"The FDA Performance and Accountability Act"

SECTION BY SECTION ANALYSIS OF SUBSTITUTE AMENDMENT

SECTION 1. SHORT TITLE AND REFERENCE

Title I. MISSION AND ACCOUNTABILITY

Sec. 101. Short Title

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

- The mission statement suggests that FDA's public health protection activities are limited to protecting the public from unsafe or ineffective products.
- This ignores the Act's premarket approval provisions. In many situations, FDA would not be able to show affirmatively that an unapproved product was unsafe or ineffective. (The likely showing would be that the product has not been shown to be safe or effective.)
- The mission statement should include protecting the public from products that do not have the requisite approval prior to marketing.

Sec. 103. Performance Standards and Review *

- Section 103 requires FDA, after external consultation, to develop performance standards for agency action on (1) applications or submissions for review of a protocol, a product investigation, a product approval, a new use approval, a manufacturing change, a labeling change, (2) letters, telephone calls, meeting requests and scheduling, and (3) the scheduling of advisory committee meetings. The performance standards must establish objectives to expedite the clinical investigation of new drugs, expedite review, reduce backlogs, and establish a schedule to bring the agency into compliance with the time periods specified in the bill by July 1, 1988. FDA also would be required to prepare and publish for comment in the Federal Register, an annual report providing information about the agency's performance re: compliance with these performance standards.
- FDA needs to have clear performance goals and it should be held accountable for meeting those goals, but FDA needs the flexibility to respond to changing

conditions and emerging issues. The outcome of S.1477 is micromanagement of how the agency will meet the requirements set forth in the bill. In addition, the deadline established to come into compliance is too brief. The rigidity of the bill will increase significantly the number of petition denials.

Sec. 104. Interagency Collaboration

- Section 104 requires FDA to implement programs and policies that will foster collaboration between FDA, NIH, and other science-based agencies to enhance scientific expertise. The policies underlying this provision are beneficial.

Sec. 105. Information Systems

- Section 105 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. 106. Policy Statements *

- Section 106 requires FDA to develop a procedure governing the development and use of all policy statements of general applicability that provide guidance. The procedure must provide an opportunity for affected persons to participate in the development/continued use both before and after adoption. It also requires FDA to establish a procedure for the periodic compilation and publication of all policy statements of general applicability.

- In connection with a citizen's petition filed by the Indiana Medical Device Manufacturer's Council, Inc. (IMDMC), FDA has been looking at ways to improve the procedures governing the development and use of guidance documents. In the March 7, 1996 Federal Register, FDA published a notice soliciting comment on these issues. FDA is seeking an approach that addresses concerns regarding adequate public participation but does not make it impractical for the agency to continue making guidance available in a timely fashion. This approach has been applauded by many industry attorneys and appears to have the support of the IMDMC petitioners.

- This section, as drafted would require FDA to provide an opportunity for affected individuals to participate in the development of most guidance before it is implemented. Under present and expected future budget constraints, FDA would have to choose between: (1) shifting resources from consumer protection programs and product review to developing policy under the procedures required in this section or (2) not expending resources to develop policy including that designed to facilitate marketing of new products. FDA anticipates, and believes that industry would agree, that not all guidance warrants the same amount of public input before implementation. This could delay policy decisions.

Sec. 107 Scientific Review Groups

- The provision restricts FDA flexibility in its use of advisory committees (e.g., requires (rather than recommends) that chair have X amount of experience).

- Section 904(c)(1) (Scope) permits advisory committees to set their own agendas. However, FDA must have the ability to put specific issues of concern before advisory committees.

- Section 904(c)(2) (Nonvoting Members) requires advisory committees to include non-voting industry and public representatives. Non-voting members should not attend closed meetings and should not receive confidential information.

- Section 904(d)(1) requires FDA to provide advisory committee materials to the affected sponsor. That material often consists of other sponsor information, which is confidential. Therefore, FDA would no longer be able to give that information to an advisory committee.

- Section 904(e) (FDA Actions) requires FDA to make a final determination within 60 days of an advisory committee recommendation. This assumes that all matters presented to advisory committees are susceptible to "final" determination. This is not always true. A better approach might be to require an update letter from the relevant FDA division within 60 days of the advisory committee meeting.

Sec. 108. Appeals within the FDA *

- Section 107 requires FDA to establish, by regulation, an appeals system. It

permits individuals to request scientific review group evaluation of any significant scientific issue pending before the agency. Section 107 provides that "any" decision can be appealed. Moreover, it appears to be a process without an end (i.e., each appeal in turn could be appealed). As a final step in the appeals process, section 107 permits individuals to request a costly scientific review group evaluation of any significant scientific issue pending before FDA.

- FDA has procedures for appeals. Some are general and many are specific to a particular situation. This section would require FDA to develop yet another appeals process that may not fit all issues and may not be necessary.

- FDA has established an agency working group to address the consistency and adequacy of the agency's appeal process. This agency review will determine what changes are needed to make FDA's appeals process more effective and efficient for the agency and industry.

- The issues that may be referred to a scientific review group include staff decisions on applications and may also include inspectional finding decisions made by the FDA field staff. It could literally encompass hundreds of decisions made by agency staff everyday. This could result in a significant drain on FDA advisory committee resources. Currently, less costly and less time-consuming approaches are used by the agency. If individuals request the costly and time-consuming scientific review rather than the less costly process now used by individuals when they disagree with an agency decision, FDA would have to shift resources from consumer protection programs and product review to resolve issues that have been handled in a less costly manner.

- The section 907(d) 60 day timetable for final determination is problematic.

Title II. EXPEDITED ACCESS TO PRODUCTS FOR SERIOUSLY ILL PATIENTS

Sec. 201. Short Title

Sec. 202. Access to Unapproved Therapies **

- Section 202 authorizes sponsors of investigational new drugs and devices, including diagnostic products and products for monitoring a condition or disease, to make these products available to individuals with a serious disease

or condition, an immediately life threatening or seriously debilitating disease or condition, or any other condition designated by FDA if there is no comparable or satisfactory alternative therapy, the risk from the product is not greater than the risk from the disease or condition, and an investigational device exemption (IDE) or an investigational new drug application (IND) is in effect.

- This provision is an expansion of what FDA already does. Much of what this section seeks to accomplish is probably acceptable. Expanded access, however, should not be allowed to interfere with trials to establish safety and efficacy. Unlimited access would lead to this. At the very least, there should be a requirement for active pursuit of testing.

Sec. 203. 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. Section 203 amends the HUD provision (section 520(m)) to require a decision on an HUD exemption request within 30 days. It also eliminates the current provision that limits the duration of an exemption and eliminates the requirement for regulations prior to implementation.

- FDA was directed to issue regulations to implement the HUD exemption when it was added to the Act. FDA issued a proposed humanitarian use devices regulation on December 21, 1992. The proposal, which sought to implement the HUD exemption by amending the investigational device exemption regulation, met with considerable criticism from industry. In comments to the proposal, industry argued that the HUD exemption was meant to provide for marketing status rather than an expansive IDE. FDA agrees with the comments and is planning to issue (as a final rule) a regulation that grants temporary (but renewable) marketing status for HUDs and that provides incentives for the sponsor to collect data post marketing with the goal of meeting the regular statutory safety and efficacy requirements. FDA expects to issue final regulations by June 1996.

- The 30 day time frame in the bill is not realistic. It does not allow enough time to do a credible job of assessing a HUD application.

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

- Section 204 would reduce, from six months to four months, the time FDA has to review applications for (1) drugs or biologics for an immediately life-threatening serious disease or condition that provides therapy or diagnosis not available or offers significant improvement over currently available therapy and (2) devices for a life threatening disease or condition, a seriously debilitating disease or condition, or for any other serious disease or condition that provides therapy or diagnosis not available from another approved device or offers a significant improvement over another approved device.

- This clearly is a difficult task for an application of any substantial size. FDA is not yet able to regularly review prescription drug applications in six months. There is no question that the four month time frame would make it impossible in all but the rarest circumstances to have drugs or devices considered by an advisory committee. The only conceivable way to meet these requirements is to have substantial pre-submissions of various parts of the data set.

Title III. REVITALIZING THE INVESTIGATION OF NEW PRODUCTS

Sec. 301. Short Title

Sec. 302. Timely Review and Reasonable Data Requirements for Clinical research on Drugs and Biological Products **

- Section 302 requires written notification of clinical hold within 30 days -- precludes telephone calls. This would allow less time to review because a letter has to be drafted. What about a call within 30 days followed by a letter within X days?

- New Section 505(i)(3) limits FDA's ability to place ongoing investigations on clinical hold.

Sec. 303. Timely Review and Reasonable Data Requirements for Clinical Research and Devices *

- Section 303 amends section 520(g) to permit developmental changes in devices

under investigational device exemptions in response to information collected during an investigation without additional approval if the changes are not a significant change in design or basic principles of operation. This generally is FDA's policy, but if this provision would prevent FDA from requiring data when it believes that the significant changes have been made, it would be problematic.

- This section also would permit changes to clinical protocols that do not affect the validity of the data so long as such changes do not affect any patient protection provisions of the protocol. The problem is that you may not know if the validity of the data will be affected until the study is completed.

Sec. 304. Collaborative Research Design

- Section 304 authorizes any sponsor of an investigation to request a meeting with FDA to review the design of one or more protocols for the preclinical or clinical testing of a drug or device. The section further provides that a protocol shall be designed so that the fewest number of patients and procedures necessary to obtain data necessary for the approval of a new drug, biological product, or device are required consistent with public health and safety. The Secretary must meet within 30 days and provide a written review of the proposal. Any agreements reached may be changed in writing by mutual consent. Unilateral changes may be made by the sponsor if the change is not one that would require FDA approval under the applicable regulations. Unilateral changes may be made by FDA only if the Office Director makes such changes in writing and specifies the basis and demonstrates a substantial public health reason. The provision also authorizes panel review of disapproval of protocols and FDA unilateral modifications.

- The written review within 30 days is a resource problem. Also, industry wants the reviewer with whom they worked on an IND to be the reviewer of the NDA. These requirements preclude that possibility.

Title IV. EFFICIENT, ACCOUNTABLE, AND FAIR PRODUCT REVIEW

Sec. 401. Reference

DRAFT

Sec. 402. The Content and Review of an Application

- Section 402 requires the Commissioner to (within 60 days of the date of enactment) establish a mechanism to ensure fair and consistent application of filing requirements.

- It further requires FDA to, within 60 days of a request, provide binding written classification of a product. If the Secretary does not provide the statement within 60 days, the classification designated by the requestor shall be final. The 60 day clock should start to run only after FDA has had an opportunity to review a request for designation and determine if it has sufficient information in the request to render a judgment. (This is codified in the current law and has been working well.) If the proposal is implemented as written, sponsors could select the Center with little or no experience in the product area under consideration.

Sec. 403. Contracts for Expert Review

- Section 403 authorizes FDA to contract with outside organizations or individuals.

- The provision directs FDA to use this authority to improve the efficiency and review of applications for food additives and devices. FDA, however, retains full authority to make determinations with respect to approval or disapproval of any product.

- The provision requires FDA to report to Congress on the use of third parties. Such report must include an evaluation of the extent to which contracting improves the efficiency of review and the expertise available to the agency.

Sec. 404. Prompt and Efficient Review ***

- Section 404 requires FDA to establish procedures and policies to facilitate a collaborative review process with the applicant.

- Section 743(b)(2) (requiring meetings unless both sponsor and FDA say unnecessary) will slow down review process. A major goal should be to complete review. If time permits, these kinds of interactions can and do occur.

- Section 743(b)(4) essentially cuts the already unrealistic review period in half by requiring FDA to provide applicants with a letter describing the petition deficiencies at the meeting. Reviewers will not know all deficiencies at this point. One possible fix might be to require FDA to identify deficiencies identified to date.

- Section 743(c) provides that if FDA fails to meet a time frame on a product application and the product offers a significant improvement over existing approved products, or in the case of a food additive has the potential to make foods more wholesome and contribute to a healthier diet and such product has been approved for marketing in the EU or UK marketing requirements, at the request of the applicant FDA must within 30 days either approve or disapprove the application.

- Section 743(c)(2) permits a person whose application has been disapproved under new section 743 (c)(1) to appeal that decision.

- Section 743(d) provides for outside review if in any fiscal year FDA fails to meet the statutory time frame for 95% of the applications in a particular category. As written, it deems a product approved when the third party determines that it should be approved, but then directs FDA to approve or disapprove the petition within 60 days. (We have been told that the "deemed approved" language was a drafting error.)

