the continued use of blood or blood components that have left the control of the licensee unless the Secretary determines, as part of the revocation or suspension order, that such use represents actual harm to the public health.

  This means that FDA cannot prevent the use of products that have left the control of the licensee unless someone has actually been harmed. Even an extremely high risk of death would not permit FDA to prevent the use of such products.

Human Tissue

- Section 26(a) defines the term "human tissue" to mean a collection of human cells that are intended for use in the diagnoses, cure, mitigation, treatment, or prevention of a disease or physiological condition in man or for the augmentation of a natural bodily function. It may be combined with biologically inactive substances and subjected to any form of processing before use subject to operating standards established under section 506(a)(2)(A) [should say 506(d)(2)(A)]. Human tissue achieves its primary intended purpose through structural support or cellular function and not systemic action. It is not a drug or device and does not include blood, blood components, organs, or milk.

The definition would include cellular and gene therapies which should be subject to the drug controls because they require safety and efficacy determinations and more stringent manufacturing controls. This may also be true of future technologies.

- Pursuant to section 26(b), which adds new section 506(d), the Secretary may regulate human tissue only if the Secretary demonstrates, in writing published in the Federal Register and after a hearing before the Commissioner, that voluntary regulation under generally accepted standards is inadequate to protect the public health with respect to any particular type of human tissue or human tissue generally. If such a determination is made, the Secretary may establish, by regulation, operating standards for the safety of human tissue and may require human tissue to be processed only in an establishment registered in accordance with the procedures for drug establishment registration.

  The voluntary standards that are in place have not been working. There have been a number of cases where people have been harmed by contaminated tissue. [add] FDA has already made the determination that regulation of human tissue is necessary. This provision requires FDA to revisit the issue. This is unjustified and a waste of resources.

  Industry has not objected to the existing regulation, only to portions of the operating procedures that FDA has since modified. During Congressional hearings in 1993, the President of the American Association of Tissue Banks supported FDA regulation to assure uniform donor selection requirements to provide the lowest possible risk of disease transmission. Representatives of the Eye Bank Association of America testified that the voluntary standards lacked the necessary process of an enforcement mechanism to mandate compliance for those banks where standards and CDC guidelines go unrecognized. Further support for the regulation was offered by the ARC and the American Academy of Orthopedic Surgeons.

  FDA would have no recourse if a tissue bank failed to follow voluntary generally accepted scientific standards.

- Pursuant to new section 506(d)(2), any operating standards that FDA would develop must be limited to the following general requirements for the recovery, processing, storage, and shipment of human tissue: (i) requirements for universal infection control designs to prevent disease transmission; (ii) good processing practices that assure the safety, maintenance of structure, and preservation of original cellular function; and (iii) labeling requirements for identification of the type of tissue, the addition of any foreign substance, and information needed to permit tracing.

These standards would be inadequate for some cellular and gene therapies.

- New section 506(d)(2)(C) provides that registered establishments are subject to FDA inspection, which may be conducted by nonprofit membership organizations that meet the requirements that the Secretary establishes for the accreditation of third parties.

  This provision may restrict third party inspections of tissue establishments to "nonprofit" organizations. This is somewhat narrower than the broader eligibility requirements for other organizations under section 712. The provision may be read to mean that, unlike members of other industries, members of the tissue industry may be inspected by the organizations that they themselves constitute -- a situation that would otherwise be read to be inherently impermissible under the terms of section 712 (because they have an organizational affiliation with the inspected entity under section 712(b)(3)). It also seems to rule out third party inspections of tissue establishments by for-profit organizations, which would be permitted for other industries.

- The requirements for human tissue shall not apply to human tissue not stored for a significant period of time or not significantly processed.

- Section 26(c) provides that the requirements of the interim tissue regulation would remain in effect for a period of 18 months so that the Secretary has an opportunity to establish general controls for tissue pursuant to new section 506(d)(1), but that the Secretary shall not regulate eyes until the Secretary finds that voluntary regulation is inadequate.

  Is 18 months enough time? If not, there will be a time period during which tissue will not be regulated. There would be a significant risk of disease transmission during this time.

Enforcement Provisions

New section 506(e) provides that the Secretary may take action to enforce the requirements of gmps for blood and blood components and good operating standards for human tissue in the same manner as is done for drugs.

Re: tissue -- is this meant to say "good processing practices" or "operating standards" -- both terms used in new section 506(d)(2)(B). Good processing practices would be a type of operating standards.

- Section 26(d) amends section 301(d) and (e) to make introducing unapproved biologics and failing to keep records or reports required for biologics prohibited acts.

  Section 304, which authorizes seizure actions, has not been amended to specifically include unapproved biologics or blood products in violation of new section 506.

- Section 26(d) amends section 501 -- apparently intending to make biological products, blood, and blood components, adulterated under section 501 if they do not comply with the new section 506 requirements.

  Because section 501 begins with the phrase "a drug or device shall be deemed adulterated" and blood and blood components are not drugs or devices, they arguably could not be seized. (Unless violation of blood gmps could lead to seizure under new section 506(e)).

- The provision in current section 351 of the PHS Act, which prohibits false labeling of a biological product whether or not interstate commerce is involved has been deleted.

- There does not appear to be express statutory authority to order the recall of dangerous blood.

Other Products

- "Organs" are excluded from the definitions of biologic products and human tissue.

  Organs could be either human or animal. Accordingly, animal organs (such as baboon hearts), which could raise serious infectious disease or other safety and effectiveness concerns, would be unregulated (unless the device provisions apply).

- Computer software developed by, modified by, and used in a human tissue establishment or in a blood or blood component establishment shall not be subject to premarket clearance, but shall be validated to demonstrate that it achieves its intended purpose and shall be subject to gmps.

  These provisions undermine FDA's effort to improve the quality of computer software used in these setting. Such software can be critical to donor screening and testing and can result in major public health risks (e.g., HIV and hepatitis) if not adequately demonstrated to work.

- Blood components and derivatives of blood and blood components intended for use as a blood test in the diagnosis of diseases are devices and are not drugs, biological products, or human tissue.

  If "blood tests" includes tests to screen blood for infectious agents, then it could be argued that some blood screening tests would not require product license applications (as currently is the case) but only 510(k)'s. For example, if viral antibodies or antigens isolated from blood were considered blood "derivatives" instead of "viruses" and were used to make blood screening tests (e.g., HIV antibody or antigen tests) then only the device authorities would apply. These would be insufficient.

