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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. fax	Laura Mastrangelo to Bob Weiner re: SSNs and DOBs (1 page)	02/29/1996	b(6)
002. list	re: New Invites [partial] (2 pages)	03/02	b(6)

COLLECTION:

Clinton Presidential Records
Domestic Policy Council
Elizabeth Drye
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FOLDER TITLE:

FDA Reform 1996 [5]

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RESTRICTION CODES

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

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

C. Closed in accordance with restrictions contained in donor's deed of gift.

PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).

RR. Document will be reviewed upon request.

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

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

THE IMPACT OF THE HOUSE FDA REFORM PROPOSALS¹

The House Commerce Committee is considering three companion bills to change the processes by which the Food and Drug Administration oversees the safety of Americans' food, drugs, blood and other biological products, medical devices, and animal drugs.

Reforming the Federal government's regulatory processes, while maintaining critical public health and safety standards, has been a top priority of the Clinton Administration. Consistent with this commitment, a year ago the President and Vice President Gore asked Health and Human Services Secretary Donna Shalala and FDA Commissioner David Kessler to help them examine the regulatory requirements of the FDA. That effort has resulted in four major reports detailing 34 reforms that the agency is moving to implement--reforms that will speed availability of new products, streamline FDA procedures, and reduce regulatory burden on industry without sacrificing public health. These reforms built upon a 1992 Congressional directive (the Prescription Drug User Fee Act) to reduce drug review times. Under that legislation, FDA has met every goal established by Congress--so that now new therapies are approved in the United States as fast or faster than anywhere in the world, with the same high standards of safety and effectiveness Americans have come to expect.

Some of the provisions in the new House bills codify the Administration reforms. FDA has also expressed its desire to pursue additional reforms that speed product approvals and otherwise improve the regulation of foods, drugs, medical devices and other FDA-regulated products. But many of the House proposals raise concerns about the direction of their reforms, as they propose major changes in the safety standards under which FDA has operated. The agency is concerned that some of these measures, if enacted into law, may undermine the agency's ability to protect American citizens from unsafe and ineffective products. Listed below are examples of these provisions.

Several Provisions in the Bill Weaken the Effectiveness Standard for New Drugs and Devices. Since the thalidomide tragedy in 1962 propelled Congress to establish today's drug approval standards, physicians and their patients have been confident that drugs are both safe and effective.

For Drugs and Biologics (including children's vaccines), this bill would allow anecdotal evidence of effectiveness to replace clinical proof. It would force FDA approval of a drug use based on common use by physicians (with no objective evidence). Thus, FDA would get less information about what works, doctors would in turn be left to prescribe drugs with far less information about the drug, patients would be subjected to drugs that don't work well or at all, and insurance companies will have to develop new methods for determining what to pay for.²

For medical devices, FDA would be prohibited from evaluating the medical outcome resulting from a device's use, unless the device's labeling claims a therapeutic effect. The result could be, for example, the implantation of an artificial heart with no evaluation of whether the patient did well or died. This is a significant change from the present system that requires devices to be shown to clinically perform as intended and to produce useful outcomes for patients. An expensive, potentially hazardous device that is well engineered and manufactured, but has no medical benefit to patients, is of no benefit to the health care system.³

For both drugs and devices, promotion by manufacturers of unproven, experimental therapies would be permitted and encouraged. Preliminary findings published in medical journals and even unpublished abstracts of preliminary research could be disseminated by manufacturers to physicians under the guise of the latest scientific proof. This would eliminate the current incentive for manufacturers to carry out the necessary studies to show that their products really work. More doctors would prescribe unproven, ineffective treatments and billions of dollars could be wasted each year on them. The human cost would be measured in the unnecessary pain and suffering patients would undergo until they were given an effective treatment.⁴

FDA Would Be Unable to Protect the Nation's Blood Supply.⁵ Under the bill, FDA's current enforcement powers to act against violative blood banks would be limited, and the agency could not even force the recall of contaminated blood. Also, blood processing and handling organizations would be able to inspect themselves, in lieu of current FDA inspections.

FDA Would No Longer Oversee Most Drug and Device Testing in Humans. Currently, FDA oversees the safety of drug and device experimentation in humans and ensures that test subjects are properly informed about the risks of being in such experiments and that they are not subjected to unreasonable risks.

For drugs, the bill takes away much of the agency ability to protect study subjects.⁶ The bill requires no notification to FDA for initial human testing, and only limited information for more extensive, later experimentation in humans. For example, a drug that was being investigated for psychosis was presented to FDA for approval of human testing. The FDA reviewer observed in his review of the animal testing data that animals on which the drug was tested suffered fatal seizures at doses comparable to those the company wished to use in human testing. FDA refused to clear the drug for further testing until the company lowered the dosage to prevent seizures from occurring. If this bill had been law, FDA would have received only a company-prepared summary of the data and would have had only 21 days to stop the company from initiating human testing. It is likely that the seizures would not have been caught by FDA, and fatal seizures would have occurred in test patients.

For medical devices, the bill opens the door to widespread commercialization of unproven, experimental devices.⁷ Patients could be subjected to highly experimental devices without FDA's knowledge or approval, and experiments with devices could be changed without notice to FDA or an ethics review panel (for example, a company could enlarge an experiment from a handful of test patients to hundreds of subjects without notifying anyone).

FDA Would Be Forced to Approve New Drugs Using Summaries of Safety Data Prepared by Drug Companies.⁸ FDA now reviews both summaries of the proof of a drug's safety and effectiveness, as well as the underlying data. At times those "raw data" reviews have detected dangers that resulted in disapproving the drug or providing for special warnings to doctors and patients. This bill would limit FDA's review to essentially company-prepared summaries making it more likely that FDA reviewers will miss underlying problems. Such an event could have occurred recently with the drug dilevalol, which was marketed in Japan and Portugal (and approved but not yet marketed in England) for hypertension. During the U.S. review, the FDA medical reviewer noted in the raw data evidence that some patients had severe liver injury. FDA refused to approve the drug and it was later taken off the market worldwide. The company did its safety summaries for foreign approval in good faith, but had simply missed these dangerous effects. If the drug had been approved for such a common condition as hypertension in this country, there could have been many serious injuries.

A Drug Manufacturer Would be Permitted to Make Potentially Dangerous Changes in a Drug Without FDA Review.⁹ Currently, a drug manufacturer must notify FDA before it makes manufacturing changes that might affect a drug's safety or effectiveness. This bill would eliminate that requirement. For example, a manufacturer of the epilepsy drug carbamazepine changed its method of manufacturing and substituted a more finely ground powder form of the active ingredient. It turned out that these changes caused the drug to become less effective, leading to an increase in epileptic seizures.