Sec. 405. Good Manufacturing Practice Inspection

- Section 405 permits FDA to accredit organizations to conduct inspections to evaluate manufacturers' compliance with requirements for GMP.

- The reporting of all inspectional findings, rather than just significant deviations, may be a disincentive for manufacturers to participate in the voluntary third party certification program.

- There is no discussion of reasonable costs. This is particularly important re: foreign inspections.

- The bill should have escape clause language stating that FDA is not bound to accept the third party assessment, but may make an independent decision that includes the third party assessment or not. This is particularly important if revocation always requires an informal hearing as suggested in section 744(d).

- Conflict-of-interest issues must be considered when organizations and individuals from outside of the agency become involved in the agency decision-making process. Agency funds saved from not having FDA staff conduct the inspections will have to be used to ensure there are no conflict-of-interest problems from those outside the agency who will conduct the inspections. If a problem does arise from a concern over conflict of interest, even more agency funds will be necessary to resolve it.

Sec. 406. Environmental Impact Review

- Section 406 eliminates the requirement to prepare an environmental analysis unless the relevant office director demonstrates a probability of substantial impact.

- As part of REGO, FDA will be proposing amendments to revise its National Environmental Policy Act procedures to provide for additional categorical exclusions for classes of actions that do not individually or cumulatively significantly affect the environment.

Sec. 407. Information Dissemination and New Use Approval ***

- Off-label promotion. Doctors are free to prescribe drugs for uses that have not been approved by FDA. Under current law, doctors are free to rely on journal articles and other information in making these prescribing decisions, but regulated companies may not use journal articles or other types of information about unapproved uses to promote those uses of their products. Section 407 would allow companies to distribute journal articles and other types of information (such as textbook chapters, continuing medical education program materials, and compendial information relating to uses recognized for purposes of third party coverage or reimbursement) to promote unapproved uses.

  This provision undercuts the efficacy standard. It allows manufacturers to promote uses that have not been proven safe and effective. There are a number of examples of off label uses that resulted in disastrous consequences.

  Moreover, although the stated purpose of the provision is dissemination of information, its effect will be less information because it will leave little incentive for companies to do scientific research and have new uses reviewed by FDA (in fact, there would be a disincentive because FDA might determine

that the new use is not supported by the evidence).

In addition, manufacturers could selectively choose which studies they want to publish and thus, skew the information that is provided regarding off label uses. Even if both positive and negative articles are published, companies would have little incentive to provide physicians with balanced information.

None of the sources of information that the bill would allow companies to distribute has procedures that confirm the validity of the data and information contained therein. For example, not even the peer review process, which is meant to ensure that the reader is provided with sufficient detail and clarity, can guarantee the correctness, authenticity, or clinical importance of an article, nor can it detect fraudulent or flawed research.

- Sound medical practice. Section 407 would establish a new process for approving new uses of existing drugs and devices that would completely bypass the approval process. It would establish a procedure for recognizing new uses based on medical practice. The bill provides that if an off-label use has existed for five years, is "common" among experienced clinicians, and is reasonably based on experience and other confirmatory evidence, that use could be included in the product's labeling. This provision moves us away from the accepted scientific standard of evidence and could perpetuate inappropriate, unproven, and ultimately unprovable medical practices.

Sec. 408. Effectiveness, Outcome, and Cost-Effectiveness Standards *

- Section 408 provides that the determination of effectiveness cannot include the evaluation of relative effectiveness, cost effectiveness, or clinical outcomes, unless the labeling references such, or any use not included in the labeling.

- With respect to relative effectiveness, 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.

Sec. 409 Definition of a Day for Purposes of Product Review

- For purposes of reviewing a submission, section 409 defines the term "day" to mean a calendar day in which FDA has responsibility to review such a submission. FDA has no responsibility to review a submission before it has

been filed or after it has been filed during any period between the date of mailing to the sponsor any letter setting forth deficiencies and the date of receipt of a full and complete response to such deficiencies.

Sec. 410 Alternate Approval of Supplemental Applications **

- Section 410 amends section 505(b) by adding a new paragraph that provides that in the case of an efficacy supplement, the reports required by paragraph (1)(A) may consist entirely of information published in independent peer-reviewed scientific and medical literature if the proposed condition of use relates to treatment of a life-threatening disease.

- Although FDA has, on occasion, relied on studies published in journal articles to approve an efficacy supplement, this is not and should not be the general rule -- regardless of the indication. The presumption should be that well-controlled studies are needed. As set forth under section 407, there are a number of problems with relying on journal articles.

Sec. 411 Pediatric Studies Marketing Exclusivity *

- Section 411 provides a 6 month marketing exclusivity for approved applications with pediatric studies submitted by an applicant.

- It is important to provide incentives for conducting pediatric studies. However, a 6 month exclusivity in many cases may be too generous an incentive.

- There are a number of other problems with this provision , which we understand that Senator Kassebaum has agreed to address.

Sec. 412 Notifications for Device Market Clearance

- Section 412 makes language change to section 510(k). The change is incomprehensible.

Title V. DRUG, BIOLOGICAL PRODUCT, AND DEVICE EXPORT REFORM

Sec. 501 Short Title

DRAFT

Sec. 502 Export of Drugs and Devices *

- Section 502(a) amends 801(d) to permit the importation of components, parts, or accessories of a drug, biological product, or device, including a drug in bulk form, provided such components, parts, or accessories will be exported from the United States in accordance with section 801(e), section 802, or section 351 of the Public Health Service Act. The provision is problematic in that such products may be diverted into domestic commerce. In addition there is concern that certain biologics (e.g., blood) brought into the U.S. under this provision could contaminate products intended for domestic commerce.

- Section 502(a) amends section 801(e)(1) to permit the export of unapproved new animal drugs provided the section 801(e)(1) (A) through (D) requirements are met. This is generally consistent with REGO. The bill should not permit the exportation of unapproved new animal drugs that have been banned in the U.S.

- Section 502(b) amends Section 802 to relax the export requirements that currently exist for unapproved new drugs. Section 802(b) provides that human drugs (including biologics) or medical devices that are not approved in the United States may be exported to a defined list of counties provided that the product complies with the laws of the importing country and has a valid marketing authorization in that country. Section 802(b) further provides that a product that is approved by one of the defined countries may be exported to any country, provided that the product complies with the laws of the importing country.

  Section 802(c) provides that export would also be allowed to another group of countries that have adequate regulatory systems in place to protect the health of their citizens. GAO, in consultation with FDA and others is directed develop a list of such counties and recommended criteria for additions and subtractions to the list.

  Section 802(d) sets forth the safeguards for exporting unapproved drugs and devices pursuant to section 802.

  New section 802 is generally consistent with REGO. Technical amendments are needed.

DRAFT

Title VI. DRUG AND BIOLOGICAL PRODUCT REGULATORY REFORM

Sec. 601. Short Title

Sec. 602. New Drug Approval Standard **

- Section 602 provides that substantial evidence may consist of data from one well-controlled clinical investigation and confirmatory evidence (obtained either before or after such investigation).

- The intent/effect of section 602 is unclear. It may lower the effectiveness requirement -- from requiring two well-controlled studies to requiring, at most, one. The provision is extremely problematic if it would prohibit FDA from requiring more than one well-controlled trial when necessary. Ordinarily, replicated evidence is expected but the Secretary, in particular circumstances, may rely on a single well-controlled trial. Language to indicate that one study is sufficient in certain circumstances (such as where the data is replicated through a multi-center study) would be acceptable.

Sec. 603. Pilot and Small Scale Manufacture

- 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 and 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 plan 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. 604. Manufacturing Changes **

- Permits manufacturers of drugs and most biologics to make minor changes in manufacturing without prior approval as long as changes are validated and records are made available to FDA during inspections.

- This provision undermines the general approach that prior evaluation of changes in the manufacture of an approved drug product may be critical to assure continued safety and effectiveness in the presence of certain changes in the manufacturing process. Prior approval is necessary for certain changes to assure that appropriate tests were performed, that the tests are performed adequately, that the data from the tests was collected and reported accurately, and that conclusions drawn from the data are appropriate. Consider a change in the manufacture of a drug product such that an in vivo bioequivalence study was necessary to assure the safety and effectiveness of the drug product after the manufacturing change, i.e., that the product after the change was bioequivalent to the product prior to the change.

- 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 does forms. Further guidance documents are planned for other types of new drug dosage formes, to include extended release solid oral dose forms, liquids and semisolids, and well-characterized 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 demonstrable effects on product purity, potency, or safety -- or when changes are readily amenable or on-site scrutiny during routine inspection of the production facility.

- 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. 605. Insulin and Antibiotics

- Repeals requirements for lot and batch verification. This is consistent with REGO.

Sec. 606. Biological Products

- Section 606 would regulate well characterized biologics as drugs.
- FDA is moving towards a single application without changing the PHS Act.

Title VII. DEVICE REGULATORY REFORM

Sec. 701. Short Title

Sec. 702. Premarket Notification (see notations on individual provisions)

* • Section 702(a) exempts all class I devices from prior FDA review. It also requires FDA to publish a list of Class II devices that do not require premarket notifications within 30 days of enactment. After publication, anyone may petition for exemption of a class II device.

- Re: Class I devices: FDA has already exempted 572 class I devices from premarket notification. Many of the 216 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 in unacceptable for a device that is important in the prevention of HIV and other blood borne diseases.

- Re: Class II devices: Giving FDA the authority to exempt class II devices from 510(k) requirements via a streamlined process would be beneficial. However, the time frames proposed are too short and it should not be limited to a one time exercise. Under REGO, FDA has probably already identified most of the devices that would be candidates for exemption, so this provision may not result in greater numbers of existing class II devices being exempted.

* - Section 702(a) would prohibit the Secretary from withholding a 510(k) decision because of failure to comply with any provision of the Act unrelated to a substantial equivalence decision. There is a need to maintain an appropriate 510(k)/GMP linkage.

** - Section 702(b) would permit 510(k) submitters to request advisory committee review of classification decisions prior to final classification. This is a workload issue. The timeframes for panel meetings are unrealistic.

*** - Section 702(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. Suppose, for example, that a cardiac catheter were originally approved for mapping the electrical activity of the heart. After it is on the market, it is offered for a new use: to save lives by preventing a fatal disturbance of the heart rhythm. Under the bill, it is unlikely that FDA would be able to ask for data showing whether the catheter worked to save lives or was just a costly and failed false hope. Even worse, if the catheter were to work some of the time, in some kinds of patients, there would be no assurance of clinical data, independent review, or accurate labeling to help doctors sort out who are those patients where it is most likely to work, or most risky. The effect of this provision is to virtually eliminate approval of devices for specific uses.

*** - Section 702(d) -- device modification-- would eliminate FDA's role in assuring that modifications made to a product do not adversely affect its safety and

effectiveness. Under the bill, unless the manufacturer's own data shows the safety and effectiveness were to diminish, FDA could not require data on the modified product. Thus, changes to biomaterials, 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.

Sec. 703. Medical Device Approval Standards **

- Section 703 would require the agency to accept "retrospective or historical clinical data as a control or for use in determining whether there is a reasonable assurance of effectiveness of a device if sufficient valid data are available and the effects of the device on the cure, mitigation, treatment, or prevention of a disease are clearly defined and well understood." FDA may not require clinical trials using prospective concurrent controls unless (i) such controls are scientifically necessary and ethically feasible, the effects of the device are not clearly defined and well understood, and retrospective or historical data are not available; or (ii) such controls are necessary to support specific marketing claims

- This provision shifts the burden. The presumption should be that the "better" studies are required unless the sponsor can show why the "lesser" studies are sufficient.

- The provision also amends section 513(a)(3) to add paragraph (E), which states that FDA may not require prospective concurrent controlled trials for a modification of an approved device if the modification does not "substantially affect a reasonable assurance of safety or effectiveness and the modified device has the same intended use and is intended for substantially similar patient populations as the approved device. This provision is similar to FDA's current regulations (21 C.F.R. § 814.39). The regulation language is preferable.

Sec. 704. Tracking *

- Section 704 amends the device tracking provision to require a regulation for imposing a tracking requirement, limits their applicability 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."

- Issuing a new regulation for each new tracking requirement will be difficult.

- The provision eliminates the "discretionary" category, which now includes infusion pumps, breast implants, and other silicone related devices.

- The provision would be more acceptable if it retained the discretionary category for tracking or it changed the "would be life threatening" language to "would be reasonably likely to have serious adverse health consequences."

Sec. 705. Postmarket Surveillance **

- Section 705 eliminates the old discretionary category and makes the old mandatory category discretionary.