Jane updates

- They could sympathize —

Drama — sizable # of D's that have problems with the FDA —
- Helpful to identify limited # of areas where we have problems
- Not helpful to draw lines in the sand
- Issue of who presents the Admin. views on the Hill — Not helpful to have FDA —
- rumors about a substitute — that's not a good idea.

to work

Kassebaum works things out
- manufacturing changes piece
- pilot — add qualifications.
- mandatory contracting out hammer...
- focus hammers on lower risk.
- European approval —
- Med guide. —

- Harkin, Mikulski, Dodd —

Friday — Jane sitting down with Kassebaum —

— Kennedy — portrayal as Rep. extremism — Dems may have to respond.

— Kennedy has 5 things they can't live

Want to get something to them they can float — Quietly —

Sec to
Secretary decides what
- Not testing at all devices

- would not want every kind of class III devices — that's where review times are longer.

Drama —

— You want a
Unified Admin position —

— HHS people on the same
page

— Constructive and
non-constructive —

— FDA — Ann Ford —

— List of ~~20~~ egregious
things — eight —

— off label. —

Jane Williams — try to
get the report filed in
next couple of weeks —
will ask for
Maybe June —

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE ASSISTANT SECRETARY FOR LEGISLATION
OFFICE OF HEALTH LEGISLATION

HHH Bldg, Room 405H
200 Independence Avenue, SW
Washington, D.C. 20201

PHONE: 690-7450 **FAX:** 690-8425

FROM: SEE BELOW **TO:** SEE BELOW

[ ] HOLLY BODE
[ ] SHARON CLARKIN
[ ] SEAN DONOHUE
[ ] SUSAN EMMER
[ ] NICOLE LAWRENCE
[ ] ANDREA LEVARIO
[ ] JUDY LEWIS
[ ] ROGER MCCLUNG
[ ] MARC SMOLONSKY
[ ] DEBRA SPEIGHT
[ ] CARL TAYLOR
[ ] _____
[ ] _____

NAME: Cathy —
OFFICE: Eliz Dky
ROOM #:
PHONE #:
FAX #: 4565557
DATE: 4/29
PAGES: 3
(INCLUDING COVER)

REMARKS:
Elizabeth — We at HHS were not satisfied w/ beginning to Kessler statement. Rich T asked me to FAX our changes to you — (1st two pages) Any comments?

260-7194

Roger

are committed, as I know you are, to

DRAFT -- DRAFT -- DRAFT -- DRAFT -- DRAFT -- DRAFT -- DRAFT

TESTIMONY OF DAVID A. KESSLER, M.D.

Chairman Bilirakis, and members of the Committee, I am pleased to be here today as you consider a ~~and want to thank you for holding these hearings on this~~ very important public health issue -- ensuring that the Food and Drug Administration (FDA) protects the nation's safety and health. The FDA's primary mission for 90 years has been to protect and promote the public health. ~~Any reform bill must be measured by how well it protects the health of all Americans.~~

Let me say at the outset that we are committed to improving FDA's procedures and practices to ensure timely access to new drugs and devices that are shown to be safe and effective. We look forward to working closely with you and your colleagues in the House and Senate on bipartisan reform legislation that accomplishes this goal.

INTRODUCTION

~~I know, Mr. Chairman, that you and members of the Committee share~~ And I know you share our ~~the Agency's~~ view that all Americans deserve the assurance ~~are best served when they are assured~~ that the medicines they take or medical devices they need are safe and really work, and that the foods they eat are safe. We are committed to maintaining high standards so that consumers can continue to have that confidence and assurance. But high standards alone are not enough. ~~FDA shares with the public the belief that~~ Timely access to ~~new drugs and devices that are shown to be~~ safe and effective products is ~~an~~ important ~~measure of how well the Agency protects and promotes~~ to the public health ~~in the United States~~ as well.

To meet the goal of timely approval of safe and effective products, FDA must be open to change. This is a time of unprecedented medical challenges and medical breakthroughs. An

important measure of our value as an Agency will be our ability to keep pace with these changes. Thomas Jefferson said it best: "Our laws and institutions must [move forward] hand in hand with the progress of the human mind."

As Commissioner, the first way I have sought to effect change is to attract a new generation of leaders to the Agency. Much of the progress FDA has made over the past few years began with our five new Center Directors. The many changes they have made have moved us closer to our goal. Second, we have vigorously pursued and implemented more than thirty FDA reinventing initiatives as part of President Clinton's and Vice President Gore's National Performance Review. Among the changes we have made, are speeding new cancer drugs to patients and targeting our limited resources on higher risk medical devices while no longer requiring FDA review of hundreds of categories of simple devices such as ____ and tongue depressors. Finally, in addition to the many changes we have already made, the administration is committed to supporting legislative reform that does not legislation that further improves FDA's regulatory processes, with one condition: it must do so without lowering current standards for product safety and efficacy, the statute.

If we are to achieve our shared goals of improving the Agency's ability to protect and promote the public health by assuring the public speedy access to safe and effective products, we must base

OFFICE OF MANAGEMENT AND BUDGET

Legislative Reference Division
Labor-Welfare-Personnel Branch

Telecopier Transmittal Sheet

SPECIAL

FROM: Bob Pellicci -- 395-4871

DATE: 9/23 **TIME:** _____

Pages sent (including transmittal sheet): 2

COMMENTS: Final of Secretary Shalala's letter re: animal drug legislation.

TO: Elizabeth Drye, OPD

PLEASE CALL THE PERSON(S) NAMED ABOVE FOR IMMEDIATE PICK-UP.

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

September 19, 1996

The Honorable Thomas J. Bliley, Jr.
Chairman, Committee on Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