Inspections to Ensure Adherence to the Law Would Be Turned Over to Industry.¹⁰ The current system of inspections by FDA experts would be largely eliminated, replaced by private inspectors paid by the firm they are inspecting. Further, even if the private inspector finds a safety problem, FDA need not be notified, and thus cannot know when to step in to address such hazards. One recent example of a third party inspection (by an agency in another country) occurred in a manufacturing plant that makes sterile drug products, where sterility is critical to the safety of the drug. The plant was given a "clean bill of health." Soon thereafter, FDA inspected the plant and found serious manufacturing problems, including non-sterile drug products and leaking packages.

Key Portions of FDA's Responsibility for Assuring Safety Would be Privatized.¹¹ The bills would allow review of new drugs, medical devices, and food additives to be done by reviewers paid by industry. If the private reviewer recommended approval of the product, FDA could deny marketing only if the agency proved that the product was unsafe. The agency would have only a short time to make such a determination; if FDA were unable to prove that the product is unsafe, FDA approval would be automatically deemed to be granted. In addition, the proposal raises major concerns about conflict of interest. FDA is experimenting with forms of third party review as part of its REGO reforms. The agency, however, has built safeguards against conflict of interest into its pilot project to test private review mechanisms.

Medical Devices on the Market Could Undergo Major Changes in Their Design or Performance Without Notification to FDA.¹² This significant "loophole" will prevent FDA from protecting Americans from faulty design and other potentially life-threatening changes that modifications in a device can cause. For example, in the 1980s, a heart valve manufacturer (Shiley) proposed "improvements" in an FDA-approved heart valve that FDA turned down because the company inadequately demonstrated the safety and effectiveness of the changes. The company then marketed the "improved" version overseas, but had to remove it from the market three years later when almost a hundred premature, sudden

deaths occurred (because the new version turned out to break easily when actually implanted in humans).

Medical Devices That Have Been Approved for A Simple Use Could be Used in High-Risk Situations Without Additional Review.¹³ Under this legislation, a device reviewed by FDA for a minor indication could be marketed by its manufacturer for high-risk conditions without additional review--where failure could cause death or serious illness. Doctors and their patients would be taking risks that a device could cause great harm because it had not been proven successful in high-risk uses. For instance, a "stent" approved by FDA to open clogged arteries in the pelvis where they are subject to very little movement was recently promoted by some for use in carotid (neck) arteries (and was widely used for that purpose in Europe). But because arteries in the neck are subject to a great deal of movement, these same stents that were successful in the simple use were breaking when used in the neck. In addition, blood clots caused by the stent that present little health risk in the pelvis caused strokes when used in the carotid artery.

FDA Would Be Hindered in its Ability to Monitor Marketed Devices That Might Subsequently Prove Harmful.¹⁴ Congress enacted legislation in 1990 to enable the agency to watch certain high-risk devices for potential failure after marketing. This bill would substantially weaken that authority, so that a manufacturer could not be required to monitor the safety of a medium-risk device (such as a hip replacement) or any pre-1991 high-risk device (such as a heart valve), even if its subsequent failure would be likely to cause devastating consequences. It also eliminates much of the current requirement that device manufacturers keep records of patients receiving devices, which was enacted to enable FDA or the manufacturer to alert patients if a device subsequently proves faulty. And finally, the bill eliminates the requirement that users such as doctors and hospitals notify FDA if a device malfunction occurs that could cause injury.

Exposure of Millions of Americans to Unsafe Food Additives. Since the 1950s Americans have known that manufacturers must prove that a food or color additive is safe before it can be used in food, and that the law bans manufacturers from adding cancer-causing substances to food (the Delaney anti-cancer clause). This bill jeopardizes public health by allowing manufacturers to hire private reviewers to approve additives for marketing; FDA would have to prove a food additive is unsafe to overturn the reviewer's decision, shifting the burden of proof.¹⁵ The bill also eliminates the Delaney anti-cancer clause and allows "de minimis," "insignificant," or "negligible," amounts of cancer causing substances in food.¹⁶

Substantially Weakens the 1990 Nutrition Labeling and Education Act (NLEA) That Made Sense Out of Food Labeling Terms. Under the House bill, a company could make a food label claim that its product prevents disease based on preliminary suggestions contained in a Federal agency's report.¹⁷ For example, National Academy of Sciences publications suggested in the past that beta carotene supplements might lessen the risk of cancer, but subsequent controlled studies found no effect in most people and increased lung cancer in smokers. If this bill had been law, foods and dietary supplements with beta carotene would have been permitted to make claims that those products lowered the risk of lung cancer, and millions of Americans would have been lured into either wasting their money or been subjected to increased lung cancer risk. The bill would also reverse the NLEA's clarification of food labeling terms. For instance, terms such as "lots of fiber" or "not much fat" could be used to inaccurately suggest high fiber or low fat.¹⁸

The States Would Be Hindered in Protecting Their Citizens.¹⁹ Currently, FDA protects many segments of the food supply through cooperative Federal-State programs, in which FDA sets national safety standards and the states carry out the day-to-day inspections and other implementing activities (e.g., for retail food stores, milk safety, and shellfish sanitation). This bill, by preempting state laws, would prevent them from carrying out those programs. Further, if a State attempts to require warnings on labels, or issue warnings--such as those required by California's Proposition 65-- the bill prevents them from taking such actions.

Exposes Americans to Increased Risk of Antimicrobial Resistance and Transmission of Disease from Animals to Man. Currently, drugs used in animals must be shown by their manufacturers to be effective, and to pose no risk to humans. This bill would eliminate those requirements in certain instances.²⁰ For example, prior to the enactment of current animal drug laws, drug manufacturers marketed drugs containing significant amounts of several powerful antibiotics to treat infections in milk cows without showing that each antibiotic added to the effectiveness of the drug. The marketing of similar products today, as this bill would permit, increases the risk of antibiotic resistance, which could result in less effective human antibiotics, and increased use of unnecessary and dangerous drugs. Another of the bill's provisions could hinder FDA's ability to approve products that will minimize the risk of transmission of dangerous microorganisms from animals to humans (because, for example, drugs used in pets other than dogs and cats need not be shown to be effective). Further, because the bill eliminates the Delaney anti-cancer clause, livestock and poultry producers would be permitted to use cancer-causing drugs whose residues could pose cancer risks to humans.²¹

The Bill Imposes Wasteful, Unnecessary Bureaucracy. FDA would be forced by this bill to create unnecessary bureaucratic mechanisms for which no funds are provided. For example, the bill mandates a tracking system for product applications that would threaten confidentiality of application information; and virtually any FDA decision about a drug or device application, including informal preliminary decisions, would be subject to judicial review (threatening to paralyze the agency in useless litigation).