- The problem with the change 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 should be eliminated.

Sec. 706. Device Distributor Reporting

- Section 706 would eliminate distributor reporting and would eliminate all reports of removals and corrections (recalls) of devices.

Sec. 707. Premarket Approval **

- Section 707 includes unrealistic timeframes. By requiring FDA to within 90 days meet with companies and present a description of deficiencies in the application and "what information is required to bring the application into a form that would require approval" it is requiring FDA to do a comprehensive review in one half the current statutory timeframe. It also would require FDA to use advisory panels much more often than is currently necessary. The provision would require panels to convene much more often than is possible.

- The provision also requires FDA to revise its regulations to eliminate PMA supplements for manufacturing and other changes that do not relate to safety and efficacy.

Sec. 708. Device Performance Standards *

- This provision requires FDA to recognize performance standards of certain standard setting organizations set forth in the statute and to establish a procedure to certify additional organization. The provision requires FDA to recognize all standards adopted by a designated standard setting organization, but it may revoke recognition of a performance standard if it determines that it is insufficient to provide a reasonable assurance of safety and effectiveness.

- The concept of greater regulatory use of consensus standards is supportable. However, there are a number of problems with the provision as drafted. For example, FDA should have the authority to decertify any standard setting organization -- e.g., even those organizations recognized by the statute, not just those that FDA has certified. FDA also should have authority to decide which standards it will recognize. FDA cannot publish or provide copies of performance standards because they are protected by copyright laws. Companies should not be permitted to self-certify compliance with recognized standards. Even the EU requires third party certification.

Title VIII. ANIMAL DRUG APPROVAL STANDARDS

Sec. 801. Short Title

Sec. 802. Evidence of Effectiveness *

- Section 802(a) amends Section 512(d)(3) of the FDC Act to redefine the "substantial evidence" criteria that currently must be met to establish efficacy. Pursuant to revised section 512(d)(3), field investigations will be required "where appropriate."

- Section 802(b) amends Section 512(d) to list factors to be considered by CVM when approving combination drugs. The concepts in this provision are supportable, but technical amendments should be made to ensure that appropriate factors are considered.

Sec. 803. Limitation of Residues

- Section 803 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 approve an optimal dose, the

minimum dose at which there is a maximum effect for the particular indication. The provision is supportable.

Sec. 804. Adulterated Drugs *

- Section 804 gives authority to the Secretary to adopt CGMP regulations that are appropriate for animals other than man.

- Currently the same CGMP regulations apply to both human and animal drugs. The bill would require the agency to issue duplicative regulations that cover only animal drugs. FDA already has authority to issue specific CGMP regulations for animal drugs where there is a need for regulations that are different than those required for human drugs. CVM has scheduled a workshop to address the issue as to whether or in what instances animal drug-specific CGMP regulations are needed.

Sec. 805 Veterinary Feed Directives

- Section 805 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.

Sec. 806 Timeframe for Approval **

- Section 806 cuts the timeframe for approval of new animal drug applications in half (from 180 days to 90 days). The 90 day timeframe is unrealistic.

The Following REGO Related Provisions Should be Added:

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.

DRAFT

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.

Title IX. FOOD REGULATORY REFORM

Sec. 901. Short Title

Sec. 902. Indirect Food Additives **

- Section 902 purports to create a notification system for indirect food additives.
- The process for indirects created by section 902 is not a true notification system because FDA is required to act by regulation to "approve" a notification and may not simply permit a "notified substance to go on the market. Because the bill calls for a regulation for each notification, it is not a true notification, but is a petition review process with a 90-day timeframe.

NOTE: A new version of the bill probably will be distributed next week.

AS1477.COM

Jeffords
Coats Dodd
Gregg
Frist Mikulski
Ashcroft Kassebaum
Abraham
Gorton
DeWine
Kennedy
Pell
Simon
Harkin
Wellstone

AMENDMENT NO. #17 Calendar No. ____

Purpose: To provide for the uniformity of Federal, State, and local requirements respecting nonprescription drugs intended for human use.

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. GREGG

Viz:

On page 64, between lines 7 and 8, insert the following:

SEC. 608. STATE AND LOCAL REQUIREMENTS RESPECTING NONPRESCRIPTION DRUGS INTENDED FOR HUMAN USE.

Chapter V (21 U.S.C. 351 et seq.) is amended by inserting after section 522 the following new section:

"SEC. 523. STATE AND LOCAL REQUIREMENTS RESPECTING NONPRESCRIPTION DRUGS INTENDED FOR HUMAN USE.

"(a) IN GENERAL.—Except as provided in subsection (b), no State or political subdivision thereof may establish or continue in effect any requirement relating to the regulation of a drug intended for human use that is not subject to the requirements of section 503(b)(1) which is different from or in addition to, or which is otherwise not identical with, a requirement of this Act or the Fair Packaging and Labeling Act, and the administrative implementation thereunder. For purposes of this section, a requirement relating to the regulation of such drug shall be deemed to include any requirement relating to the subject matter in any provision of this Act, the Fair Packaging and Labeling Act, and any requirement relating to the dissemination of information in any manner about such drug, but shall not include any requirement relating to the dispensing of a drug only upon prescription of a practitioner licensed by law to administer such drug.

"(b) EXEMPTION.—Upon application of a State, the Secretary may by regulation, after providing notice and an opportunity for written and oral presentation of views, exempt from the provisions of subsection (a), under such conditions as the Secretary may impose, a proposed re-

O:\RDB\RDB96.173

NEW MARK-UP COPY S.L.C. 3/27 3/28

Y
Jeffords
Coats
Gregg
Frist
DeWine
Gorton
Ashcroft
Abraham
Faircloth
Mikulski
Dodd
Harkin

N
Kennedy
Wells
Pell
Simon

AMENDMENT NO. ____ Calendar No. ____

Purpose: To provide for a substitute amendment.

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 IN THE NATURE OF A SUBSTITUTE intended to be proposed by Mrs. KASSEBAUM

Viz:

Strike all after the enacting clause and insert the following:

SECTION 1. SHORT TITLE.

This Act may be cited as the "Food and Drug Administration Performance and Accountability Act of 1996".

SEC. 2. TABLE OF CONTENTS.

The table of contents for this Act is as follows:

Sound medical practice

See 4/1

TITLE I—MISSION AND ACCOUNTABILITY

TITLE II—EXPEDITED ACCESS TO PRODUCTS FOR SERIOUSLY ILL PATIENTS

TITLE III—REVITALIZING THE INVESTIGATION OF NEW PRODUCTS

TITLE IV—EFFICIENT, ACCOUNTABLE, AND FAIR PRODUCT REVIEW

TITLE V—FOOD AND DRUG EXPORT REFORM

TITLE VI—DRUG AND BIOLOGICAL PRODUCTS REGULATORY REFORM

SEC. 3. REFERENCES.

Except as otherwise expressly provided, whenever in this Act an amendment or repeal is expressed in terms of an amendment to, or repeal of, a section or other provision, the reference shall be considered to be made to a section or other provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.).

TITLE I—MISSION AND ACCOUNTABILITY

SEC. 101. SHORT TITLE.

This title may be cited as the "Food and Drug Administration Regulatory Reform Act of 1996".

SEC. 102. THE MISSION OF THE FOOD AND DRUG ADMINISTRATION.

Section 903(a) (21 U.S.C. 393(a)) is amended by adding at the end thereof the following: "The mission of the Administration is to promote and protect the health of the American public by—

"(1) facilitating the rapid and efficient development and availability of products subject to its regulation; and

"(2) protecting the public from unsafe or ineffective products subject to its regulation; and

"(3) enforcing the applicable statutes and regulations in a timely, fair, consistent, and decisive manner.".

SEC. 103. PERFORMANCE STANDARDS AND REVIEW.

Section 903(b) (21 U.S.C. 393(b)) is amended by adding at the end thereof the following new paragraph:

"(3) PERFORMANCE STANDARDS AND REVIEW.—

"(A) IN GENERAL.—Within 180 days of the date of enactment of this paragraph (3), the Secretary, after consultation with experts in the development, clinical investigation, and regulation of drugs, biological products, new animal drugs, devices, and food additives, and representatives of patient and consumer advocacy

groups, health and technology professionals, and the regulated industries, shall publish in the Federal Register quantifiable performance standards for action by the Administration on—

"(i) applications or submissions (including petitions, notifications, or any other similar form of request) for review of a protocol, a product investigation, a product approval, a new use approval, a manufacturing change, a change in labeling, or any other form of regulatory action relating to the review of a product that is a new drug, biological product, new animal drug, device, food additive, or color additive and that is subject to premarket review or approval under this Act; and

"(ii) the scheduling of advisory committee meetings, and the action taken following an advisory committee recommendation, relating to the applications and submissions described in clause (i).

"(B) REVIEW OF PERFORMANCE STANDARDS.—The performance standards required in subparagraph (A) shall be reviewed annually by

the Secretary, and after consultation with experts in the development, clinical investigation, and regulation of drugs, devices, biological products, and food additives, and representatives of patient and consumer advocacy groups, health and technology professionals, and the regulated industries, may be revised, annually by the Secretary.

"(C) AGENCY OBJECTIVES.—The performance standards shall establish objectives for the Administration that—

"(i) expedite the clinical investigation of new drugs, devices, and biological products through closer collaboration between the Administration and new product sponsors;

NOT TAKEN

"(ii) expedite actions on applications for new drugs, devices, and biological products—

"(I) for an immediately life-threatening disease or condition; or

"(II) for any other serious condition if a new drug, device, or biological product provides therapy not available from other approved therapy or

offers significant improvement over other approved therapy;

"(iii) reduce backlogs on all applications with the objective of eliminating all backlogs by January 1, 1998;

"(iv) establish a schedule to bring the Administration into full compliance by July 1, 1998, with the time periods specified in this Act on all applications; and

"(v) improve the consistency and fairness of the Administration's regulatory process.

The Secretary shall also issue such other performance standards that the Secretary determines will contribute to the efficient, fair, and effective operation of the Administration.

"(D) ANNUAL REPORT.—The Secretary shall prepare and publish in the Federal Register for public comment an annual report—

"(i) providing detailed data on the actual performance of the Administration relating to each of the types of actions covered by this paragraph;

"(ii) comparing the performance of the Administration with the applicable per-

formance standard for each of the types of actions covered by this paragraph:

"(iii) describing any priorities established with respect to the types of actions covered by this paragraph, how such priorities are implemented, and the data on each priority category;

"(iv) analyzing any failure to achieve any of the standards;

"(v) identifying regulatory policies that have a significant impact on compliance with the standards and analyzing how such policies could be modified in order to achieve compliance with the standards; and

"(vi) setting forth a plan to achieve compliance with the standards that have not been met.

"(E) STATISTICAL INFORMATION.—The report described in subparagraph (D) shall include a full statistical presentation relating to all applications and petitions for a new drug, device, biological product, new animal drug, food additive, or color additive approved by the Administration during the year, taking into account the date of—

"(i) submission of any investigational application;

"(ii) any clinical hold;

"(iii) submission of the application or petition for approval;

"(iv) acceptance for filing of the application or petition for approval;

"(v) any unapprovable action;

"(vi) any approvable action; and

"(vii) the approval.".

SEC. 104. INTERAGENCY COLLABORATION.

Section 903(b) (21 U.S.C. 393(b)), as amended by section 103, is further amended by adding at the end thereof the following new paragraph:

"(4) INTERAGENCY COLLABORATION.—The Secretary shall implement programs and policies that will foster collaboration between the Food and Drug Administration, the National Institutes of Health, and other science-based agencies, to enhance the scientific expertise available to the Commissioner for the evaluation of emerging medical therapies, including complementary therapies, and advances in nutrition and food science.".

SEC. 105. INFORMATION SYSTEM.

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

NOT TAKEN
We suggested to information regarding the status and progress of their specific application notwithstanding any other provision of the law and if the Secretary determines that dissemination of information regarding the safety and effectiveness of the drug product would enhance the public health such information shall be available to the public

"SEC. 906. INFORMATION SYSTEM.

"The Secretary shall establish and maintain an information system to track the status and progress of each application or submission for the approval or clearance of a drug, biological product, new animal drug, device, or food additive (including a petition, notification, or other similar form of request) submitted to the Food and Drug Administration. The system shall permit access by the applicant or petitioner.".

SEC. 106. POLICY STATEMENTS.