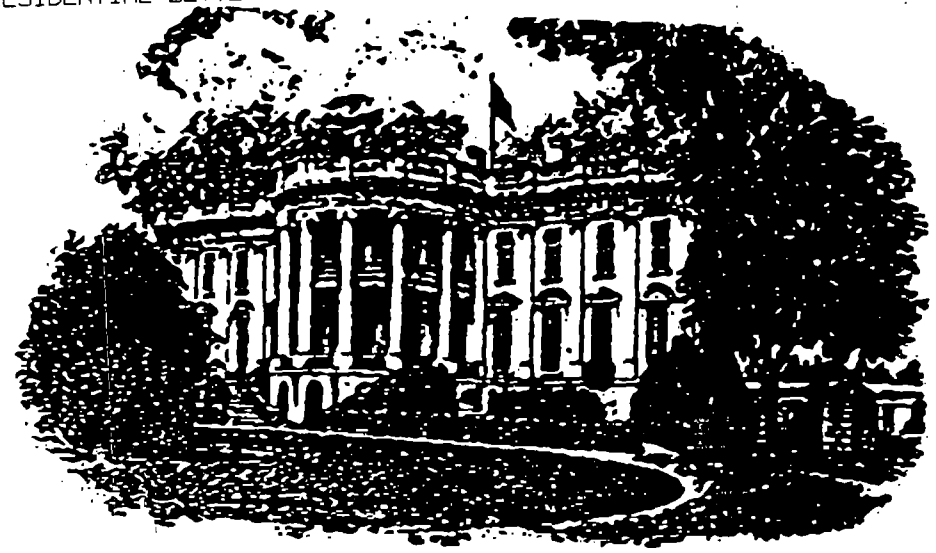
As your Committee prepares to consider a substitute to H.R. 2508, the "Animal Drug Availability Act of 1996", we take this opportunity to inform you that the Administration concurs with the provisions of the substitute as negotiated between the industry, the Food and Drug Administration, and your staff.

We urge expeditious action by Congress on this bill. If H.R. 2508 is presented to the President without further amendments, we will urge him to sign it into law.

The Office of Management and Budget has advised that there is no objection to the transmittal of this report, and that enactment of H.R. 2508 would be in accord with the program of the President.

Sincerely,

Donna E. Shalala



The White House
Office of Presidential Letters and Messages

TO: Elizabeth Drye
67028

Date: 7-26-96

FROM: Tracy Sisser
Presidential Letters and Messages
456-5516/456-5426
Room 93, OEOB

Request For:
- ☐ Draft
- ☐ Information
- ☒ Clearance
- ☐ Other – See Below

Number of pages including cover: 6

The following is a draft of a letter that needs OPD clearance. I have included a copy of the draft as well as a copy of the incoming. (Please refer to my voice-mail message 7/26/96.)

I look forward to hearing from you.

Tracy 65576

July 26, 1996

Arthur D. Levinson, Ph.D.
President and
Chief Executive Officer
Genentech, Inc.
460 Point San Bruno Boulevard
South San Francisco, California 94080

Dear Art:

Thank you so much for your kind letter. It was a pleasure to see you, and I'm glad we had a chance to talk about medical research and so many other issues of importance to our nation's future.

Please know that I will continue to work to enact a permanent, retroactive extension of a research and development tax credit, and that I remain committed to improving the speed and effectiveness of the Food and Drug Administration -- without compromising its safety standards. Meanwhile, I will certainly keep your views in mind, and I'm grateful you took the time to write.

Sincerely,

BC/SEM/JFB/jfc (Corres. #3050348)
(7.levinson.ad)

cc: Jim Dorskind/TDS

cc: Tracy Sisser, 93 OEOB

Xeroxed copy of personally signed original to NH through Todd Stern

CLEAR THRU TODD STERN

PRESIDENT TO SIGN

THE PRESIDENT HAS SEEN
7-16-96

(C) **Tyson memo on Wanninski paper.** Laura writes that Wanninski's description of a crisis in capitalism based on "massive underemployment" is a gross mischaracterization. He is an unrepentant supply-sider whose diagnosis and prescriptions (e.g., zero capital gains, gold standard) are off base. Laura notes that Administration has addressed two of the problems Wanninski identifies -- too low economic growth and stagnant wages -- by efforts to boost productivity via creating a climate for increased business investment and technological progress, and bolstering education and training. Administration has also focussed on increasing incomes for those at the bottom, via minimum wage, EITC, etc. In view of your economic team, Wanninski's proposals would do more harm than good for the economy.

(D) **Lake memo on Gen. O'Neill's alleged criticism of the NIE.** The June 14 Washington Times published an article charging that Gen. O'Neill (recently retired Director of the Ballistic Missile Defense Organization) had faulted the National Intelligence Estimate's forecast of the Third World ballistic missile threat. Defense Daily, however, reported that the General described the NIE as a "good, well done and predictable document." O'Neill recently wrote a letter of clarification to the Times, noting that while he has some "discomfort" in how the NIE dealt with uncertainties in estimating when a Third World missile threat would develop,, he does not believe the analysis was "politicized." He also strongly supports DOD's "3 plus 3" national missile defense program as a hedge against these uncertainties.

(E) **Stiglitz memo on educational infrastructure and "flypaper effect."** Joe says evidence does NOT support notion of perfect fungibility of funds -- i.e., that State and local governments can simply shift funds to ensure that Federal financing for one activity substitutes for spending that would have otherwise occurred. Rather, money tends to stick where it hits. Grants for education tend to increase total education spending, and grants for infrastructure tend to increase total infrastructure spending.

(F) **Walter Slocombe information sheet on our missile defense policy.** Via Phil Jamison. Designed to counter mischaracterizations of our policy by GOP. Prepared by Slocombe with some input by Jamison for a new on-line policy wonk magazine."

(G) **Letter from Art Levinson, President/CEO of Genentech.** Via Tony Podesta. Following an evening spent with you, he describes himself as startled by the scope and reach of your vision for our country" and says "what particularly struck me was your genuine personal commitment to do what is morally right and practically important to help all Americans." He compliments you on the appointment of Harold Varmus, and he urges you to (i) support tax credits to encourage increases in R & D spending by the private sector and (ii) promote policies that "best" allow the FDA and the industry to work together to develop "effective, safe, innovative drugs."

(H) **Letter from Gerald Greenwald, CEO, United Airlines.** your commitment to seeing that current U.S. carrier rights agreement are fully honored. He believes the 3-phased ap Administration to the negotiations is likely to produce sign results, and he expresses United's full support for your ne

JIM DORSKIND:
Please coordinate the reply.

cc: Jim Dorskind/TDS

PODESTA
associates, inc.

THE PRESIDENT HAS SEEN
7/16/96

96 JUL 10 AM 11:23

July 9, 1996

cc: Dorslund
VP
Emerson
Caron

Mr. Todd Stern
Special Assistant to the President and
Deputy Staff Secretary
The White House
1600 Pennsylvania Avenue, N.W.
Washington, D.C. 20500

Dear Todd:

Enclosed is a letter from Art Levinson, President and CEO of Genentech, to the President. I wanted to make sure this received special attention.

And as always thanks.

Regards,

Anthony T. Podesta

1001 G Street, NW · Suite 900 East · Washington, DC 20001
202 393-1010 / Fax 202.393.5510 / Web Site: http://www.podesta.com

Genentech, Inc.