A New FDA Statement of Mission Would Put Industry Profits Ahead of Public Health.²² FDA's current mission is to protect Americans from unsafe foods, drugs, and medical devices, and to promote the public health through education and speedy access to proven therapies. This bill would change that focus to one of maximizing industry access to the marketplace and putting the speed of that access ahead of the safety of the product. FDA already gives the highest priority to life-saving therapies; this bill would force such priorities for every new product. Further, although attempting to promote the interests of U.S. industries, the bill might have the opposite effect, as it would open U.S. markets to cheap, unproven imported therapies and food additives from around the world, devalue significantly the "Made in the USA" label that signifies the high standards and successful sales of most new drugs and devices developed here, and threaten the decades old leadership U.S. companies have had in the development of those products.

4-26-96

ENDNOTES

1. H.R. 3199-Drug and Biologic Products Reform Act of 1996;
H.R. 3200-Food Amendments and the Animal Drug Availability Act; H.R. 3201-Medical Device Reform Act of 1996.
2. Section 5, H.R. 3199.
3. Section 8, H.R. 3201.
4. Section 20, H.R. 3199; Section 18, H.R. 3201.
5. Section 26, H.R. 3199.
6. Section 3, H.R. 3199.
7. Section 4, H.R. 3201.
8. Section 4, H.R. 3199.
9. Section 13, H.R. 3199.
10. Section 10, H.R. 3199; Section 17, H.R. 3201.
11. Section 7, H.R. 3199; Sections 9 & 11, H.R. 3201; Section 105, H.R. 3200
12. Section 9, H.R. 3201.
13. Section 9, H.R. 3201.
14. Sections 14 & 15, H.R. 3201.
15. Section 105, H.R. 3200.
16. Section 107, H.R. 3200.
17. Section 102, H.R. 3200.
18. Section 103, H.R. 3200.

19. Section 108, H.R. 3200.

20. Section 201, H.R. 3200.

21. Section 107, H.R. 3200.

22. Section 2, H.R. 3199, Section 101, H.R. 3200, Section 2, H.R. 3201.

FDA Reform

Diane

- 1400
- Export
- Annual stuff.
- early access

- Schulz

- Diane

- Jerry (Log)

-

Diane

- drug wants off-label ← Schulz ^{people talk}
- device wants to ~~go~~ ^{make a move}
- fundamentally change -
- basic officers std.

Export — Cyron bill — that Admin has problems with —
is on the CP. —

Keith Gregg has a separate amendment
bill on food labels — pre

Bill — Farm out devices —

— User Fees

— Watch on

Diane — Put in statute — Codify —
Rigo



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FAX TRANSMITTAL

DATE: March 18, 1996
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Total number of pages (Including Transmittal Sheet): 4

Recipient's Fax Number: 456-7028

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Comments:

I understand from Dan Chenok that you want a copy of my analysis of Senator Kassebaum's FDA reform bill (S.1477) and FDA's relevant completed/planned initiatives. You should be aware that I prepared this overview for a meeting in late January and that it does not reflect recent activity by the Labor and Human Resources Committee or FDA. Please call me if I can be of any further assistance.

BRIEFING MATERIALS FOR SALLY KATZEN

From: Jonathan Winer
 Date: January 30, 1996
 Subject: FDA Reform Material for Schultz Meeting

The following summary is of Senator Kassebaum's FDA reform bill (S.1477) and FDA's relevant completed/planned initiatives. The former is denoted by "O" and the latter is denoted by "*". The piece at the end is a brief write-up of FDA and Congressional opinion on the bill.

FDA Performance and Accountability Act of 1995 S.1477 -- Senator Kassebaum

Summary

- **Mission and Accountability**
 - Makes clear that FDA's prime mission is facilitating the rapid and efficient development and availability of safe and effective products, including new drugs and biologics, devices, food additives, color additives, animal drugs, and animal foods containing a new animal drug.
 - Requires the Commissioner of FDA, after consultation with private sector interests, to develop and publish in the Federal Register within 180 days of enactment quantifiable performance standards for the review of applications for products subject to premarket review or approval.
 - Requires the Secretary to publish an annual report in the Federal Register comparing the performance of the agency with the applicable performance standards, analyzing any failure to achieve the standards, and setting forth a plan to achieve compliance with unmet standards.
 - Enhances the independence of advisory committees.
- **Expedited Access to Products for Seriously Ill Patients**
 - Requires the Secretary to approve/deny within 30 days applications for an exemption from effectiveness requirements for devices used in the treatment and diagnosis of fewer than 4000 individuals (humanitarian use of devices).
 - Requires the FDA to act within 120 days (as opposed to proposed 180 days) on applications for new drugs and devices for the treatment of serious, life-threatening, or seriously debilitating diseases and conditions if the product provides therapy not currently available or offers a significant improvement over currently available therapies.
 - * *FDA published an NPRM which permitted informed consent to be waived in cases when the patient is in a life-threatening situation.*
- **Revitalizing the Investigation of New Products**
 - Establishes that clinical investigations of new drugs may begin 30 days after the Secretary receives notification from the sponsor containing the data necessary to assess the safety of the product in clinical study.
 - Requires the Commissioner of FDA to establish a mechanism to assure the fair and consistent application of safety standards for clinical investigations.
- **Efficient, Accountable, and Fair Product Review**

The provisions of this section apply to applications for approval for new drugs and biologics, devices, food additives, color additives, and animal drugs.

 - Requires the Commissioner of FDA to establish a mechanism to ensure the fair and consistent application of filing requirements.