Section 701(a) (21 U.S.C. 371(a)) is amended—

(1) by striking "(a) The" and inserting "(a)(1) The"; and

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

"(2)(A) Within 180 days of the date of enactment of Food and Drug Administration Performance and Accountability Act of 1996, the Secretary shall establish a procedure governing the development and use of all policy statements of general applicability that provide guidance relating to the conduct of preclinical or clinical investigations or other testing to support an application, petition, or notification under section 409, 505, 510(k), 512, 515,

or 721 or that provide guidance on the submission of applications, petitions, or notifications under section 409, 505, 510(k), 512, 515, or 721 (including any guidance, guideline, points-to-consider, protocol, recommendation, or similar document regardless of the form or designation). The procedure shall provide an opportunity for affected persons to (i) participate in the development ~~and~~ or continued use of a policy statement by sharing expertise, experience, or providing comment before the policy statement is issued or (ii) by providing an opportunity to comment ~~adopted and~~ after the policy statement is ~~implemented~~ issued, ~~except that if the Secretary determines that there is a public health need to issue the policy statement immediately, the Secretary shall provide an opportunity for affected persons to provide comment promptly after the policy statement is issued.~~

NOT TAKEN

"(B) The Secretary shall establish a procedure for the periodic compilation and publication of all policy statements of general applicability (including any guideline, points-to-consider, protocol, recommendation, or similar document regardless of the form or designation).".

SEC. 107. SCIENTIFIC REVIEW GROUPS.

Section 904 (21 U.S.C. 394) is amended—

(1) by striking "Without" and inserting "(a) IN GENERAL.—Without"; and

(2) by adding at the end thereof the following new subsections:

"(b) DELEGATION OF APPOINTMENT AUTHORITY.—The Commissioner may not delegate the appointment and oversight authority granted under subsection (a).

"(c) MEMBERSHIP AND MEETING REQUIREMENTS.—

"(1) SCOPE.—The Commissioner shall consult with a scientific review group in determining the matters that the group will consider and in establishing an appropriate agenda with respect to the determination of the matters.

"(2) ~~NONVOTING~~ OTHER MEMBERS.—A scientific review group shall include a nonvoting industry representative and a ~~nonvoting public representative~~ voting consumer representative, including a patient or patient advocate who represents the perspective and reports back to the affected community.

"(3) NOTIFICATION OF SCOPE OF DISCUSSION.—To the extent feasible, the specific matters and questions to be discussed at a meeting of a scientific review group shall be publicly announced and published in the Federal Register at least 30 days prior to the date of the meeting.

"(4) TERMS.—A member of a scientific review group shall serve for a term of 3 years, which may be renewed for a second term. An individual may serve on more than one scientific review group. The chairperson of a scientific review group shall be a

TAKEN

Wellstone Amendment (#15)

passed by unanimous consent

AMENDMENT NO. 15 Calendar No. _____

Purpose: To ensure that consumers retain their role as voting members on scientific review groups.

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. WELLSTONE:

Viz:

On page 12, line 12 strike "Nonvoting" and insert "Other".

On page 12, line 14 strike "nonvoting public representative" and insert "voting consumer representative, including a patient or patient-nominated individual, who represents the perspective of and reports back to the affected community."

member who has served at least 3 years. The term of the chairperson may be renewed for not more than 3 terms.

"(5) TRAINING.—Prior to service on a scientific review group, a member of the group shall be given adequate education and training relating to the responsibilities of the member.

"(6) FREQUENCY OF MEETINGS.—The Secretary shall take whatever action is necessary to ensure that regular meetings are held by scientific review groups, at appropriate intervals and for a sufficient length of time. The meetings shall occur not less than 3 times each year unless there are reasons for fewer meetings.

"(d) ACCESS TO INFORMATION; PARTICIPATION BY INTERESTED PERSONS IN MEETINGS.—

"(1) IN GENERAL.—When a scientific review group reviews a product application, petition, or notification for approval or clearance, or some part thereof, submitted under section 409, 505, 510(k), 513(f), 512, 515, or 721, the Secretary shall provide the product sponsor with copies of all documents provided to the members of the scientific review group in preparation for a meeting. The Secretary shall provide such documents to the product sponsor

NOT APPROVED

except documents exempt from public disclosure pursuant to 5USC 552(b)(4) and (b)(7)

at the same time such documents are given to the members of the scientific review group. Before the meeting, the product sponsor shall have an opportunity to submit documents to the members of the scientific review group in response to the Secretary's documents. The product sponsor shall provide the response to the Secretary, who shall immediately provide copies to the members of the scientific review group.

"(2) PARTICIPATION IN MEETINGS.—Any meetings of a scientific review group shall provide adequate time for initial presentations and for response to any differing views and shall encourage free and open participation by all interested persons.

"(c) FDA ACTIONS.—Within 60 days after the date a scientific review group makes its conclusions and recommendations on any matter under review of the group, the Food and Drug Administration official responsible for the matter shall review the conclusions and recommendations of the group, and (1) shall make a final determination on the matter, and shall notify the affected persons of the determination in writing and, if the determination differs from the conclusions and recommendations of the group, shall include the reasons for the difference, or (2) notify the affected persons that a decision has not been made and the time by which a decision will be made.

NOT TAKEN

SEC. 108. APPEALS WITHIN THE FOOD AND DRUG ADMINISTRATION.

Chapter IX (21 U.S.C. 391 et seq.), as amended by section 105, is further amended by adding at the end thereof the following new section:

"SEC. 907. APPEALS WITHIN THE FOOD AND DRUG ADMINISTRATION.

"(a) EMPLOYEE DECISIONS.—The Secretary shall by regulation establish a system for the appeal within the Food and Drug Administration of any decision by an employee of the Food and Drug Administration, except that this subsection shall not apply to decisions involving formal administrative or judicial proceedings. As the final stage in the internal appeal system, the Secretary shall provide for the right to request an evaluation by an appropriate scientific review group of a final decision of the Secretary on an appeal involving a significant scientific issue. Upon receipt of such a request, the Secretary shall refer the request to the chairperson of the appropriate scientific review group, or a member designated by the chairperson, who shall review the request and determine whether the scientific review group should conduct an evaluation. The Secretary shall make publicly known the existence of the internal appeal system and the procedures for an internal appeal.

"(b) REVIEW BY SCIENTIFIC REVIEW GROUP.—

"(1) IN GENERAL.—The product sponsor or applicant shall have the right to request an evaluation by an appropriate scientific review group established under section 904 of any ~~significant scientific issue pending before, or~~ significant scientific decision made by, the Secretary under this Act. An appropriate scientific review group, or representative there of, shall review the request and determine whether to conduct an evaluation within 30 days after the date the request is received by the Secretary.

"(2) SCOPE.—The significant scientific ~~issues~~ decisions a scientific review group may evaluate for a request under subsection (a), may include, but not be limited to, matters involving a decision by the Secretary not to permit a clinical investigation to begin or to continue, a refusal by the Secretary to file an application, a protocol design, and decisions relating to a pending application, petition, or notification, where the same issue has not previously been reviewed by a scientific review group.

"(3) TIME LIMITATION.—If a scientific review group agrees to conduct an evaluation on an issue under paragraph (1), the evaluation shall be scheduled for the next meeting of the group.

"(c) ADDITIONAL INFORMAL AND FORMAL PROCEDURES.—

"(1) IN GENERAL.—For purposes of obtaining conclusions and recommendations regarding the resolution of any significant scientific dispute, the Secretary is authorized to use such additional informal and formal procedures as may be considered useful. The procedures may include, but not be limited to, the use of—

"(A) panels of qualified Food and Drug Administration officials;

"(B) panels of qualified government employees who are not employees of the Food and Drug Administration; and

"(C) outside mediators and arbitrators who are not government employees.

"(2) APPLICATION OF FACA.—The Federal Advisory Committee Act (5 U.S.C. App) shall not apply to a panel described in paragraph (1).

"(d) REVIEW OF RECOMMENDATIONS.—Within 60 days after any matter that is presented for resolution pursuant to this section has been the subject of conclusions and recommendations, the Food and Drug Administration official responsible for the matter shall personally review the conclusions and recommendations, and shall; (1) make a final determination on the matter, and notify the parties of the determination in writing, ~~and if the determination differs~~ or, (2) notify the parties of the reason why a decision has not been made and the time by which a decision will be made.

NOT TAKEN

from the conclusions and recommendations, the reasons for the difference.".

TITLE II—EXPEDITED ACCESS TO PRODUCTS FOR SERIOUSLY ILL PATIENTS

SEC. 201. SHORT TITLE.

This title may be cited as the "Patient Rights Regulatory Reform Act of 1996".

SEC. 202. ACCESS TO UNAPPROVED THERAPIES.

Chapter V (21 U.S.C. 351 et seq.) is amended by adding at the end thereof the following new section:

"SEC. 543. EXPANDED ACCESS TO UNAPPROVED THERAPIES AND DIAGNOSTICS.

"(a) IN GENERAL.—Any person, through a licensed health care practitioner or licensed health care professional, acting in accordance with state law may request from a manufacturer or distributor, and any manufacturer or distributor may provide to a person after compliance with the provisions of this section, an investigational drug (including a biological product) or investigational device for the diagnosis, monitoring, or treatment of a serious disease or condition, an immediately life-threatening or seriously debilitating disease or condition, and any other disease or condition designated by the Secretary as appropriate for expanded access under this section by the person if—the Secretary determines

"(1) the person has no comparable or satisfactory alternative therapy available to treat, diagnose, or monitor the disease or condition;

"(2) the risk to the person from the investigational drug or device is not greater than the risk from the disease or condition; and

"(3) an exemption for a drug or device is in effect under a regulation promulgated pursuant to section 505(i) or 520(g) and the sponsor and investigators comply with such regulation.

"(b) PROTOCOLS.—A manufacturer or distributor may submit to the Secretary one or more expanded access protocols covering expanded access use of a drug or device described in subsection (a). The protocols shall be subject to the provisions of section 505(i) for a drug and section 520 (g) for a device and may include any form of use of the drug or device outside a clinical investigation, prior to approval of the drug or device for marketing, including but not limited to protocols for treatment, use, parallel track, single patient protocols, emergency use, and uncontrolled trials.

"(c) FEES.—A manufacturer or distributor may charge for an investigational drug or device under an expanded access protocol, but the price of the drug or device may not be more than that necessary to recover the costs

of manufacture and handling for the drug or device, and the Secretary shall be notified in advance of assessing any such charges.

"(d) NOTIFICATION OF AVAILABILITY.—The Commissioner shall inform national, State, and local medical associations and societies, voluntary health associations, and other appropriate persons about the availability of investigational drugs and devices that are available under expanded access protocols pursuant to this section. Such notification shall identify—

"(1) the investigational product;

"(2) the expanded access use; and

"(3) the name and address of the manufacturer or distributor that is providing the investigational product for expanded access use.".

SEC. 203. EXPANDING HUMANITARIAN USE OF DEVICES.

Section 520(m) (21 U.S.C. 360j(m)) is amended—

(1) in paragraph (2), by inserting at the end thereof the following flush sentences:

"The request shall be in the form of an application to the Secretary. Within ~~30~~ 180 days of the date of the receipt of the application, the Secretary shall issue an order approving or denying the application.";

(2) by striking paragraph (5); and

(3) by striking paragraph (6).

Sec. 407

NOT TAKEN

(e) TERMINATION- FDA may, at any time, terminate expanded access under subsect. (a) if the requirements under this section are no longer met.

If within 120 days of enactment final regulations are not been issued implementing section 522

This provision shall expire when final regulations are issued implementing Section 522.

SEC. 204. EXPEDITING APPROVAL OF NEW DRUGS, BIOLOGICS, AND MEDICAL DEVICES FOR SERIOUS CONDITIONS.

(a) NEW DRUGS.—Section 505(c)(1) (21 U.S.C. 355(c)(1)) is amended by adding at the end thereof the following flush sentence:

"In a case in which an application is submitted under section 505(b)(1) for a new drug, or section 351(a) of the Public Health Service Act for a biological product, that is intended for use for an immediately life-threatening or serious disease or condition and that provides therapy or diagnosis not available from another approved drug or biological product or offers significant improvement over another approved drug or biological product, the Secretary shall approve or deny approval of the application within 180 days after the receipt of the application.".

Kennedy Amendment (#2)

CHANGED → 180

(b) PREMARKET APPROVAL.—

(1) AMENDMENT.—Section 515(d)(1)(A) (21 U.S.C. 360e(d)(1)(A)) is amended by adding at the end thereof the following flush sentence:

"For an application submitted under this subsection for a device for a life-threatening disease or condition, a seriously debilitating disease or condition, or for any other serious disease or condition that provides therapy or diagnosis not available from another approved device or offers

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, change "120 days" to "180 days."
Page 22, l. 10, change "120 days" to "180 days."