460 Point San Bruno Boulevard
South San Francisco, CA 94080
(415) 225-1102
FAX: (415) 225-6241

Arthur D. Levinson, Ph.D.
President and
Chief Executive Officer

6-30-96

Dear Mr. President,

As the relatively recently appointed CEO of Genentech I thought I knew something about pressure, but having spent an evening with you and hearing about the issues you confront daily left me startled by the scope and reach of your vision for our country. Your intelligence and insights are well known; what particularly struck me was your genuine personal commitment to do what is morally right and practically important to help all Americans.

As you look forward to the next four years I hope you will continue your understanding of the positive economic and human consequences of nurturing biomedical research. As I said during

Our dinner, your appointment of Harold Varmus was inspired. For the promise of the NIH's basic research programs to bear fruit will require your continued support for tax credits to encourage incremental increases in R+D spending by the private sector, and ongoing attention to promoting policies that best allow the FDA and the industry to work together to develop effective, safe, innovative drugs.

I hope to see you again in California. You will always be welcome at Genentech.

Respectfully,

Art Levinson

United States Senate

WASHINGTON, DC 20510

May 10, 1996

The Honorable Tom Daschle
Minority Leader
United States Senate
S-221 The Capitol
Washington, DC 20510

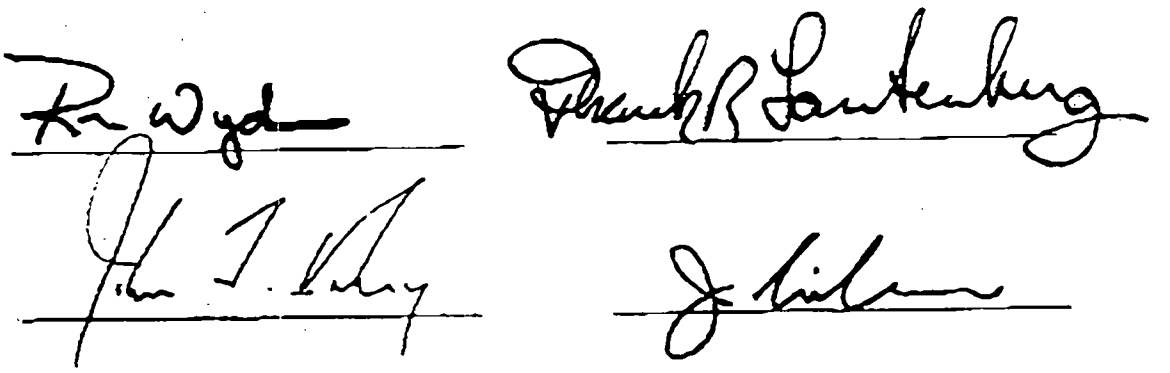
Dear Mr. Leader:

We are writing to express our support for legislation to improve the efficiency and effectiveness of the U.S. Food and Drug Administration and to ask you to join with us in assuring enactment of bi-partisan, moderate reforms this year. We do so on behalf of patients who are anxiously awaiting new medical treatments and on behalf of doctors who want to provide the most current drugs and devices to their patients.

Regulatory delays put lives at risk just as surely as undue haste. We believe there is much that can be done to speed the FDA approval process without harm to public health and safety. Senator Kassebaum's bill, S.1477 is a step in that direction and was reported by the Committee on Labor and Human Resources by a bipartisan 12-4 vote.

We recognize that further improvements to this legislation can and should be made before it is approved by the Senate and enacted into law and are committed to working on a bi-partisan basis to make several key changes. We urge you to contact us with any concerns or questions you might have. But for all the patients, doctors, and U.S. companies who have so much at stake, we ask that you join with us in constructive bi-partisan discussions with the goal of supporting early and favorable action on the legislation.

Sincerely,



** TOTAL PAGE.03 **

E X E C U T I V E O F F I C E O F T H E P R E S I D E N T

17-May-1996 05:27pm

TO: (See Below)

FROM: Sally Katzen
Office of Mgmt and Budget, OIRA

SUBJECT: fda reform

thanks to chris, i was to be the raw meat to be fed to a panel of congressional staffers appearing before the mdma on the subject of fda reform. because of my instinct for survival, i asked to go first, to talk about fda reform the administrative way, and then VERY briefly mentioned how we wanted a bi-partisan and balanced bill that would not sacrifice safety and efficacy to sign. i then said i had to go -- before the staffers got to do their prepared talks. i was not great, but i think i didn't do any harm.

then, as i was walking (running) out the door, a man with a pencil and pad (news media style) stopped and said how interested he was in my comment that we would sign a bill, since earlier in the day, other speakers had quite clearly stated that fda was out to kill the bill -- pointing the finger at diane thompson and bill schultz. i said that i said what i meant about the administration's intentions (and i meant what i said), that i was tired of these unfounded rumors and ad hominem attacks, that we should focus on the merits and not the motives, and that there were pieces of these bills that were not acceptable and that if we could not point out these problems without being accused of trying to kill the bill, maybe the environment was too sour to enable us to find common ground. i smiled sweetly, turned on my heel, and truly left the place.

thanks a lot chris . . .

Distribution:

TO: Christopher C. Jennings
TO: Elizabeth E. Drye
TO: Gregory C. Simon
TO: Daniel Tate
TO: Tracey E. Thornton
TO: Ira C. Magaziner

CC: Jonathan Winer

CC: Michael A. Fitzpatrick

Withdrawal/Redaction Marker
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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. memo	Denise Ricketson to Elizabeth Drye re: FDA briefing [partial] (1 page)	05/15/1996	b(6)

COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

FOLDER TITLE:
FDA Reform 1996 [6]

2014-0046-S
rc1404

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.
PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).
RR. Document will be reviewed upon request.

Freedom of Information Act - [5 U.S.C. 552(b)]

b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

Denise Brfg -

EXECUTIVE OFFICE OF THE PRESIDENT

15-May-1996 11:57am

TO: Elizabeth E. Drye

FROM: Denise Ricketson
Domestic Policy Council

SUBJECT: RE: FDA briefing

Elizabeth,

As of right now, anytime after 11:15am is good.

3:00

Mary Katona -
(301) 827-3370
- w/Bill Schultz

Bill Schultz
Burlington
Donald B
3-4

(b)(6)

[001]

E X E C U T I V E O F F I C E O F T H E P R E S I D E N T

15-May-1996 12:00pm

TO: Elizabeth E. Drye

FROM: Denise Ricketson
Domestic Policy Council

SUBJECT: RE: FDA briefing

Elizabeth,

already an update, depending upon how much time we need to allot for this meeting, 9:00 to 10:15am is free or anytime after lunch.