- Requires the Secretary, after consulting with private sector interest groups, to develop and publish in the Federal Register criteria for the type and amount of data that must be submitted with a new product application.
- Provides statutory authority for the Secretary to contract with outside organizations and individuals for the evaluation of all or parts of new product applications. Requires FDA to make a final decision within 60 days on the recommendations of an expert review organization or individual.
- Permits Secretary to accredit organizations to conduct inspections to evaluate manufacturers' compliance with applicable requirements for good manufacturing practices.
- Prohibits Secretary from requiring environmental impact statement.
- Establishes an alternative basis for the approval of new uses for already approved devices and drugs/biologics.
- Establishes that in the review of an application for a new product, the determination of effectiveness shall not include the evaluation of relative effectiveness, any potential use not explicitly included in the labeling, cost-effectiveness, and the clinical outcome resulting from use of a diagnostic device.
- * FDA is preparing to publish a notice which would harmonize more than 20 drug and biologic applications.
- * FDA is preparing a notice of a pilot program for third-party review of selected medical devices.
- * FDA is preparing an NPRM to eliminate the requirement of doing environmental impact statements when not needed.
- * FDA published a statement to clarify its evaluation of effectiveness in the context of overall review of product approval.
- Drug, Biological Product, and Device Export Reform
 - Incorporates S. 593 as reported by the Committee on Labor and Human Resources
 - * FDA published an NPRM which expands opportunities for export of unapproved medical devices. *
- Drug and Biological Product Regulatory Reform
 - Provides that "substantial evidence" criteria from Federal Food, Drug, and Cosmetic Act (FFDCA) may consist of data from one well-controlled clinical investigation and confirmatory evidence.
 - Provides that a new drug/biological product 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.
 - Specifies that a change in the manufacturing of a new drug, a biologic which is the subject of a monograph in an official compendium, a biologic that can be adequately characterized, or a new animal drug can be made at any time if the change does not affect the approved qualitative or quantitative formulation or the approved release time.
 - Repeals batch and lot certification requirements for insulin and antibiotics.
 - Amends PHS Act relating to regulation of biological products to replace the requirement for an establishment license with a requirement for good manufacturing practices (making biological product regulation consistent with the regulation of drugs under the FFDCA).
 - * FDA published a notice which permits use of pilot facilities during the development of biologics.
 - * FDA published a notice eliminating many requirements for approval of manufacturing changes in drugs.
 - * FDA published a notice eliminating lot release requirements for insulin and antibiotics.

- * *FDA published an NPRM eliminating requirement for establishment license applications for most biotech drugs.*
- **Device Regulatory Reform**
 - Exempts class I devices and those class II devices designated by the Secretary from premarket notification requirements.
 - Prohibits the Secretary from withholding the initial classification determination for a device for any reason, including the finding that the manufacturing facility is not in compliance with good manufacturing practices.
 - Permits that minor modifications may be made without notification provided the modifications do not adversely affect safety and effectiveness.
 - Requires the Secretary to review premarket applications for breakthrough devices within 120 days and for other devices within 180 days.
- * *FDA has been actively down-classifying medical devices from class III to class I.*
- * *FDA eliminated the use of the reference list.*
- **Animal Drug Regulatory Reform**
 - Modifies the definition of "substantial evidence" to include from one scientifically sound study and confirmatory evidence.
 - Establishes that the Secretary may require good manufacturing practices for animal drugs that differ from human drugs.
- **Food Regulatory Reform**
 - Defines an indirect food ingredient as a substance that contacts food but that is not intended for consumption as a food ingredient.
 - Permits individuals to notify FDA at least 90 days before introducing a new indirect additive into commerce and requires the Secretary, within 90 days of receiving the notification to either approve it or disapprove it, publish a notice in the Federal Register, and if it is approved, promulgate an appropriate regulation. If the Secretary does not publish a notice in the Federal Register, the indirect food additive shall be deemed to be approved.
- * *FDA published an NPRM which reformed GRAS, food additives, and color additives procedures.*
- * *FDA is preparing to publish a notice enhancing use of private sector in monitoring imported foods (guidance).*

Discussion

- FDA has completed or planned initiatives in many of the areas that Kassebaum's bill (S.1477) covers. However, in most cases, FDA's actions fall short of what S.1477 proposes.
- FDA would likely be opposed to the provisions in S.1477 which:
 - enhance the independence of advisory committees;
 - decrease product review time or allows applicant to go ahead if the agency does not respond within given time;
 - expand ability of product sponsors to disseminate information and seek approval of new uses;
 - allow the agency to make determination on drug or biologic application based on one well-controlled clinical investigation; and
 - go beyond anything the agency has done or is planning to do through regulation or initiative.
- According to Hill staff, Congressional support for S.1477 is weak. Republicans and Democrats feel that it represents too much of a compromise. A Hill staffer predicted that S.1477 will not go very far.

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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

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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.

DRAFT**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

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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.

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- 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.) 7

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).

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- 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

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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

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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 countries 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 countries 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.

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- 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 dose forms. Further guidance documents are planned for other types of new drug dosage forms, 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 to 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

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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,

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and serious illness resulting from complications caused by their design, performance etc.

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

- 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

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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.

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- 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.

DRAFT**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

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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.

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001. fax	Laura Mastrangelo to Bob Weiner re: SSNs and DOBs (1 page)	02/29/1996	b(6)
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COLLECTION:

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

FOLDER TITLE:

FDA Reform 1996 [5]

2014-0046-S

rc1403

RESTRICTION CODES

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

- P1 National Security Classified Information [(a)(1) of the PRA]
- P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
- P3 Release would violate a Federal statute [(a)(3) of the PRA]
- P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
- P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [(a)(5) of the PRA]
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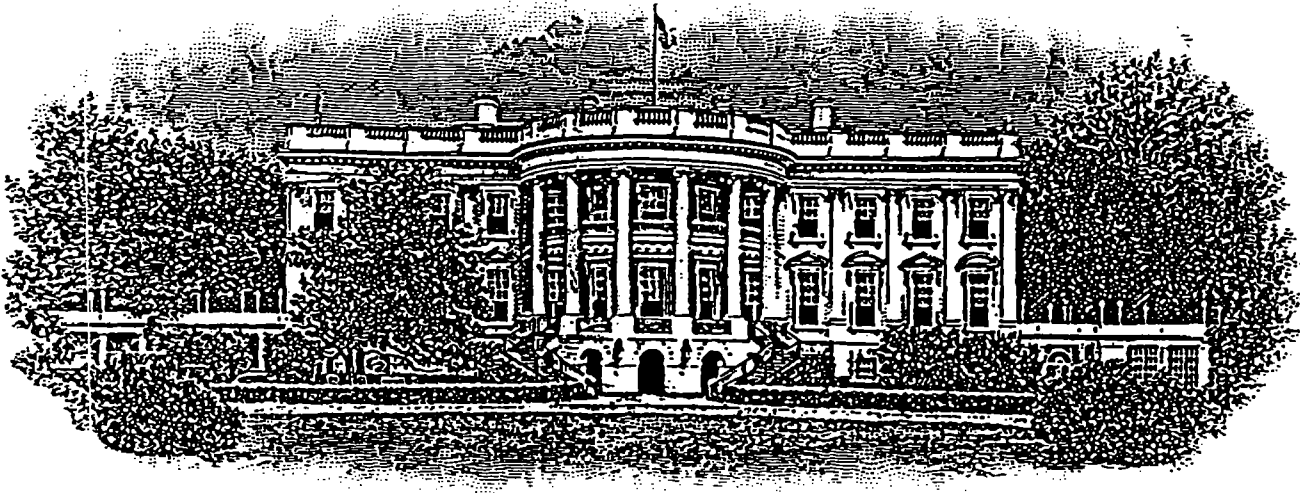
PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).