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

"(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) 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, l. 1-4.

Section 901 and 902. Food and Regulatory Reform.

~~Delete p. 118, l. 5-25, and p 119, l. 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".

a significant improvement over another approved device, the Secretary shall take such action within 180 days.".

(2) EFFECTIVE DATE.—The amendment made by paragraph (1) shall take effect on July 1, 1998.

TITLE III—REVITALIZING THE INVESTIGATION OF NEW PRODUCTS

SEC. 301. SHORT TITLE.

This title may be cited as the "Investigational Products Regulatory Reform Act of 1996".

SEC. 302. TIMELY REVIEW AND REASONABLE DATA REQUIREMENTS FOR CLINICAL RESEARCH ON DRUGS AND BIOLOGICAL PRODUCTS.

Section 505(i) (21 U.S.C. 355(i)) is amended—

(1) by striking "(i) The" and inserting "(i)(1) The";

(2) by redesignating paragraphs (1), (2), and (3) as subparagraphs (A), (B), and (C), respectively; and

(3) by adding at the end thereof the following new paragraphs:

"(2)(A) A clinical investigation of a new drug (including a biological product) may begin 30 days after the date the Secretary receives from the sponsor a notification containing information about the drug and the clinical inves-

tigation unless, prior to the 30-day period, the Secretary informs the sponsor ~~in writing~~ that the investigation may not begin, and specifies the basis for the decision, ~~and the~~ within an additional 30 days, the Secretary shall specify the deficiencies and the information needed in order for the clinical investigation to commence, in writing

NOT TAKEN

"(B) Within 1 year after the date of enactment of the Food and Drug Administration Performance and Accountability Act of 1996, the Secretary, after consultation with experts in the development, clinical investigation, and regulation of drugs, physicians and other health care practitioners and representatives of patient and consumer advocacy groups and the regulated industries, shall publish in the Federal Register criteria for the type and amount of information relating to the safety of an investigational drug to be included in a notification described in subparagraph (A), taking into account the recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The Secretary shall periodically review, and may revise, the criteria.

"(C) The Commissioner shall establish a mechanism to ensure the fair and consistent application of safety standards for clinical investigations.

"(3)(A) The Secretary may place a clinical hold on any ongoing clinical investigation if the Secretary deter-

mines that such action is necessary for the protection of human subjects, or for other reasons set forth by the Secretary in regulations. NOT TAKEN

"(B) If the Secretary places a clinical hold on a clinical investigation, the Secretary shall immediately advise the applicant for such investigation in writing of such action, and provide such applicant an opportunity to confer within 10 working days of the receipt of such a communication to discuss the clinical hold. Within 10 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 removed shall receive a decision, in writing and specifying the reasons therefor, within 20 working days of the receipt of the request.".

SEC. 303. TIMELY REVIEW AND REASONABLE DATA REQUIREMENTS FOR CLINICAL RESEARCH ON DEVICES.

Section 520(g) (21 U.S.C. 360j(g)) is amended by adding at the end thereof the following new paragraphs:

"(6) The procedures and conditions prescribed pursuant to paragraph (2)(A) shall be subject to subparagraphs (B) and (C) of section 505(i)(2), except that the provision of subparagraph (B) of such section relating to the consideration of the recommendations of the International Conference on Harmonization of Technical Requirements for

Registration of Pharmaceuticals for Human Use shall not apply to this paragraph.

"(7) The Secretary shall, within 120 days of the date of enactment of this paragraph, by regulation amend the content of parts 812 ~~and 813~~ of title 21 of the Code of Federal Regulations to update the procedures and conditions under which devices intended for human use may upon application be granted an exemption from certain requirements under this Act. The regulation shall—

"(A) permit developmental changes in devices, including manufacturing changes, in response to information collected during an investigation without requiring an additional approval of an application for an investigational device exemption or the approval of a supplement to the application, if the sponsor determines that, prior to making any changes, the changes do not constitute a significant change in design or a significant change in basic principles of operation; and

"(B) permit, without approval of a supplement to an application for an investigational device exemption, changes or modifications to clinical protocols that do not affect the validity of data or information resulting from the completion of an approved

protocol so long as such changes do not affect any patient protection provisions of the protocol.".

SEC. 304. COLLABORATIVE RESEARCH DESIGN.

Chapter V (21 U.S.C. 351 et seq.), as amended by section 202, is further amended by adding at the end thereof the following new section:

"SEC. 544. COLLABORATIVE RESEARCH DESIGN.

"(a) REVIEW OF DESIGN.—

"(1) REQUEST.—Any person who intends to sponsor a preclinical or clinical investigation of a drug (including a biological product) or device may request a meeting with the Secretary to review the design of one or more protocols for the preclinical or clinical testing of the drug or device.

"(2) FORM.—A request described in paragraph (1) shall be in writing and shall include any protocol for which the review is requested. A protocol shall be designed so that the fewest number of patients and procedures necessary to obtain data necessary for the approval of a new drug, biological product, or device are required, consistent with public health and safety.

NOT CLEAR [illegible] We don't know what this means [illegible] should be deleted or clarified [illegible] not to limit [illegible] necessary [illegible] safety and efficacy

"(3) WRITTEN REVIEW.—The Secretary shall meet with the person within ~~30~~ 60 days of the request and shall provide to the person a written review of

This is not [illegible] by PDUFA fees. Need longer [illegible] to [illegible] meet PDUFA requirement

the protocol, including any deficiencies in the protocol. A written summary shall be made of the meeting. The summary shall include the written review of the protocol and, after agreement by the person and agency shall be made part of the product review file maintained by the Food and Drug Administration.

"(b) MODIFICATION OF AGREEMENTS.—Any agreements reached through meetings with respect to the design of any protocol under subsection (a) may be modified only in accordance with the following provisions:

"(1) At any time by mutual consent of the sponsor and the Secretary.

"(2) By the sponsor unilaterally, if the change is to a protocol and the change is one that would not require the approval of the Secretary under the applicable regulations.

"(3) By the Secretary unilaterally, if the change is made—

"(A) by the director of the office of the Food and Drug Administration responsible for regulating the drug or device that is the subject of the agreement, who may not delegate such responsibility; and

"(B) in writing and specifying the scientific or clinical need therefor.

"(e) APPEALS.—Any person requesting a meeting under subsection (a) may appeal the decision of the Secretary to disapprove or modify an agreement or protocol under section 907.

"(d) GUIDELINES AND LIMITATION.—The Secretary shall issue guidelines to implement this section. Such guidelines shall address the responsibilities of the person requesting the meeting, as well as the Secretary's responsibilities. Repeated failure to follow the guidelines may be grounds for a refusal by the Secretary to meet with a person requesting a meeting under this section.".

TITLE IV—EFFICIENT, ACCOUNTABLE, AND FAIR PRODUCT REVIEW

SEC. 401. SHORT TITLE.

This title may be cited as the "Product Review Regulatory Reform Act of 1996".

SEC. 402. THE CONTENT AND REVIEW OF AN APPLICATION.

Chapter VII (21 U.S.C. 371 et seq.) is amended by adding at the end thereof the following new subchapter:

"SUBCHAPTER D—REVIEW OF APPLICATIONS

"SEC. 741. CONTENT AND REVIEW OF AN APPLICATION.

"(a) IN GENERAL.—This section applies to any application, petition, or notification submitted for approval or clearance of a food additive, new drug, device, biological

product, new animal drug, animal feed bearing or containing a new animal drug, or color additive.

"(b) FILING REQUIREMENTS.—Within 60 days of the date of enactment of this section, the Commissioner shall establish and publish in the Federal Register a mechanism to ensure the fair and consistent application of filing requirements.

"(c) CLASSIFICATION OF A PRODUCT.—Within 60 days of the receipt of a written request of an applicant for information respecting the classification of a product as a drug, biological product, or device or the component of the Food and Drug Administration that will regulate the product (including a request respecting a combination product subject to section 503(g)), the Secretary shall provide the person a written statement of the classification of the product or the component of the Food and Drug Administration that will regulate the product. The Secretary's statement shall be binding and may not be changed by the Secretary except with the written agreement of the person who submitted the request. If the Secretary does not provide the statement within the 60-day period, the classification and component designated by the person submitting the request shall be final and binding and may not be changed by the Secretary except with the written agreement of the person.

"(d) REASONABLE DATA REQUIREMENTS.—Within 1 year after the date of enactment of the Food and Drug Administration Performance and Accountability Act of 1996, the Secretary, after consultation with experts in development and testing of products that are drugs, biological products, devices, and food additives, experts in the regulation of such products, consumer and patient advocacy groups, and the regulated industries, shall publish in the Federal Register criteria for the type and amount of information relating to safety and effectiveness to be included in an application for the approval of a product, or a new use of an approved product, described in subsection (c). In developing the criteria for drugs, the Secretary shall consider any recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.".

SEC. 403. CONTRACTS FOR EXPERT REVIEW.

Chapter VII (21 U.S.C. 371 et seq.), as amended by section 402, is further amended by adding at the end thereof the following new section:

"SEC. 742. CONTRACTS FOR EXPERT REVIEW.

"(a) IN GENERAL.—

"(1) AUTHORITY.—The Secretary may contract with outside organizations and individuals, with expertise in relevant disciplines, to review, evaluate,

and make conclusions and recommendations to the Secretary on parts or all of any application (including a petition, notification, or other similar request for Food and Drug Administration action). The Secretary shall retain full authority to make determinations with respect to the approval or disapproval of any product, or the classification of a device under section 513(f)(1). Any such contract shall be subject to the requirements of section 708. Funds obtained under part 2 of subchapter C may be used for external review of any drug (including a biological product) for which a user fee was paid.

"(2) INCREASED EFFICIENCY AND EXPERTISE THROUGH CONTRACTS.—The Secretary shall use the authority granted in paragraph (1)—

"(A) for the review of categories of indirect food additive petitions and submissions under section 510(k);

"(B) whenever contracts will improve the efficiency, timeliness, and quality of the review of applications, petitions, and notifications for the approval or clearance of new drugs, new animal drugs, biological products, devices, and food additives; and

"(C) whenever contracts will increase the scientific and technical expertise necessary to keep informed of emerging new therapies and technologies posing significant new scientific and technical issues.

The Secretary shall retain full authority to make determinations with respect to the approval or disapproval of a product, or the classification of a device under section 513(f)(1).

"(b) ELIGIBILITY REQUIREMENTS.—Within ~~90 days~~ one year of the date of enactment of this section, the Secretary shall by regulation establish the requirements that an organization shall meet to be eligible to conduct reviews under subsection (a). Such regulations shall provide for the protection of confidential or proprietary information and shall provide for protection against conflicts of interest.

"(c) REVIEW OF EXPERT'S EVALUATION.—

"(1) IN GENERAL.—Subject to paragraph (2), the Food and Drug Administration official responsible for any matter for which expert review is used pursuant to this section shall personally review the conclusions and recommendations of the expert review organization or individual and shall make a final decision regarding the matter ~~under review~~ contracted out

within 60 days after receiving the conclusions and recommendation.

"(2) LIMITATION.—A final decision under paragraph (1) shall be made within the applicable prescribed time period for review of an application as set forth in this Act.

"(d) REPORT TO CONGRESS.—Within 2 years of the enactment of this section, the Secretary shall provide to Congress a report on the use of the authority to contract with outside individuals and organizations for expert reviews. Such report shall include an evaluation of the extent to which such contracting improves the efficiency of review and the expertise available to the agency.".

SEC. 404. PROMPT AND EFFICIENT REVIEW.

Chapter VII (21 U.S.C. 371 et seq.), as amended by section 403, is further amended by adding at the end thereof the following new section:

Kennedy Amendment (17)

"SEC. 743. PROMPT AND EFFICIENT REVIEW.

"(a) IN GENERAL.—The provisions of this section shall apply to any of the following applications, petitions, and notifications:

"(1) A petition for the issuance of a regulation prescribing the safe use of a human food additive or animal feed additive under section 409.

"(2) An application for approval of a new drug under section 505.

"(3) An application for approval of a new animal drug or an animal feed bearing or containing a new animal drug under subsection (b) or (m) of section 512, respectively.

"(4) A notification submitted under section 510(k) for classification of a device.

"(5) An application for approval of a device under section 515. PMA

"(6) An petition for issuance of a regulation for the listing of a color additive under section 721.