E X E C U T I V E O F F I C E O F T H E P R E S I D E N T

15-May-1996 02:49pm

TO: Elizabeth E. Drye

FROM: Phyllis E. Kaiser-Dark
Office of Mgmt and Budget, OIRA

SUBJECT: RE: FDA briefing

Unless someone adds a couple more hours to the day, or individuals with the monogram WJC or AG, there isn't a free moment for Sally to meet with anyone.

Without making any promises, I may have 1 hour on Tuesday afternoon, another hour on Thursday, but the best options are on Friday.

Jane/Diana — Dodd —
– Alex Clyde – Wellstone
– Ann Ford – Harkin
– Leanne Lawrence Mikulski

FDA Reform Legislation Hill Staff 5/4/94

Bill Schultz
Corr –
Greg –
Sally –
Rick –

Sally – follow-up re. broad device proposal. –

— Pilots —
– devices w/some of [struck] req. for clinical data
Alex ideas
– contract parts of devices out
– FDA staff (+) rxn.

— Conflicts of interests —
Bill more enthusiastic —
will there be real choice?
– Agency isn't there yet but Bill optimistic

— Transcripts — Jane looking for it

Alex's ideas - performance stds -- put
where that FDA adopts
where they are reg. stds.
- could be for part of
device (class III) or
all (Cass I and II).

* - as a grp. - haven't decide
keep clinical data out. -

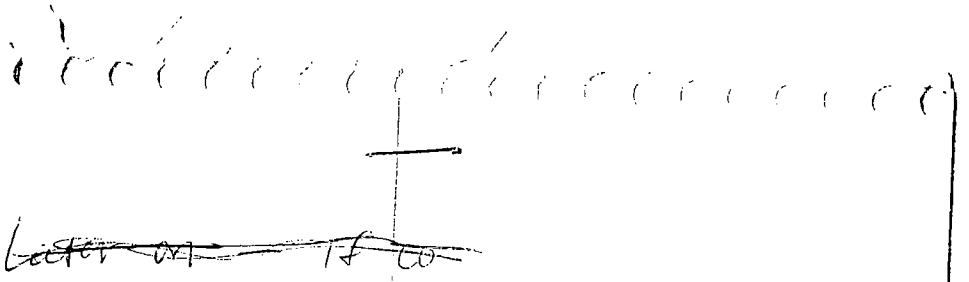
- Diana -
- off-label - Dodd said -
has told industry that
must be changed

Sally - strong bright line on class 3.

Alex - while very proposal - would want
to thoroughly review
question about -

Rich proposes - If she (Kassebaum) is willing
to work on it then 4 pens
are too.

Diane - Also reinforce that we have concerns about
various concerns



~~Letter of Tf to~~

Greg - have to look at how much has to be in a bill. —

B. Serious Concerns

4. Medication Guides (Section 607)

AMENDMENT NO. ___ Calendar No. ____

Purpose: To provide for the development of a long-range comprehensive plan to assess effective methods for the provision of oral and written prescription information to consumers.

IN THE SENATE OF THE UNITED STATES—104th Cong., 2d Sess.

S. 1477

To amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes.

Referred to the Committee on _____
and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENT intended to be proposed by Mr. COATS

Viz:

On page 86, between lines 12 and 13, insert the following:

SEC. 607. EFFECTIVE MEDICATION GUIDES.

Chapter IX (21 U.S.C. 391 et seq.), as amended by section 108, is further amended by adding at the end thereof the following new section:

SEC. 908. EFFECTIVE MEDICATION GUIDES.

"(a) IN GENERAL.—Not later than ~~30~~ 180 days after the date of enactment of this section, the Secretary shall ~~re~~ 2

~~quest that~~ in consultation with national organizations representing health care professionals, consumer organizations, voluntary health agencies, the pharmaceutical industry, drug wholesalers, patient drug information database companies, and other relevant parties, ~~collaborate to~~ develop a long-range comprehensive action plan to achieve goals consistent with the goals of the Food and Drug Administration's proposed rule on 'Prescription Drug Product Labeling: Medication Guide Requirements (60 Fed. Reg. 44182; relating to the provision of oral and written prescription information to consumers).

"(b) PLAN.—The plan described in subsection (a) shall—

"(1) identify the plan goals;

"(2) assess the effectiveness of the current private-sector approaches used to provide oral and written prescription information to consumers;

"(3) develop guidelines for providing effective oral and written prescription information consistent with the findings of any such assessment;

"(4) develop a mechanism to assess periodically the quality of the oral and written prescription information and the frequency with which the information is provided to consumers; and

"(5) provide for compliance with relevant State board regulations.

"(c) LIMITATION ON THE AUTHORITY OF THE SECRETARY.—The Secretary shall have no authority to ~~develop or implement any new regulation, rule, or other policy statement or guideline related in any manner to~~

~~"(1) medication guide or patient package insert requirements;~~

~~"(2) an affirmative obligation to provide written information about prescription drugs to consumers;~~

~~"(3) a specified uniform content, format, or any other policy statements or guidelines for written information provided to consumers about prescription drugs,~~

~~including the implementation of~~ implement the proposed rule described in subsection (a), ~~if, not later than 120 days after the date of enactment of this section, the national organizations described in subsection (a) develop and begin to implement a comprehensive, long-range action plan (as described in subsection (a)) regarding the provision of oral and written prescription information.~~ prior to January 1, 2001 except for human prescription drug products and biological products that the Secretary determines would pose a serious and significant risk in the absence of FDA-approved prescription information

"(d) SECRETARY REVIEW.—Not later than January 1, 2001, the Secretary shall review the status of private-sector initiatives designed to achieve the goals of the plan described in subsection (a). and if such goals are not

OK TO DEVELOP ANY SIMILAR REGULATION, POLICY STATEMENT OR OTHER GUIDANCE RELATED TO UNAPPROVED CONTENT OR FORMAT FOR WRITTEN INFORMATION VOLUNTARILY PROVIDED TO CONSUMERS ABOUT PRESCRIPTION DRUGS

achieved, shall seek public comment on ~~other~~ and initiatives that may be taken to meet such goals. The Secretary shall not delegate such review authority to the Commissioner.".

~~The limitation in subsection (c) shall not apply~~ and The Secretary

- Renores FDA authority to enforce 404 rulemaking
- Finalizing — could finalize at any time —
  - Hammer not finalized
  - Hammer finalized — required immediately

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NATIONAL JOURNAL'S
CongressDaily/A.M.