RR. Document will be reviewed upon request.

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

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

The White House



DOMESTIC POLICY

FACSIMILE TRANSMISSION COVER SHEET

TO: Jerry Mande

FAX NUMBER: 301-594-6777

TELEPHONE NUMBER: _____

FROM: Elizabeth Dye

TELEPHONE NUMBER: 456-5573

PAGES (INCLUDING COVER): 3

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Elizabeth Drye
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FOLDER TITLE:

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2014-0046-S
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- Tentative

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Senior Vice President
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(b)(6)

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Member, Board of Trustees
American Medical Association
1101 Vermont Avenue, N.W.
Washington, D.C. 20005

DENNIS BURKE

per conversation. Bob
(again! see
earlier confirmation)

cc: P. Diaz
F. Garcia
M. Gold
K. Landgraf

February 9, 1996

MR. BOB WEINER
Director, Public Affairs
White House Office of National Drug Control Policy
202-395-6730

**OFFICE OF NATIONAL DRUG CONTROL POLICY/
NATIONAL PHARMACEUTICAL COUNCIL
PREVENTION AND TREATMENT EDUCATION PROGRAM**

Thank you for your interest in hosting a press conference announcing the private/public prevention partnership of the ONDCP and the pharmaceutical industry. As we discussed, the purpose of the initiative is to distribute important educational materials to physician practices to assist in the prevention, early detection and treatment of alcohol, tobacco and other drug use. This new education partnership is a valuable asset to the efforts of the ONDCP because research indicates that Americans most trust and respect their physicians. The medical community is among the most credible and trusted influence in America and provides an excellent avenue to the youth and families of our country. We will be assisting primary physicians in turning their offices into disease prevention centers.

As you will agree, the news value of the collaboration is substantial. First, as you mentioned, the news of the new director's appointment is a great lead. Second, the ONDCP is breaking ground on the way it approaches the nation's drug and alcohol problem --- by adding a medical focus to 'prevention'. Physicians for Prevention has called prevention the most underutilized, yet at the same time, essential medical treatment. In addition to current aggressive programs, the new strategy reduces illicit substance demand through education, diagnosis and screening of the problem, and, if necessary, treatment of the addiction.

Program Overview

This private/public initiative is a clear win/win for the country, and the partners. Fred Garcia has driven this program and has met with the National Pharmaceutical Council and leading medical specialists in the country to understand the current trends and excellent outcomes of addiction medicine. A new organization, Physicians for Prevention, was formed to educate physicians on prevention and treatment through medical schools and physician practice initiatives. They will develop the materials on behalf of the ONDCP.

The role of distribution will be coordinated by the pharmaceutical industry, which has daily direct access to physicians through their dedicated sales representatives. More than 17,000 sales representatives will personally deliver the communications materials to approximately 400,000 physicians nationwide. The benefit to ONDCP is that the distribution time and resource from the pharmaceutical industry is approximately \$30 million. We will validate and confirm the exact number once all participants report their final distribution plans. The benefit to the industry is that the sales representatives get to participate in a socially responsible program and can provide their customers an important new educational tool.

cont. →

Jennis Burke, conf.

Page Two

The following materials are currently in development -- by Physicians for Prevention:

- Medical Patient Screening instrument to quickly identify drug and alcohol abuse.
- Talking Points for Physicians on current drug trends (ONDCP Pulse Beat).
- Analysis of America's Youth Drug Use, using the PRIDE and NIDA annual surveys.
- Web site on alcohol and drug abuse for physician access. Materials from Web Site will be appropriate for downloading, printing and patient distribution.
- In-Office Stands with Patient Self Screening Instruments to create patient awareness of drug and alcohol abuse.
- Drug Prevention Artwork with messages suitable for framing in physicians offices developed in cooperation with the Partnership for a Drug Free America.

The mission of the National Pharmaceutical Council (NPC) is to undertake educational activities concerning health care. They are not a lobbying organization. Kurt Landgraf, CEO of DuPont Merck lead the initiative and the following pharmaceutical companies have agreed to join DuPont Merck in the program:

ALZA	Bayer
Astra Merck	Bristol Myers Squibb
CIBA-Geigy	DuPont Merck
Hoechst Marion Roussel	Hoffman La Roche
Boehringer Ingelheim	Knoll
Parke Davis	Sanofi
Searle	SmithKline
Wyeth-Ayerst	

As soon as possible, please provide one or two tentative dates so I can coordinate the schedules of the following executives who will represent the National Pharmaceutical Council and the entire industry in a press conference:

Kurt M. Landgraf, President and CEO of The DuPont Merck Pharmaceutical Company
(Past Chairman, National Pharmaceutical Council, ONDCP Program Driver)
Stephen G. Sudovar, Senior Vice President, Pharmaceuticals Division, Hoffman-La Roche
(Current Chairman, National Pharmaceutical Council)
Sam L. Barker, President, US Pharmaceutical Division, Bristol-Myers Squibb Company
Carter H. Eckert, President and CEO, Knoll Pharmaceuticals

Over the next week, I will gather distribution information and financial statistics to strengthen the news value of the press conference and/or materials.
Thank you, please call me at 302-892-8453 to discuss.