"(b) REVIEW PROCEDURES AND POLICIES.—The Secretary shall establish procedures and policies to facilitate a collaborative review process between the Food and Drug Administration and the applicant with respect to an application, petition, or notification described in subsection (a). As part of this collaborative process—

"(1) open, informal, and prompt communications shall be encouraged;

"(2) meetings (except meetings with respect to submissions to determine substantial equivalence of a device to a predicate device) shall be held ~~before the expiration of one-half of the statutory time period for review of the application and before the ex-~~

NOT TAKEN

at the request of the applicant,
1) one pre-submission meeting
2 one half-way through
3 [illegible] throughout, [illegible]

~~piration of three-quarters of such period, or within 15 days after a scientific review group has convened and made recommendations on an application, unless the Food and Drug Administration and the applicant determine that a meeting is unnecessary; and~~

"(3) by mutual consent, the agency and the applicant or petitioner may establish a different schedule for meetings required under paragraph (2);

"(4) the Secretary shall, prior to the meetings described in paragraph (2), present to the applicant in writing a description of any deficiencies of the application identified to date with respect to those deficiencies, and ~~the information necessary to bring~~ what would be necessary to remedy them. the application ~~into a form that would require approval~~.

NOT TAKEN

The Secretary and the applicant may agree to supersede any procedures and policies adopted under this section and the requirements of paragraphs (2) and (3). Any such agreement shall be in writing, and shall specify how any such agreement shall be modified or set aside.

~~"(c) APPROVAL, DISAPPROVAL, AND CLASSIFICATION.—~~

"(1) CONSIDERATION OF INTERNATIONAL APPROVALS.—Beginning July 1, 1998, if the Secretary fails to meet a time period for action on an application or notification for the approval or clearance of a new drug, device, biological product, or new animal

NOT DELETED

drug that offers a significant improvement over existing approved products or a petition for the approval of a direct food additive that has the potential to make foods more wholesome and contribute to a healthier diet, and such a product has been approved for marketing in the European Union or the United Kingdom, at the request of the applicant or petitioner, the Secretary shall within 30 days either approve or disapprove the application, notification, or petition and notify the person who submitted the application, notification, or petitioner in writing of that decision. In the case of a disapproval, or a determination of not substantially equivalent such notification shall set forth the reasons for such actions.

"(2) APPEAL.—A person whose application, notification, or petition has been disapproved or found not substantially equivalent under paragraph (1) may obtain judicial review under—

"(A) section 505(h) for the disapproval of a new drug under paragraph (1);

"(B) section 517 for the disapproval of a device or a determination of not substantially equivalent relating to a device under paragraph (1);

"(C) chapter VII of title 5, United States Code, for the disapproval of a license for a biological product under paragraph (1);

"(D) section 512(h) for the disapproval of a new animal drug under paragraph (1); and

"(E) section 409(g) for the disapproval of a direct food additive under paragraph (1).

"(d) CONTRACTS FOR EXPERT REVIEW.—

"(1) IN GENERAL.—Beginning July 1, 1998, if the Secretary in any fiscal year fails to meet the statutory time period for action on an application, notification, or petition for at least 95 percent of the applications, notifications, and petitions in a particular product category, the Secretary shall in the following fiscal year, with the consent of the persons who submit applications, notifications, or petitions, contract with expert individuals and organizations under section 742 to review new applications, notifications, and petitions and review applications, notifications, and petitions for which the Secretary has failed to meet the statutory time period for action for the particular product category.

"(2) APPROVAL.—If an individual or organization selected to conduct a review under paragraph (1) recommends the approval or clearance of an ap-

NOT DELETED

NOT CHANGED

We suggested language that if the Secretary fails to meet the deadlines, the Secretary must report to Congress why the deadlines were not met and what actions were being taken to enable meeting the deadlines

Contract but hammer

plication, notification, or petition described in paragraph (1), the Secretary shall, within 60 days of receiving the determination of the individual or organization but not later than the time period for review set forth in this Act, either approve or disapprove the application or petition, and, in the case of a disapproval, notify the applicant or petitioner in writing of the basis for the disapproval. An applicant or petitioner may appeal an adverse decision under subsection (e)(2).".

SEC. 405. ~~GOOD MANUFACTURING PRACTICE INSPECTION.~~ INSPECTIONS BY ACCREDITED ORGANIZATIONS

Chapter VII is (21 U.S.C. 371 et seq.), as amended by section 404, is further amended by adding at the end thereof the following new section:

"SEC. 744. GOOD MANUFACTURING PRACTICE INSPECTION.

"(a) IN GENERAL.—In order to comply with inspection requirements of this Act, the Secretary may accredit organizations to conduct inspections under section 704 to evaluate compliance of a manufacturer with applicable requirements including requirements for good manufacturing practice.

"(b) ELIGIBILITY REQUIREMENTS.—If the Secretary elects to accredit organizations to conduct inspections under section 704, the Secretary shall by regulation, within ~~90 days~~ one year of the date of enactment of this section, establish the requirements that an organization shall meet to

be eligible to be accredited to participate as a qualified organization to conduct inspections under subsection (a). Such regulation shall provide for the protection of confidential or proprietary information and shall provide for protection against conflicts of interest.

NOT TAKEN

"(c) ACCREDITATION.—Within 90 days after the date the Secretary receives an application for accreditation under this section, the Secretary shall review the application and determine whether an applicant is in compliance with the requirements established under this section. Within the 90-day period, the Secretary shall grant accreditation or shall deny accreditation and specify in writing the reasons for the denial and the requirements that shall be met to obtain accreditation.

"(d) REVOCATION OF ACCREDITATION.—The Secretary may at any time revoke accreditation granted under subsection (c) for failure to comply with the requirements established under this section after specifying in writing the reasons for the revocation and the requirements that shall be met to retain accreditation and after an ~~informal hearing~~ opportunity to present views on the revocation.

NOT TAKEN

"(e) INSPECTIONS.—Any organization accredited under this subsection that conducts an inspection under this subsection at the request of the Secretary shall—

"(1) apply all relevant principles of good manufacturing practice established in this Act and in regulations promulgated by the Secretary;

"(2) provide to the Secretary and the manufacturer within 30 days after the completion of the inspection an adequate report of the findings of the inspection; and

"(3) immediately provide the Secretary with a notice of any condition that could cause or contribute to a significant threat to the public health.".

SEC. 406. ENVIRONMENTAL IMPACT REVIEW.

Chapter VII (21 U.S.C. 371 et seq.), as amended by section 405, is further amended by adding at the end thereof the following new section:

"SEC. 745. ENVIRONMENTAL IMPACT REVIEW.

"Notwithstanding any provision of other law, no action by the Secretary pursuant to this Act shall be subject to an environmental assessment, an environmental impact statement, or other environmental consideration unless the director of the office responsible for the action demonstrates, in writing and specifying the basis therefore—

"(1) that there is a reasonable probability that the environmental impact of the action is sufficiently substantial and within the factors that the Secretary is authorized to consider under this Act; and

NOT CHANGED

"(2) that consideration of the environmental impact will directly affect the decision on the action.".

SEC. 407. INFORMATION EXCHANGE.

Chapter VII (21 U.S.C. 371 et seq.), as amended by section 406, is further amended by adding at the end thereof the following new sections:

"SEC. 746. DISSEMINATION OF TREATMENT INFORMATION ON DRUGS AND BIOLOGICAL PRODUCTS.

Strike Entire Section

"(a) DISSEMINATION OF TREATMENT INFORMATION.—

"(1) IN GENERAL.—Notwithstanding sections 301(d), 502(f), 505, and 507 and section 351 of the Public Health Service Act (42 U.S.C. 262), and subject to the requirements of paragraph (2) and subsection (b), a manufacturer may disseminate to any person that is a health care practitioner or other provider of health care goods or services, a pharmacy benefit manager, a health maintenance organization or other managed health care organization, or a health care insurer or governmental agency, written information, concerning—

Kassebaum successfully moved to delete this entire section— For further consideration by the committee separate from this bill [illegible] [illegible]

"(A) a treatment use for an investigational new drug or an investigational biological prod-

uct approved by the Secretary for such treatment use; or

"(B) the safety, effectiveness, cost, benefit, use (whether or not such use is contained in the official labeling), or any other attribute (including comparisons to another drug, biological product, or alternate therapy), of a new drug (including any antibiotic drug) or a biological product for which an approval of an application filed under section 505(b), 505(j), or 507, or a product license issued under the Public Health Service Act, is in effect.

"(2) REQUIREMENTS.—A manufacturer may disseminate information under paragraph (1)(B) only if —

"(A) the information is an unabridged—

"(i) reprint or copy of a peer-reviewed article from a scientific or medical journal that is published by an organization that is not controlled by the pharmaceutical industry; or

"(ii) reference textbook that is published by an organization that is not controlled by the pharmaceutical industry; or

"(B) the information relates to a use of a drug, or reflects the safety, effectiveness, cost, benefit, or other attribute of a drug, that is recognized under Federal law for purposes of third-party coverage or reimbursement, and the information is part of a disease management program or treatment guideline.

"(3) SPECIAL RULE.—If concurrent or new information with respect to a use of a drug or biological product (including new information relating to safety or efficacy of the off-label use of a drug or biological product) is published with respect to any information disseminated under paragraph (1) and (2), the manufacturer that disseminated the information under paragraph (1) shall notify the Secretary with respect to the new information. If the Secretary determines that the new information demonstrates that a new drug or biological product presents a significant risk to public health, the Secretary shall, in consultation with the manufacturer, take such appropriate action as the Secretary determines necessary to ensure public health and safety.

"(4) SPONSORED RESEARCH.—If a manufacturer has sponsored or underwritten research that results in information described in paragraph (2)(A)(i), then only such manufacturer may distribute the information under this section.

"(b) DISCLOSURE STATEMENT.—In order to afford a full and fair evaluation of the information described in subsection (a), a manufacturer disseminating the information shall include—

"(1) a prominently displayed statement that discloses—

"(A) if applicable, that the new use or other attribute of a drug or biological product described in subparagraph (B) of subsection (a)(1) and the information with respect to the new use or other attribute is different from the information in the official labeling;

"(B) if applicable, that the information is being disseminated at the expense of the manufacturer;

"(C) if applicable, the name of any authors of the information being disseminated who are employees of or consultants to the manufacturer; and

"(D) the official labeling for the drug or biological product, or in the case of a treatment use of an investigational drug or biological product, the investigator brochure and all updates thereof; and

"(2) a statement on whether there are other articles that have been previously published about any off-label use covered by the information disseminated.

"(c) DEFINITIONS.—As used in this section:

"(1) HEALTH CARE PRACTITIONER.—The term 'health care practitioner' means a medical provider that is licensed to prescribe a drug or biological product for the treatment of a disease or other medical condition.

"(2) REFERENCE TEXTBOOK.—The term 'reference textbook' means a reference publication that—

"(A) has not been written, edited, excerpted, or published specifically for, or at the request of, a manufacturer of a drug or biological product;

"(B) has not been edited or significantly influenced by a manufacturer of a drug or biological product;

"(C) is not solely distributed through a manufacturer of a drug or biological product, but is generally available in bookstores or other distribution channels where medical textbooks are sold; and

"(D) does not focus on any particular drug or biological product of a manufacturer that disseminates information under subsection (a), and does not have a primary focus on off-label uses of drugs or biological products that are marketed or under investigation by a manufacturer supporting the dissemination of the information.

"(3) SCIENTIFIC OR MEDICAL JOURNAL.—The term 'scientific or medical journal' means a scientific or medical publication—

"(A) that is published by an organization that—

"(i) has an editorial board and that utilizes experts, who have demonstrated expertise in the subject of the article under review and who are not employees of the organization, to review and objectively select, reject, or provide comments about proposed articles; and

"(ii) has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors or contributors involved with the journal or organization;

"(B) whose articles are peer-reviewed and published in accordance with the regular peer-review procedures of the organization;

"(C) that is generally recognized to be of national scope and reputation;

"(D) that is indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health; and

"(E) that presents materials that are truthful and not misleading.

"(d) SPECIAL RULE.—In the case of a professional disagreement between the Secretary and a manufacturer who disseminates information with respect to the application of section 502(a), the Secretary may not use section 502 to prohibit the dissemination of information in the types of circumstances and under the conditions set forth in subsections (a) and (b).

"SEC. 747. DISSEMINATION OF INFORMATION ON DEVICES.

"(a) DISSEMINATION OF INFORMATION.—Notwithstanding sections 301, 501(f), 501(i), 502(a), 502(f), and 502(o), or any other provision of law, and subject to subsections (b) and (c), a manufacturer may disseminate to any person that is a health care practitioner or other provider of health care goods or services, a pharmacy benefit manager, a health maintenance organization or other

managed health care organization, or a health care insurer or governmental agency, written or oral information (including information exchanged at scientific and educational meetings, workshops, or demonstrations) relating to a use, whether or not the use is described in the official labeling, of a device produced by a manufacturer registered pursuant to section 510.