FRIDAY, MARCH 29, 1996

Congress OKs Debt Bill As FY96 Bill Talks Continue

A nearly six-month-long House Republican attempt to use a needed debt limit increase as leverage to force President Clinton to accept GOP budget priorities he did not share ended Thursday — when Congress sent the White House a bill Clinton will sign that raises the debt ceiling from $4.9 trillion to $5.5 trillion. That should be enough additional government borrowing authority to last until at least October 1997, almost a year after this fall's presidential and congressional elections. The action came as House-Senate conferees — facing the expiration today of the short-term continuing resolution — worked throughout the day and late into the night Thursday on the FY96 omnibus appropriations bill. *(See related story, Page 4.)*

BUDGET

Although technically titled the Contract With American Advancement Act, the debt limit legislation contained only three other provisions the White House could accept. One of those — the line item veto — was technically stripped out of the bill and sent to Clinton separately Thursday. The two remaining riders gradually raise to $30,000 by 2002 the amount of outside income senior citizens can earn without losing their Social Security benefits, and deal with regulatory reform for small businesses. The House passed the bill on a 328-91 vote, with 30 Republicans, 60 Democrats and the lone House independent voting against it. The Senate approved the House measure on voice vote — deeming it as having passed upon receipt from the House. That sent the bill to Clinton for his expected signature. The administration in a statement Thursday reiterated it "strongly supports" the bill and "urges the Congress to send it to the president immediately to prevent a default."

House Republicans since last fall have tried unsuccessfully to use the debt ceiling increase — which the administration needed — to force Clinton's hand on accepting some GOP

Continued on Page 4

SCHEDULE

SENATE

Convenes at 10 a.m.

HOUSE

Convenes at 10 a.m.

SENATE COMMITTEES

ARMED SERVICES

DEFENSE AUTHORIZATION

Airland Forces Subcommittee hearing on the FY97 defense authorization request for Army modernization programs, 222 RSOB, 9 a.m.

DEFENSE AUTHORIZATION

Strategic Forces Subcommittee hearing on the FY97 defense authorization request for arms control and chemical demilitarization programs, 222-A RSOB, 11 a.m.

Continued on Page 9

Hoekstra Eyeing Reform Rebellion

The chairman and several members of the House Republican leadership's reform task force have threatened rebellion if **Speaker Gingrich** and **Majority Leader Armey** do not move quickly to agree on a schedule for bringing campaign reform legislation to the House this year. The showdown could come at a meeting set for late this morning in Gingrich's office between the speaker and several task force members, including the chairman, **Rep. Peter Hoekstra**, R-Mich. The session follows a shot across the bow initiated by Hoekstra, who has been a Gingrich loyalist and trouble-shooter. "For six months, we have worked to develop a consensus within the Republican Conference on reform issues," six House Republicans, including Hoekstra, wrote to Gingrich in a letter dated Thursday. "Unfortunately, the early months of the second session of the 104th Congress have come and gone without any firm leadership commitment to move ahead on a reform agenda."

CAMPAIGN REFORM

Hoekstra's office provided a copy of the letter, which was delivered to Gingrich late Thursday afternoon. A spokesman would not identify the other five signers, but did confirm they are members of Hoekstra's GOP task force. Some task force mem-

Continued on Page 9

CongressDaily/A.M. publishes Monday through Friday when Congress is in session. Due to the uncertainty at presstime surrounding Congress' scheduled two-week Easter break — originally expected to begin today — our publishing schedule for next week is uncertain as well.

7/8

Repub. all N, Kass N

Dems K yes, P yes, D yes, S yes, H yes, M yes; Wells yes

AMENDMENT NO. 2 Calendar No.____

Purpose: To establish more realistic time frames and appropriate incentives to achieve targets.

IN THE SENATE OF THE UNITED STATE--104th Cong.,2d Sess.

An Amendment to the amendment offered by Senator Kassebaum to S. 1477

To amend the Federal Food, Drug, and Cosmetic Act and Public Health Service Act to impeove the regulation of food, drugs, devices, and biological products, and for other purposes.

Referred to the Committee on ______________________________
and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENTS intended to be proposed by Senator KENNEDY

~~Section 204. Expediting Approval of New Drugs, Biologies, and Medical Device for Serious Conditions--~~
~~Page 21, l. ~~22~~ 1, change "120 days" to "180 days."~~
~~Page 22, l. ~~10~~ 2, change "120 days" to "180 days."~~

Section 404. Prompt and Efficient Review.
Delete p. ~~36~~ 35 ll. ~~11~~ 8-25, ~~all of p. 37~~, ~~and p. 38 ll. 1-21~~ 36, 37 and substitute the following: and p. 38 ll. 1-10

If the Sec [illegible] by [illegible] 1, 1996

"(c) Beginning July 1, 1998, ~~if the Secretary fails to meet the statutory~~ targets for action on an application or notification or petition for the approval or clearance of a device, a new animal drug, or a direct food additive or fails to meet the targets established for the Prescription Drug User Fees Act for action on an application for a new drug or biological product for 90% of the annual actions in a particular category, then--

(1) By April —, 199_ the Secretary shall report to Congress an action plan for meeting the targets (including, as applicable, a projection of resources and any statutory changes that might be necessary to meet the targets), which will be publicly available, and shall report to Congress every six months on progress toward achieving the goals of the plan. Such action plan may include a program of contracting out all or parts of product reviews, with the Secretary retaining final approval authority, if contracting out would assist in achieving targets under the Act without diminishing the quality of review.

(2) This subsection does not apply if the failure to meet a target for a category consists of only one application, notification, or petition."

Section 806. Timeframes for Approval.
Delete p. ~~114~~ 118, ll. 1-4.

Section 901 and 902. Food and Regulatory Reform.
~~Delete p. 118, ll. 5-25, and p 119, ll. 1-17~~
on p. 118, line 22 strike "90" and replace with "180".)
and on page 119, line 1, strike "90" and replace with "180".

AMENDMENT NO 6 Calendar No____

Purpose: To clarify the meaning of substantial equivalence ~~improve the regulation of food and cosmetics~~.

IN THE SENATE OF THE UNITED STATE--104th Cong., 2d Sess.

An Amendment to the amendment offered by Mrs. Kassebaum to S. 1477

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AMENDMENTS intended to be proposed by Mr. Kennedy

On page 92, strike line 16 through line 25 and on page 93, strike line 1 through line 4 and replace with:

"(c) Section 513(i)(1)(A)(21 U.S.C. 360c(i)(1)(A)) is amended by inserting after "intended use":

"which, as determined by the Secretary, shall include each use reasonably included within a general use".