Laura A. Mastrangelo
LAURA A. MASTRANGELO
Manager, Public Affairs



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**OFFICE OF NATIONAL DRUG CONTROL POLICY/
NATIONAL PHARMACEUTICAL COUNCIL
PREVENTION AND TREATMENT EDUCATION PROGRAM**

MR. BOB WERNER
Director, Public Affairs
White House Office of National Drug Control Policy
202-395-4730

February 9, 1996

cc: P. Diaz
M. Gold
R. Landgraf

DENNIS BURKE
Per [Signature]

02/09/96 15:20 DU PONT LEBRON - 2023954730

TRANSMISSION REPORT

**THIS DOCUMENT WAS CONFIRMED
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No.	REMOTE STATION	START TIME	DURATION	#PAGES	MODE	RESULTS
1	267028	2-20-96 5:27PM	1'08"	2/ 2		COMPLETED 14400

TOTAL 0:01'08" 2

NOTE:

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PD : POLLED BY REMOTE SF : STORE & FORWARD R1 : RELAY INITIATE RS : RELAY STATION
MB : SEND TO MAILBOX PG : POLLING A REMOTE MP : MULTI-POLLING RM : RECEIVE TO MEMORY

DENNIS BURKE
-3-

ACCELERATING ACCESS TO AND APPROVAL OF CANCER THERAPIES

The Food and Drug Administration is undertaking four new initiatives to improve patient access to promising new cancer therapies. FDA will:

- shorten approval times for cancer treatments by recognizing tumor shrinkage as an early and reliable indicator of a treatment's effectiveness;
- make cancer therapies approved by foreign countries more quickly available in the U.S. by working with companies to bring these therapies into trial use;
- improve the therapy review process by insuring that all FDA cancer-therapy advisory committees include a cancer patient who has experienced the illness for which a new product is being considered; and
- make it easier for sponsors to test new uses for cancer therapies already on the market.

Until now, FDA has required that a cancer therapy's sponsor demonstrate improvements in survival time or quality of life before a therapy could be approved. Based on years of accumulated evidence, FDA now believes it is appropriate to approve products that show evidence of tumor shrinkage for patients that have no satisfactory alternative therapy. Companies can more quickly demonstrate tumor regression than improvements in survival time or quality of life. By allowing companies to provide additional evidence of increased survival or improved quality of life associated with that therapy after marketing approval, FDA will substantially shorten (sometimes by years) the total time needed for marketing approval in many situations.

Cancer patients and their families sometimes believe that they must travel to a foreign country to receive the newest cancer therapies. While this is rarely so, FDA will make it even less likely by actively encouraging companies to submit expanded access protocols in the U.S. for cancer therapies that have been approved by recognized foreign regulatory authorities.

FDA advisory committees play a critical role in product review. FDA will improve the review provided by its cancer-therapy advisory committees by adding patient representatives who have experience with the illness for which a therapy is under consideration.

FDA will reduce the number of Investigational New Drug Applications filed for additional studies of already-approved therapies. This change will make it easier for researchers to study new uses of already approved therapies.

FDA is undertaking these initiatives after careful consideration of suggestions and advice offered by patients and their advocates, pharmaceutical industry representatives, and physicians and researchers. FDA will continue to seek the views of these interested parties as well as those of the Agency's advisory committees and the National Cancer Institute. FDA's goal is

to significantly improve patient access to promising cancer treatments. FDA recognizes that these initiatives may also apply to therapies for patients with other serious and life-threatening diseases. FDA intends to consider expanding these initiatives to cover other serious conditions, as appropriate, if this experience with cancer treatments shows that these initiatives can be applied more broadly.

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**OFFICE OF NATIONAL AIDS POLICY
EXECUTIVE OFFICE OF THE PRESIDENT**

750 17th Street, N.W.
Washington, DC 20503

Phone: 202-632-1090
Fax: 202-632-1096

FACSIMILE COVER SHEET

TO:

Elizabeth Dwyer

FAX NUMBER:

FROM:

DATE:

PAGES INCLUDING COVER SHEET:

4

COMMENTS:

THE WHITE HOUSE
OFFICE OF THE VICE PRESIDENT

FOR IMMEDIATE RELEASE

CONTACT: 202-456-7035

WEDNESDAY, February 21, 1996

Vice President Gore Says Meeting
With Pharmaceutical Firms,
AIDS Researchers, An Important Step
in Fight Against Disease

WASHINGTON -- Highlighting his and President Clinton's commitment to AIDS drug development, Vice President Gore met Tuesday (2/20) with pharmaceutical company representatives and leading government researchers. He said the private and public sectors should accelerate their joint effort to find and develop as quickly as possible AIDS vaccines, therapeutics, and microbicides.

Attending the meeting were representatives of 11 pharmaceutical companies and leading AIDS researchers and officials from the National Institutes of Health, the Department of Defense, and the Food and Drug Administration. They discussed ways to accelerate the development of AIDS vaccines, therapeutics, and microbicides.

"This meeting was an important step in strengthening the government-industry partnership that is essential to finding and developing effective treatments -- and ultimately a cure -- for AIDS," Vice President Gore said. "We are committed to marshalling our best minds and resources in the fight against AIDS."

At the December 6, 1995, White House Conference on HIV and AIDS, President Clinton asked Vice President Gore to convene this meeting to "identify all the ways in which we might accelerate the development of vaccines, therapeutics, and microbicides that can protect people from HIV and the infections it causes." The meeting reflects President Clinton's commitment to bring the AIDS epidemic to an end.

In his three years in office, President Clinton has increased funding for AIDS research by 26 percent, expedited AIDS drug approval, and strengthened the Office of AIDS Research at the National Institutes of Health.

At the conclusion of the two-hour meeting, Vice President Gore announced the following steps:

The Administration will join with pharmaceutical manufacturers, health insurance companies and other third-party payers, and patient advocacy organizations to develop

a collaborative system of clinical trials of AIDS drugs that have been approved by the FDA under expedited procedures to determine the best uses and the long-term effectiveness of those drugs.

The Administration will work with international organizations -- such as the World Bank -- to increase investment in AIDS vaccine development and trials worldwide.

The Administration will help facilitate the development of microbicides to enable women to protect themselves from HIV infection.

The Vice President will facilitate ongoing discussions between the government and the pharmaceutical industry to identify promising areas of AIDS research that the government can support in order to stimulate private sector investment in the next generation of AIDS vaccines, therapeutics, and microbicides.

The Food and Drug Administration will pursue additional measures to increase the number of anti-HIV therapeutics with pediatric indications.

Participants in Vice President Gore's Meeting
with Pharmaceutical Companies and AIDS Researchers
2/20/96

The following pharmaceutical company representatives participated in the February 20 meeting on AIDS drug development with Vice President Gore:

Anne-Marie Corner
President, Chief Executive Officer
BIOSYN

Manuel Navia, PhD
Vice President, Senior Scientist
Vertex Pharmaceuticals Inc.

Michael Riordan
President, Chairman
Gilead Sciences

Joseph Pittalli
Senior Vice President for Clinical Research
Wyeth-Ayerst Research

George Morrow
Group Vice President, Commercial Operations
Glaxo Wellcome, Inc.