"(b) DISCLOSURE STATEMENTS AND REQUIREMENTS.—

"(1) DISCLOSURE STATEMENTS.—To the extent practicable, the requirement with respect to a statement of disclosure under subsection (b) of section 746 shall apply to the dissemination of written and oral information under this section, except that this paragraph shall not apply to the dissemination of written or oral information with respect to the intended use described in the labeling of a device.

"(2) ADDITIONAL REQUIREMENTS.—A manufacturer may disseminate information under subsection (a) only if—

"(A) the information is an unabridged—

"(i) reprint or copy of a peer-reviewed article from a scientific or medical journal

that is published by an organization that is not controlled by the medical device industry; or

"(ii) recognized reference textbook that is published by an organization that is independent of the medical device industry;

"(B) the information has been approved by a continuing medical education accrediting agency that is independent of the medical device industry as part of a scientific or medical educational program approved by such agency;

"(C) the information relates to a use of a device or reflects the safety, effectiveness, cost, benefit, or other attribute of a device that is recognized under Federal law for purposes of third-party reimbursement and the information is part of a disease management program or treatment guideline; or

"(D) the oral or written information is—

"(i) part of an exchange of information solely among health care practitioners, health care reimbursement officials, and the industry;

"(ii) exchanged for educational or scientific purposes; and

"(iii) presented at continuing medical education programs, seminars, workshops, or demonstrations.

"(3) SPECIAL RULE.—If concurrent or new information (including new information relating to safety or efficacy of the off-label use of a device) is published with respect to any information disseminated under paragraph (1), the manufacturer that disseminated the information under paragraph (1) shall notify the Secretary with respect to the new information. If the Secretary determines that the new information demonstrates that a device presents a significant risk to public health, the Secretary shall, in consultation with the manufacturer, take such appropriate action as the Secretary determines necessary to ensure public health and safety.

"(4) APPLICABILITY.—The requirements under subsection (a)(1)(A) and (B) of section 746 shall not apply with respect to devices.

"(c) DEFINITIONS.—As used in this section:

"(1) HEALTH CARE PRACTITIONER.—The term 'health care practitioner' means a medical provider that is licensed to prescribe or use a device for the treatment of a disease or other medical condition.

"(2) REFERENCE TEXTBOOK.—The term 'reference textbook' means a reference publication that—

"(A) has not been written, edited, excerpted, or published specifically for, or at the request of, a manufacturer of a device;

"(B) has not been edited or significantly influenced by a manufacturer of a device;

"(C) is not solely distributed through a manufacturer of a device, but is generally available in bookstores or other distribution channels where medical textbooks are sold; and

"(D) does not focus on any particular device of a manufacturer that disseminates information under subsection (a), and does not have a primary focus on off-label uses of devices that are marketed or under investigation by the

manufacturer supporting the dissemination of the information.

"(3) SCIENTIFIC OR MEDICAL JOURNAL.—The term 'scientific or medical journal' has the meaning given to such term by section 746(c)(3).

"SEC. 748. ESTABLISHMENT OF LIST OF ARTICLES AND TEXTBOOKS DISSEMINATED AND LIST OF PROVIDERS THAT RECEIVED ARTICLES AND REFERENCE TEXTBOOKS.

"A manufacturer that disseminates articles or reference textbooks as information under sections 746 and 747 shall prepare and submit to the Secretary biannually—

"(1) a list containing the titles of the articles and reference textbooks relating to off-label uses of drugs, biological products, and devices that were disseminated by the manufacturer to a person described in sections 746(a)(1) and 747(a) for the 6-month period preceding the date on which the manufacturer submits the list to the Secretary; and

"(2) a list that identifies the categories of providers (as described in sections 746(a)(1) and 747(a)) that received such articles and reference textbooks for the 6-month period described in paragraph (1).

"SEC. 749. CONSTRUCTION.

"(a) DISSEMINATION OF INFORMATION ON NEW DRUGS OR DEVICES NOT EVIDENCE OF INTENDED USE.—Notwithstanding section 502(a), 502(f), 502(o), or any other provision of law, the written or oral dissemination of information relating to a new use of a new drug or device, in accordance with section 746 or 747, shall not be construed by the Secretary as evidence of a new intended use of the new drug or device that is different from the intended use of the new drug or device set forth on the official labeling of the new drug or device. Such dissemination shall not be considered by the Secretary as labeling, adulteration, or misbranding of the new drug or device.

"(b) DISSEMINATION POLICY OF MANUFACTURERS.—Nothing in sections 746 and 747 shall affect the ability of manufacturers to respond fully to unsolicited questions from health care practitioners and other persons about drugs, biological products, or devices.

"(c) PATENT PROTECTION.—Nothing in sections 746 and 747 shall affect patent rights in any manner.

"(d) AUTHORIZATION FOR DISSEMINATION OF ARTICLES AND FEES FOR REPRINTS OF ARTICLES.—Nothing in sections 746 and 747 shall be construed as prohibiting an entity that publishes a medical or scientific journal (as defined in section 746(e)(3) of the Federal Food, Drug,

and Cosmetic Act) from requiring authorization from the entity to disseminate an article published by such entity and from charging fees for the purchase of reprints of published articles from such entity.

"SEC. 750. APPROVAL OF ADDITIONAL USES.

"(a) IN GENERAL.—As an alternative to the procedures established in section 505(c)(1) for a new drug (including a biological product) and section 515(d)(1)(A) for a device, the Secretary may approve an application under this section for a new use of a previously approved new drug or device if experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs or devices conclude that a new use that has not been reviewed or approved by the Secretary represents sound medical practice based upon reliable clinical experience and other confirmatory information.

"(b) PETITION.—The holder of an approved application may submit a petition to the Secretary presenting information that new use of a previously approved new drug or device meets the criteria for approval established in this subsection. The petition shall include data and information relating to the new use and shall demonstrate that the new use—

"(1) has existed in clinical practice for at least five years;

"(2) is common among clinicians experienced in the field; and

"(3) represents reasonable medical practice based upon reliable clinical experience and other confirmatory information.

"(e) ACTION ON PETITION.—Upon receipt of the petition, the Secretary shall obtain the conclusions and recommendations of a scientific review group established under section 904 and grant or deny the petition within 180 days of the receipt of the petition.".

SEC. 408. EFFECTIVENESS, OUTCOME, AND COST-EFFECTIVENESS STANDARDS.

NOT CHANGED We suggest this section needs to be revised to permit group to evaluate if relevant information and to require inclusion on label of warning contraindications, but not to deny approval because not on label

Section 741, as added by section 402, is amended by adding at the end thereof the following new subsection:

"(e) LIMITATION ON DETERMINATION OF EFFECTIVENESS.—In reviewing an application for a product that is a new drug, biological product, new animal drug, animal feed bearing or containing a new animal drug, or device the determination of effectiveness shall not include the evaluation of—

"(1) any potential use not included in the labeling;

"(2) the cost-effectiveness of a product described in this subsection, unless the proposed label-

ing explicitly includes a representation about cost-effectiveness; and

"(3) the clinical outcome resulting from the use of a diagnostic device, unless the labeling explicitly includes a representation regarding clinical outcome.".

SEC. 409. DEFINITION OF A DAY FOR PURPOSES OF PRODUCT REVIEW.

Section 201 (21 U.S.C. 321) is amended by adding at the end thereof the following:

"(gg) For purposes of reviewing any application, notification or petition, or any document, with respect to a product that is a new drug, biological product, new animal drug, device, or food additive that is submitted to the Secretary to obtain marketing approval, or classification under section 513(f)(1), or to establish or clarify the regulatory status of the product, the term 'day' means a calendar day (excluding any calendar day between the date of receipt by the submitter of a written communication from the Secretary setting forth the action of the Secretary on a submission and the date of receipt by the Secretary of the written response of the submitter to the action) in which the Secretary has responsibility to review such a submission.".

SEC. 410. ALTERNATIVE APPROVAL OF SUPPLEMENTAL NEW DRUG APPLICATIONS.

Substitute the Kennedy amendment #12

(a) DRUGS.—Section 505(b) of the Federal Food, Drug, and Cosmetic Act is amended by adding the following new paragraph at the end:

"(4) The reports required by paragraph (1)(A) may consist entirely of information published in independent peer-reviewed scientific and medical literature, in the case of a supplement to a previously approved application that seeks approval for changes in the conditions of use prescribed, recommended, or suggested in the labeling of the drug or device subject to the application.".

(b) DEVICES.—Section 515(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e(a)) is amended by adding the following new paragraph at the end:

"(3) The reports required by paragraph (1)(A) may consist entirely of information published in independent peer-reviewed scientific and medical literature, in the case of a supplement to a previously approved application that seeks approval for changes in the conditions of use prescribed, recommended, or suggested in the labeling of the device subject to the application.".

SEC. 411. PEDIATRIC STUDIES MARKETING EXCLUSIVITY.

Chapter V of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351 et seq.) is amended by inserting after section 505 the following new section:

Current Kassebaum Draft

"SEC. 505A. PEDIATRIC STUDIES FOR NEW DRUG APPLICATIONS.

NOT CHANGED
Suggested-
This should be limited to important life-saving drugs.
The Secretary should have to find that the additional indication is in advance of public health.

"(a) MARKET EXCLUSIVITY FOR APPROVED APPLICATIONS WITH PEDIATRIC STUDIES SUBMITTED BY AN APPLICANT.—If an application submitted under section 505(b)(1) is approved on or after the date of enactment of this section, and such application includes reports of pediatric studies described and requested in subsection (c), and such studies are completed and the reports thereof submitted in accordance with subsection (c)(2) or completed and the reports thereof accepted in accordance with subsection (c)(3), the Secretary may not make the approval of an application submitted under section 505(b)(2) or 505(j) that refers to the drug for which the section 505(b)(1) approval is granted effective prior to the expiration of 6 months from the earliest date on which the approval of such application for the drug under section 505(b)(2) or 505(j), respectively, could otherwise be made effective under the applicable provisions of this chapter.

Pediatric Studies

"(b) MARKET EXCLUSIVITY FOR APPROVED APPLICATIONS WITH PEDIATRIC STUDIES REQUESTED BY THE SECRETARY.—If the Secretary makes a written request for pediatric studies described in subsection (c) to the holder of an approval under section 505(b)(1) for a drug, and such studies are completed and the reports thereof submitted in accordance with subsection (c)(2) or com-

pleted and the reports thereof accepted in accordance with subsection (c)(3), the Secretary may not make the approval of an application submitted under section 505(b)(2) or 505(j) that refers to the drug subject to the section 505(b)(1) approval effective prior to the expiration of 6 months from the earliest date on which an approval of such application under section 505(b)(2) or 505(j), respectively, could otherwise be made effective under the applicable provisions of this chapter. Nothing in this subsection shall affect the ability of the Secretary to make effective a section 505(b)(2) or 505(j) approval for a subject drug if such approval is proper under such subsection and is made effective prior to the submission of the reports of pediatric studies described in subsection (c).

"(c) CONDUCT OF PEDIATRIC STUDIES.—

"(1) AGREEMENT FOR STUDIES.—The Secretary may, pursuant to a written request for studies after consultation with the sponsor of an application or holder of an approval for a drug under section 505(b)(1), agree with the sponsor or holder for the conduct of pediatric studies for such drug.

"(2) WRITTEN PROTOCOLS TO MEET THE STUDIES REQUIREMENT.—If the sponsor or holder and the Secretary agree upon written protocols for such studies, the studies requirement of subsection

(a) or (b) is satisfied upon the completion of the studies in accordance with the protocols and the submission of the reports thereof to the Secretary. Not later than 60 days after the submission of the report of the studies, the Secretary shall determine if such studies were or were not conducted in accordance with the written protocols and reported in accordance with the requirements of the Secretary for filing and so notify the sponsor or holder.

"(3) OTHER METHODS TO MEET THE STUDIES REQUIREMENT.—If the sponsor or holder and the Secretary have not agreed in writing on the protocols for the studies, the studies requirement of subsection (a) or (b) is satisfied when such studies have been completed and the reports accepted by the Secretary. Not later than 90 days after the submission of the reports of the studies, the Secretary shall accept or reject such reports and so notify the sponsor or holder. The Secretary's only responsibility in accepting or rejecting the reports shall be to determine, within 90 days, that the studies fairly respond to the written request, that such studies have been conducted in accordance with commonly accepted scientific principles and protocols, and that such

studies have been reported in accordance with the requirements of the Secretary for filing.