AMENDMENT NO_____ Calendar No____

Purpose: To clarify substantial evidence standard.

IN THE SENATE OF THE UNITED STATES--104th Cong., 2d Sess.

An Amendment to the amendment offered by Mrs. Kassebaum to S. 1477

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AMENDMENTS intended to be proposed by Mr. Kennedy

On page ~~xx~~ 80, strike lines ~~xx~~ 21 through ~~xx~~ 23 and replace with:

"Substantial evidence may, as appropriate, consist of data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained either before or after such investigation).".

AMENDMENT NO_____ Calendar No____

Purpose: To improve the patient access to information about drugs, biologics and devices.

IN THE SENATE OF THE UNITED STATE--104th Cong., 2d Sess.

An Amendment to the amendment offered by Mrs. Kassebaum to S. 1477

To amend the Federal Food, Drug, and Cosmetic Act and Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes.

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AMENDMENTS intended to be proposed by Mr. Kennedy

On page 10, line 12 insert after the period "Notwithstanding any other provisions of law, and to the extent the Secretary determines that dissemination of information regarding the safety and effectiveness of a product would enhance the public health, such information shall be made available to the public."

AMENDMENT NO_____ Calendar No____

Purpose: To ensure reinstate requirement that device companies report removals and corrections.

IN THE SENATE OF THE UNITED STATE--104th Cong., 2d Sess.

An Amendment to the amendment offered by Mrs. Kassebaum to S. 1477

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AMENDMENT'S intended to be proposed by Mr. Kennedy

On page ~~93~~ 97, line ~~15~~ 18, strike "; and" and insert a period; and

strike line ~~16~~ 19.

AMENDMENT NO_____ Calendar No____

Purpose: To delete preference for foreign products

IN THE SENATE OF THE UNITED STATE--104th Cong., 2d Sess.

An Amendment to the amendment offered by Mrs. Kassebaum to S. 1477

To amend the Federal Food, Drug, and Cosmetic Act and Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes.

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AMENDMENTS intended to be proposed by Mr. Kennedy

1 Strike from page 35, line 19 though page 37, line 7.

AMENDMENT NO_____ Calendar No____

Purpose: To protect patients receiving investigational therapies.

IN THE SENATE OF THE UNITED STATES--104th Cong., 2d Sess.

An Amendment to the amendment offered by Mrs. Kassebaum to S. 1477

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AMENDMENTS intended to be proposed by Mr. Kennedy

On page ~~xx~~ 18, line ~~xx~~ 25, strike "person if" and replace with:

"person if the Secretary determines -- "

On page ~~xx~~ 19; line ~~xx~~ 6, strike "and" and insert between lines ~~x~~ 6 and ~~x~~ 7:

"(3) the manufacturer or distributor is actively pursuing marketing approval with due diligence; and"

On page ~~xx~~ 19, line ~~xx~~ 7, strike "(3)" and replace with "(4)";

One page ~~xx~~ 20, inset between lines ~~xx~~ 15 and ~~xx~~ 16:

"(e) TERMINATION.--The Secretary may terminate expanded access under this section if the requirements under subsection (a) are no longer met or expanded access is interfering with the conduct of ongoing clinical trials."

AMENDMENT NO_____ Calendar No____

Purpose: To reduce overly burdensome, bureaucratic, and unnecessary requirements.

IN THE SENATE OF THE UNITED STATES--104th Cong., 2d Sess.

An Amendment to the amendment offered by Mrs. Kassebaum to S. 1477

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AMENDMENTS intended to be proposed by Mr. Kennedy

On page xx, strike lines xx-xx and replace with:

"(ii) requests for meetings and the scheduling of meetings relating to reviews of protocols and relating to review of applications or submissions (including petitions or notifications) for product approval or clearance; and";

On page ~~xx~~ 22, strike lines ~~xx through xx~~ 22 through P. 23, line 5 and replace with:

"(2)(A) A clinical investigation of a new drug (including a biological product) may begin thirty days after the date the Secretary receives from the sponsor a notification containing information about the drug and the clinical investigation unless, prior to the thirtieth day, the Secretary

informs the sponsor that the investigation may not begin and specifies the basis for the decision. Within an additional twenty days, the Secretary shall specify in writing the deficiencies and the information needed in order for the clinical investigation to commence.

On page ~~xx~~ 24, strike lines ~~xx~~ 24 through xx 25 and replace with: strike on page 24 line 1 through line 2

"(3)(A) The Secretary may place a clinical hold on any ongoing clinical investigation if the Secretary determines that such action is necessary for the protection of human subjects or for other reasons set forth by the Secretary in regulations.

"(B) If the Secretary places a clinical hold on an ongoing investigation, the Secretary shall immediately advise the sponsor of such investigation in writing of such action, and provide such sponsor an opportunity to confer within ten working days of receipt of such communication to discuss the basis for the clinical hold. Within ten working days of such conference, the Secretary shall provide to the sponsor a written list of conditions for the withdrawal of the clinical hold. Any written request from the sponsor requesting that a clinical hold be withdrawn shall receive a decision in writing and specifying the reasons therefor, within twenty working days of the receipt of the request."

On page ~~xx~~ 16, , strike lines ~~xx~~ 1 through line ~~xx~~ 10 and replace with:

"(b) REVIEW BY SCIENTIFIC REVIEW GROUP.--

"(1) In General.--The product sponsor or applicant shall have a right to request an evaluation by an appropriate scientific review group established under section 904 of any significant scientific decisions made by the Secretary under this Act. In addition, a product sponsor or applicant shall have a right to request an evaluation by an appropriate scientific review group established under section 904 of any significant scientific issue under this Act appealed by such person under subsection (a) that has been pending before the Secretary, without final resolution, for more than 180 days."

AMENDMENT NO._____ Calendar No.____

Purpose: ~~To maintain standards for approving supplemental applications that will continue the guarantee of safety and effectiveness and~~ To facilitate the submission and approval of such supplementals

IN THE SENATE OF THE UNITED STATE--104th Cong., 2d Sess.

An Amendment to the amendment offered by Senator Kassebaum to S. 1477

To amend the Federal Food, Drug, and Cosmetic Act and Public Health Service Act to impeove the regulation of food, drugs, devices, and biological products, and for other purposes.