Dan Hoth
Senior Vice President, Chief Operating Officer

Cell Genesys, Inc.

Peter Johnson
President, Chief Executive Officer
Agouron Pharmaceuticals, Inc.

Patrick Zenner
President, Chief Executive Officer
Hoffman-La Roche

Rajen Dalal
Vice President for Corporate Planning and Business Development
Chiron Corporation

David Pizzuti
Vice President for Anti-Infective Development and Medical Affairs
Abbott Laboratories

Eve Slater
Senior Vice President for Clinical and Regulatory Development
Merck

##

-
- Separate bill on
kids and cancer
drugs. Konstant
 - Not version that's close
to something we can get solved
at this pt.
-

○ Caynor / mand to ^{DR Council} ~~Secret~~ members w/ pat

- scheduling request for oncology initiative -
will get beat up Feb 21, 22nd -

- Can do it out

- Commerce Cmt.
Bilirakis hearing - beginning of March

- Kevin Thurm - working on moving to

PHOTOCOPY
PRESERVATION

closed

2/13/96

FDA REFORM -- KASSEBAUM BILL

Although there are several provisions in S.1477 that FDA believes could lead to constructive improvements and that FDA believes could be negotiated (e.g., the export and animal drug provisions), the bill as a whole is problematic. In particular, there are a number of provisions that we believe would compromise the health and safety of the American public. Most problematic are the provisions that undercut the efficacy standard, set unrealistic review times, impose the judgment of foreign governments, permit manufacturers to promote unapproved uses, and micromanage day-to-day Agency activities.

- **Undercutting the efficacy standard:** There are a number of provisions in the bill that would seriously undercut the efficacy standard -- either by changing the approval standard or by changing the approval process. For example, section 703 would require the Agency to accept "scientifically sound" studies in lieu of well-controlled clinical trials for medical devices. Section 407 would allow marketing and promotion of products on the basis of "sound medical practice." There are numerous examples of untested medical practices that turned out to be wrong (after all, the use of leeches was once a "sound medical practice" for treatment of a range of diseases). The key to the efficacy standard is that the use of a drug or device must be proven to be effective before it can be marketed or promoted. As a result, the U.S. probably has the most reliable drug supply in the world.
- **Shortened review times without adequate resources.** S.1477 would require FDA to meet extremely short deadlines (for example, 4 months for medically important drugs and 6 months for all drugs). Because no new resources are provided, the deadlines are unrealistic. Imposing such deadlines will undercut the progress we have made under the Prescription Drug User Fee Act of 1992 and may undermine the progress we are making toward shortening the overall time it takes to get drugs to patients. For example, because reviewers will be unable to spend time with sponsors clarifying information or answering questions, the only way sponsors will be able to get that information will be through additional review cycles. That means it will take longer for drugs to get to market. The alternative, though less likely, outcome would be that reviewers will approve drugs based on less information, with fewer analyses and much greater uncertainty about how the drug works and how safe it is. Shortened review times without adequate resources also means that the agency will have to strip away all work other than product approval reviews. We will no longer be able to guide companies as to what they need to do for approval. In addition, FDA will have limited involvement in the production and post approval stages. This will adversely impact the Agency's programs not related to product review (e.g., blood safety, food tampering, mammography).

- **Substitution of Judgment.** S.1477 would allow decisions of foreign governments or private reviewers to override FDA if the Agency does not meet the extremely short deadlines in the bill. The European system is untested and unevaluated. Moreover, although the bill would tie the FDA's hands regarding drug and device approvals, it would not require the same allegiance to foreign decisions to withdraw marketing approval or not to approve the product in the first place. With third party reviews, the risk is that we lose the independence and objectivity that FDA currently provides. The result of this provision will be that patients would no longer have the assurance that new drugs and devices are safe and effective. The substitution of foreign government approvals for U.S. approval is a particular vulnerability of the bill.
- **Promotion of off label uses.** Doctors are free to prescribe drugs for uses that have not been approved by FDA. Under current law, doctors are free to rely on any information they choose in making these prescribing decisions. Regulated companies, however, may not promote a use until the company provides FDA with evidence that the use is effective. S. 1477 would allow companies to distribute journal articles and other types of information about unapproved uses to promote those uses. The provision's advocates argue that it would encourage dissemination of useful scientific information, but in fact, drug company sales representatives can be expected to aggressively use journal articles to promote unapproved uses.

This too undercuts the efficacy standard. It allows manufacturers to promote uses that have not been proven safe and effective. Moreover, it would 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). As Joe Stiglitz pointed out at one of our meetings with the Vice President, such a provision would give the companies the incentive to get drugs approved for a very narrow use and then use journal articles and other means to promote for a much broader use. Companies would also have little incentive to provide physicians with balanced information (in fact, oftentimes only the positive articles are published). A better way to address off label uses is to get them on the label. In an effort to encourage companies to submit supplemental applications for off label uses, we are looking at ways to improve the Agency's performance in reviewing and approving efficacy supplements.

- **Micromanagement.** Although the stated purpose of S.1477 is improvement of FDA's management of the product approval process, the outcome is micromanagement of how the agency will meet the requirements set forth in the bill. 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.

FDA's Improved Performance

The driving force behind S. 1477 seems to be the argument that FDA takes too long to approve drugs and devices and that breakthrough drugs and devices reach the European market first. In the past five years, however, FDA has made tremendous progress in reducing drug approval times. FDA internal reforms, as well as new resources provided by the Prescription Drug User Fee Act of 1992 have resulted in the U.S. approving drugs as fast or faster than any country in the world. Since 1992, median drug approval times have decreased by 38%. In the past year alone, drug approval time was reduced by 13%. A recent study by the General Accounting Office found that the drug approval time in the United Kingdom was greater than in the United States.

Perhaps most telling, are our accomplishments under PDUFA. Under PDUFA, within 5 years (i.e., by 1997), decisions on important drugs are to be made within 6 months 90% of the time and decisions on all other drugs are to be made within 12 months 90% of the time. PDUFA also sets forth interim goals for approvals. FDA has not only exceeded the interim PDUFA goals, it is already meeting some of its 1997 goals. FDA's goals and actual review times for applications submitted in 1994 are listed below:

Standard applications (applications for new products)
goal -- 55% within 12 months
actual -- 96% within 12 months

Efficacy Supplements (applications for new indications)
goal -- 55% within 12 months
actual -- 73% within 12 months

Manufacturing Supplements (applications for manufacturing changes)
goal -- 55% within 6 months
actual -- 69% within 6 months

Resubmitted applications (for new products)
goal -- 55% within 6 months
actual 81% within 6 months

Despite the absence of user fees for device applications, the Device Center also has made significant progress over the past fiscal year in improving its premarket review program for new medical devices. The Center has virtually eliminated the 510(k) backlog -- from 500 a year ago to nine at the end of fiscal year 1995. The Center also has reduced the average review time for 510(k)'s from 182 days in fiscal year 1994 to 138 days in fiscal year 1995.