"(d) DELAY OF EFFECTIVE DATE FOR CERTAIN APPLICATIONS; PERIOD OF MARKET EXCLUSIVITY.—If the Secretary determines that an approval of an application under section 505(b)(2) or 505(j) for a drug may be made effective after submission of reports of pediatric studies under this section but before the Secretary has determined whether the requirements of subsection (c) have been satisfied, the Secretary may delay the effective date of any approval under section 505(b)(2) or 505(j), respectively, until the determination under subsection (c) is made, but such delay shall not exceed 90 days. In the event that the requirements of this section are satisfied, the 6-month period referred to in subsection (a) or (b) shall be deemed to have begun on the date an approval of an application under section 505(b)(2) or 505(j), respectively, would have been permitted absent action under this subsection.

"(e) NOTICE OF DETERMINATIONS ON STUDIES REQUIREMENT.—The Secretary shall publish notice of any determination that the requirements of subsection (c) (2) or (3) have been met and that approvals under section (505)(b)(2) or (j) for a drug will be subject to deferred effective dates under this section.

NOT TAKEN
We suggested the value of the extension should be limited -> not greater than 10 x the cost of the study

"(f) DEFINITIONS.—As used in this section, the term 'pediatric studies' or 'studies' means at least 1 human clinical investigation in a population of adolescent age or younger. At the Secretary's discretion, pharmacokinetic studies may be considered as clinical investigations.".

SEC. 412. NOTIFICATIONS FOR DEVICE MARKET CLEARANCE.

Section 510(k) (21 U.S.C. 360(k) is amended by striking "report to" and inserting "shall notify the Secretary to report to".

TITLE V—FOOD AND DRUG EXPORT REFORM

SEC. 501. SHORT TITLE, REFERENCE.

This title may be cited as the "FDA Export Reform and Enhancement Act of 1996".

SEC. 502. EXPORT OF DRUGS AND DEVICES.

(a) EXPORT AND IMPORTS.—Section 801 (21 U.S.C. 381) is amended—

(1) in subsection (d), by adding at the end thereof the following new paragraphs:

"(3) No component, part, or accessory of a drug, biological product, or device, including a drug in bulk inform, shall be excluded from importation into the United States under subsection (a) if—

Kennedy

approved by unanimous consent

AMENDMENT NO. 12 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.

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

~~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.

"(2) is not intended for sale in the United States; and

"(3) is intended for further manufacture into final dosage form outside the United States,

shall be subject to no restriction on the export of the product under this Act or the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.) if the product is manufactured, processed, packaged, and held in conformity with current good manufacturing practice and meets the requirements in section 801(e)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 381(e)).".

TITLE VI—DRUG AND BIOLOGICAL PRODUCTS REGULATORY REFORM

SEC. 601. SHORT TITLE.

This title may be cited as the "Drug and Biological Product Regulatory Reform Act of 1996".

SEC. 602. NEW DRUG APPROVAL STANDARD.

Section 505(d) (21 U.S.C. 355(d)) is amended by adding at the end thereof the following new sentence: "Substantial evidence may, as appropriate, consist of adequate and well-controlled clinical investigation and confirmatory evidence (obtained either before or after such investigation).".

NOT TAKEN

Manufacturing Changes

SEC. 603. PILOT AND SMALL SCALE MANUFACTURE.

Section 505(e) (21 U.S.C. 355(e)) is amended by adding at the end thereof the following new paragraph:

"(4) A new drug or biological product manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug or product and to obtain approval prior to scaling up to a larger facility, unless the Secretary demonstrates in writing and specifying in detail the reasons, after an informal hearing, that a full scale production facility is necessary to ensure the safety or effectiveness of the drug or product.".

SEC. 604. MANUFACTURING CHANGES.

NOT CHANGED We offered substitute language

Chapter VII (21 U.S.C. 371 et seq.), as amended by section 407, is further amended by adding at the end thereof the following new section:

"SEC. 751. MANUFACTURING CHANGES.

"(a) IN GENERAL.—A change in the manufacture of a new drug, biological product, or new animal drug, may be made in accordance with this section.

"(b) DRUG AND BIOLOGICAL PRODUCT.—A change in the manufacture of a new drug, a biological product that is the subject of a monograph in an official compendium, a biological product that can be adequately characterized by chemical, physical, or biological means, or a new animal drug shall require—

monograph

define

"(1) validation; and

different than initial approval?

[Substitute language for sec. 604 of S. 1477]

(b)(1) Before distributing a product made using a change in the manufacture of the product (including, if the Secretary determines it is appropriate, facilities and personnel) from that established in the approved new drug application, license application, or new animal drug application, the applicant must validate the effect on the safety, purity, potency, and effectiveness of the product.

(2) The applicant must report such changes to the Secretary and may distribute products as follows:

(i) If the change is of a type that the Secretary has determined has substantial potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product, the applicant must submit a supplemental application to the Secretary and receive approval of the supplement before distribution of the product.

(ii) If the change is of a type that the Secretary has determined has moderate potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product, the applicant must notify the Secretary at least 30 days before distribution of the product. Unless the Secretary notifies the applicant within 30 days not to distribute the product, the applicant may proceed with distribution.

(iii) If the change is of a type that the Secretary has determined has minimal potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product, the applicant must report the change in a annual report. The applicant may distribute the product without prior notification to or approval by the Secretary.

Different from [illegible] or the same

"(2)(A) if there is no change in the approved qualitative and quantitative formulation or in the approved release specifications, or if there is a change in the approved qualitative or quantitative formula or in the approved release specifications of a type permitted by the Secretary by regulation, may be made at any time and shall be reported annually to the Secretary; and

"(B) for any other change, shall require completion of an appropriate study demonstrating equivalence according to criteria established by the Secretary (unless such requirement is waived by the Secretary), may be made at any time, and shall be reported to the Secretary through a supplement or amendment submitted at the time the change is made.

"(c) BIOLOGICAL PRODUCT NOT SUBJECT TO A MONOGRAPH.—A change in the manufacture of a biological product that is not the subject of a monograph in an official compendium and cannot be adequately characterized by chemical, physical, or biological means shall require validation and—

"(1) if the change relates solely to a modification of the manufacturing facility or change in personnel, with no change in the approved manufactur-

ing process or release specifications, may be made at any time and shall be reported annually to the Secretary; and

"(2) for any other change, shall require completion of a bioassay or other appropriate study demonstrating equivalence according to criteria established by the Secretary (unless such requirement is waived by the Secretary), may be made at any time, and shall be reported to the Secretary through an amendment submitted at the time the change is made.

"(d) SPECIAL DETERMINATION FOR A BIOLOGICAL PRODUCT.—A determination shall be made prior to approval of a biological product under section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)) whether the product can be adequately characterized for purposes of this subsection. With respect to biological products approved prior to the date of enactment of the Food and Drug Administration Performance and Accountability Act of 1996, the determination shall be made within 90 days after the date of enactment of such Act. Any determination under this subsection is subject to change based upon new scientific information.".

SEC. 605. INSULIN AND ANTIBIOTICS.

(a) CERTIFICATION OF DRUGS CONTAINING INSULIN.—Section 506 (21 U.S.C. 356) is repealed.

NOT TAKEN our additional language

(b) CERTIFICATION OF ANTIBIOTICS.—Section 507 (21 U.S.C. 357) is repealed.

(c) EXPORTATION.—Section 802 (21 U.S.C. 382), as amended by section 502(b), is further amended by adding at the end thereof the following new subsection:

"(g) EXPORTATION OF UNAPPROVED PRODUCTS.—Insulin and antibiotics may be exported without regard to the requirements in this section if the insulin and antibiotics meet the requirements in subsection (e)(1).".

SEC. 606. MODERNIZATION OF REGULATION OF BIOLOGICAL PRODUCTS.

(a) IN GENERAL.—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended by striking "SEC. 351.(a)" and all that follows through "exchange the same." and inserting the following:

"SEC. 351. (a)(1) Except as provided in paragraph (6), no person shall introduce or deliver for introduction into interstate commerce any biological product unless—

"(A) a license is in effect for the biological product; and

"(B) each package of the biological product is plainly marked with the proper name of the biological product contained therein, the name, address,

Recommended Statutory Language

"Section 506 of the Federal Food, Drug, and Cosmetic Act, Certification of Drugs Containing Insulin, is repealed. Section 507, of the Federal Food, Drug, and Cosmetic Act, Certification of Antibiotics, is repealed.

Section 505 is amended by adding at the end the following new subsection:

(n) Application to Antibiotic Drugs.--(1) In General.--On and after the effective date of this subsection, antibiotic drugs shall be considered new drugs subject to the provisions of this section, and an antibiotic drug certified pursuant to section 507 prior to such effective date shall be considered a new drug for which an application has been approved pursuant to subsection (b) (or, in the case of an abbreviated application under such section 507, pursuant to subsection (j)). (2) Exception.--The provisions of subsection (j)(4)(D) shall not apply in the case of an antibiotic drug certified, or exempted from certification pursuant to section 507 prior to such effective date."

, or exempted from certification pursuant to section 507 prior to such effective date,

and applicable license number of the manufacturer of the biological product, and the expiration date of the biological product.

"(2) The license required under paragraph (1)(A) shall, as determined by the Secretary, cover the biological product; any facility in which the biological product is manufactured, processed, packed, or held; or both the product and facility.

"(3)(A) The Secretary shall establish, by regulation, requirements for license applications for biological products.

"(B) Except as provided in subparagraph (D), a license application that covers a biological product shall be approved based upon a demonstration that the product that is the subject of the application—

~~"(i) is safe and effective in accordance with sections 505(c) and 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d)); or~~

~~(ii)~~ meets standards designed to ensure that such product is safe, pure, and where appropriate, potent; and

"(C) A license application that covers a facility shall ~~and the facility~~ ensure that the product and the facility meet standards designed to ensure that the product meets applicable requirements of subparagraph (B).

NOT TAKEN our amended language

"(B) Except as provided in subparagraph (D), a license application that covers a biological product shall be approved based upon a demonstration that the product that is the subject of the application—

~~"(i) is safe and effective in accordance with section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d)); or~~

"(ii) meets standards designed to ensure that such product is safe, pure, and where appropriate, potent; and

"(iii) the methods used in, and facilities and controls used for, the manufacture, processing, packing, and holding of such product meet standards designed to assure the continued safety, purity and where appropriate, potency of the product.

"(C) A license application that covers a facility shall ensure that ~~the product~~ such facility meets standards designed to ensure that ~~the~~ any product manufactured, processed, packed or held therein meets applicable requirements of subparagraph ~~(A)~~ (B).

"(D) A license application for blood or a blood component (including plasma but not blood derivatives) shall be approved based on a demonstration that the product is safe, pure, and where appropriate, potent, and that the facility in which the product is manufactured, processed, packed, or held meets standards designed to ensure that such product is safe, pure, and where appropriate, potent.

"(4) Requirements prescribed under paragraph (2) shall include a requirement for preapproval inspection under subsection (c).

(5) All licenses shall be approved upon condition that the licensee will permit inspection of their facilities in accordance with subsection (c).

If reference to Section 505 of FD&C Act remains, need at a minimum report language making it clear that the bill does not intend to change FDA's longstanding interpretation of potency in Section 351 of the PHS Act.

1st Choice - delete

2nd - Substitute: (i) meets the criteria in section 505(c)(1)(A) of the FD&C Act (21 USCode 355 (c)(1)(A)

"(D) A license application for blood or a blood component (including plasma) shall be approved based on a demonstration that the product is safe, pure, and where appropriate, potent, and that the facility in which the product is manufactured, processed, packed, or held meets standards designed to ensure that such product is safe, pure, and where appropriate, potent.

"(4)(A) Requirements prescribed under paragraph (2) shall include a requirement for preapproval inspection under subsection (c).

"(B) A license shall be approved only on condition that the licensee agrees to permit inspection of its facility in accordance with subsection (c).

"(5)(A) Except as provided in subparagraph (C), an approved license for a biological product may be revoked if the Secretary determines, on the record after providing opportunity for a hearing in accordance with section 554 of title 5, United States Code, that the requirements for approval specified in paragraph (2) are no longer met with respect to such product, or that other public health reasons, prescribed by regulation, exist. No action to revoke a license based on findings of an inspection shall be initiated prior to submission and review by the Secretary of a written response submitted by the licensee to a notice of inspectional findings so long as such written response