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AMENDMENTS intended to be proposed by Senator KENNEDY

~~Strike new Sec. 750 of the Food, Drug and Cosmetics Act, Approval of Additional Uses and~~ Strike Sec. 410. Alternative Approval of Supplemental New Drug Applications and replace with new:

SEC. 410 APPROVAL OF SUPPLEMENTAL APPLICATIONS FOR APPROVED PRODUCTS

(1) Performance Standards - Within 180 days after enactment of this section, the Secretary shall publish in the Federal register performance standards for the prompt review of supplemental applications for approved products.

(2) Guidance to Industry - Within 180 days after enactment of this section, the Secretary shall issue guidances to clarify the requirements and facilitate the submission of data to support approval of supplemental applications for approved products. The guidances shall -

(a) clarify circumstances in which published articles may be the basis for approval of a supplemental application;
(b) specify data requirements what will avoid duplication by

recognizing the availability of data previously submitted in support of the original application; and

(c) define supplemental applications that are eligible for priority review.

(3) Organization - The Secretary shall designate an individual in each Center (except Foods) with responsibility for -

(a) encouraging prompt review of supplemental applications for approved products; and

(b) working with sponsors to facilitate the development and submission of data to support supplemental applications.

(4) Collaboration - (i) The Secretary shall implement programs and policies that will foster collaboration between the Food and Drug Administration, the National Institutes of Health, professional medical and scientific societies, and others, to identify published and unpublished studies that could support a supplemental application, and to encourage sponsors to make application or conduct further research in support of an application based, in whole or in part, on such studies.

AMENDMENT NO_____ Calendar No____

Purpose: To improve the regulation of food and cosmetics.

IN THE SENATE OF THE UNITED STATES--104th Cong.,2d Sess.

An Amendment to the amendment offered by Senator Kassebaum to S. 1477

To amend the Federal Food, Drug, and Cosmetic Act and Public Health Service Act to impeove the regulation of food, drugs, devices, and biological products, and for other purposes.

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AMENDMENTS intended to be proposed by Senator KENNEDY

Sec. 746. DISSEMINATION OF TREATMENT INFORMATION ON DRUGS AND BIOLOGICAL PRODUCTS.

Amendment to S. 1477

Sec. 746. Dissemination of treatment information on drugs and biological products.

is amended by:

page 41, lines 23-24: delete

page 42, lines 1-2: delete

page 42, line 3: delete: "(B)"

page 42, line 15: delete: "if" and replace with: "if the requirements of subsection (C) have been met and"

page 42, line 17: delete the word "an" and replace with "a balanced and.."

page 43: add after line 7:

"(C) In the case of a drug, antibiotic or biological which has in effect an approved application filed under section 505(b), section 507, or licenses under the Public Health Service Act, the holder of such application may disseminate information which is consistent with the treatment use of such drug, antibiotic or biological product or consistent with the intended use not contained in the official labeling only if-

(i) the holder has submitted to the Secretary an

application for the additional use under section 505(b), section 507, or section 351 of the Public Health Services Act (42 USC 262) and

(I) has demonstrated due diligence for completion of such process and

(II) at the request of the Secretary will provide corrective information regarding the outcome of the supplemental NDA process to all recipients of the initially disseminated information or-

(ii) the holder has requested an exemption from such requirement.

(I) A request for exemption shall be submitted in such form and manner as the Secretary may prescribe and shall demonstrate that--

(A) due to the size of the patient population or the lack of potential benefit to the

sponsor, the cost of obtaining clinical information makes submission of a supplemental application economically prohibitive; or

(B) it is unethical to obtain adequate clinical evidence for inclusion in a supplemental application.

(II) A request for exemption under this subsection shall be deemed approved unless denied by the Secretary within 30 days of receipt.

(III) Any information disseminated pursuant to an exemption shall have a clear label stating that this information describes an unapproved use of this drug and the information is not part of an application for supplemental use approval.

(D) When the treatment use or use not contained in the official labeling relates to the treatment of cancer, paragraph (C) shall not apply if--

(i) the application holder files with the Secretary all available literature and clinical data on the indicated use of the product and a statement of evidence establishing good faith intent to pursue a supplemental new drug application under section 505(b), section 507 or a product license supplement under the Public Health Service Act for the treatment use or use not contained in the official labeling, and

(ii) the Secretary meets annually with the application holder to evaluate progress made toward submission of a supplemental new drug application for the treatment use or use not contained in the official labeling that is the

subject of information being disseminated.

(E) If the Secretary determines, after an informal hearing, that the application holder has failed to make sufficient progress under paragraph (D)(i), toward submission of a supplemental application for the treatment use or use not contained in the official labeling that is the subject of information being disseminated, the Secretary may direct the application holder to cease all dissemination of information and provide corrective information regarding this action to all recipients of the initially disseminated information.

page 43, line 13: after "(1) shall" add: "disseminate such information to all recipients of the initially disseminated information and"

page 44, line 3: after "(a)" add: "and relating to a product described in (C)(i) or (D).

page 44, line 5: delete "prominently displayed statement" and replace with: "statement prominently displayed on each article and textbook"

page 44, line 21-24: change "," to a "." and delete the rest

page 47, lines 11-17: delete

page 48, line 2-4: delete: "written....demonstrations)"

page 48, lines 15-16: delete: "and oral"

page 48, line 18: delete: "or oral"

page 48, lline 23: delete "an" and replace with "balanced and"

page 49,lines 7-11: delete

page 49, line 12: change "(C)" to "(B)"

page 49, lines 21-25: delete

page 50, lines 1-5: delete

page 50, line 12: after "shall" insert: "disseminate such information to all recipients of the intially disseminated information and "

AMENDMENT NO_____ Calendar No____

Purpose: To encourage approp-te contracting [redacted].

IN THE SENATE OF THE UNITED STATES--104th Cong., 2d Sess.

An Amendment to the amendment offered by Mrs. Kassebaum to S. 1477

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AMENDMENTS intended to be proposed by Mr. Kennedy

On page ~~xx~~ 31, delete lines ~~xx~~ 13 through ~~xx~~ 24 and on p 32, delete lines 1-9 and insert the following:

"(2) Increased Efficiency and Expertise Through Contracts.--The Secretary shall use the authority granted in paragraph (1) to --

"(A) improve the efficiency, timeliness, and quality of the review of applications, petitions, and notifications (or any part thereof) for the approval or clearance of devices and direct and indirect food additives; and

"(B) ensure that the agency has the scientific and technical expertise available to the agency necessary to keep informed of emerging new therapies and technologies posing significant new and technical

issues.

The Secretary shall retain full authority to make determinations with respect to the approval, disapproval, or clearance of a product.