Over one-half of these devices were reviewed in 91 days or less. Finally, the Center was able to modestly decrease the average time it took to review a PMA from 21.5 months in fiscal year 1994 to 20 months in fiscal year 1995.

The Device Center also has been looking for ways to lighten its workload. As part of REGO, we recently announced that we are exempting 122 categories of low risk devices from premarket review, adding to the nearly 450 categories already exempted from such review. With this action, nearly 1/3 of all medical devices will be exempt from premarket review. We also are implementing a large pilot to look at third party review of certain low and moderate risk devices. It will probably be difficult to make dramatic additional progress on devices without additional resources. HIMA, the industry's largest trade association agreed to user fees in 1994, but the legislation was not enacted. Although the Administration has continued to include device user fees in the budget, the prospects for device user fees are not good at this time.

Conclusion

Despite all of the problems with S.1477, we are likely to see a much more sweeping "reform" bill coming out of the House. The bill has no cosponsors. Moreover, it appears that both parties are split on the issue. For example, on the Republican side, Senator Hatch does not think that Senator Kassebaum has gone far enough. A number of Democrats still have no firm position on FDA legislation. It is for this reason that, as you pointed out at our last meeting, it is critical that the Agency have strong, solid support from the White House.

The Agency has already gone a long way toward addressing industry concerns in our REGO proposals. We want to reaffirm that we are open to discussions and negotiated legislation is a possibility. At the same time, we want to strongly defend the statute's basic safety and efficacy standards. This consistently has been the position the President and Vice President have taken in the context of FDA reform efforts.

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

LRM NO: 4248

FILE NO: 1746

URGENT

4/29/96

LEGISLATIVE REFERRAL MEMORANDUMTotal Page(s): 3

TO: Legislative Liaison Officer - See Distribution below:

FROM: Janet FORSGREN *B. Pellicci* (for) Assistant Director for Legislative Reference

OMB CONTACT: Robert PELLICCI 395-4871 Legislative Assistant's Line: 395-7362

C=US, A=TELEMAIL, P=GOV+EOP, O=OMB, OU1=LRD, S=PELLICCI, G=ROBERT, I=J
pellicci_r@a1.eop.gov

SUBJECT: HHS Fact Sheet on "one-pager" of concerns about S. 1477, Kassebaum's FDA reform bill.

DEADLINE: 10:00 a.m. Tuesday, April 30, 1996

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

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

COMMENTS: HHS staff intend to distribute the attached "one-pager" to congressional staff tomorrow afternoon.

DISTRIBUTION LIST:

AGENCIES: -Executive Office of the President - EOP Review Only, See Distribution -

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Greg Simon
Elizabeth Dyre
Chris Jennings
Ira Magaziner
Dan Tate
Barry Clendenin
Richard Turman
Jim Esquea
Jonathan Winer
Jim Murr
Janet Forsgren

FILE NO: 1746

Please include the LRM number shown above, and the subject shown below.

_____ Concur

_____ No Objection

_____ No Comment

_____ See proposed edits on pages _____

_____ Other: _____

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

KASSEBAUM BILL**A. Most Serious Concerns**

1. Contracting Out/Timeframes/Hammers (Sections 103, 403, 404, 709, 806)
2. Privatization (Section 709)
3. Off Label Use (Formerly Section ~~607~~)
4. Health Claims (Section 903)
5. Medication Guides (Section 607)

B. Serious Concerns That Probably Can Be Readily Resolved

1. Product Approval Standards (Sections 602, 703, 802(a))
2. Product Erosion (Manufacturing Changes/Modifications)(Sections 604 & 702(d))

C. Other Significant Concerns

1. Mission Statement (Section 101)
2. Information Systems/Policy Statements (Sections 105 and 106)
3. Advisory Committees/Appeals (Sections 107 and 108)
4. Access to Unapproved Uses/HUD Exemptions (Section 202 and 203)
(Humanitarian Use Device)
5. Clinical Research of Drugs, Biologics, & Devices (Sections 302 & 303)
6. Effectiveness Determination (Uses not on label)(Section 408)
7. Pediatric Labeling (Section 411)
8. State and Local Requirements Respecting OTC Drugs (Section 608)
9. Initial Classification of Devices (Section 702(b))
10. Device Tracking (Section 704)
11. Combination Animal Drugs/Minor Species (Sections 802(b) and (d))
12. Indirect Food Additives (Section 902)

* Section 406 - Environmental Assessment Provision - should be Reviewed by CEO/White House.

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

4/25/96

LEGISLATIVE REFERRAL MEMORANDUM

LRM NO: 4220

FILE NO: 1746

Total Page(s): 7

TO: Legislative Liaison Officer - See Distribution below:

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

OMB CONTACT: Robert PELLICCI 395-4871 Legislative Assistant's Line: 395-7362
C=US, A=TELEMAIL, P=GOV+EOP, O=OMB, OU1=LRD, S=PELLICCI, G=ROBERT, I=J
pellicci_r@a1.eop.gov

SUBJECT: HHS Fact Sheet RE: S1477, Food and Drug Administration Performance and
Accountability Act of 1995

DEADLINE: NOON Monday, April 29, 1996

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

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

COMMENTS: According to HHS staff, Senate Democrats have requested the attached Fact Sheet as soon
as possible.

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Jim Esquea
Jonathan Winer
Janet Forsgren

**RESPONSE TO
LEGISLATIVE REFERRAL
MEMORANDUM**

LRM NO: 4220

FILE NO: 1746

If your response to this request for views is short (e.g., concur/no comment), we prefer that you respond by e-mail or by faxing us this response sheet.

If the response is short and you prefer to call, please call the branch-wide line shown below (NOT the analyst's line) to leave a message with a legislative assistant.

You may also respond by:

- (1) calling the analyst/attorney's direct line (you will be connected to voice mail if the analyst does not answer); or
- (2) sending us a memo or letter

Please include the LRM number shown above, and the subject shown below.

TO: Robert PELLICCI 395-4871
Office of Management and Budget
Fax Number: 395-8148
Branch-Wide Line (to reach legislative assistant): 395-7362

FROM: _____ (Date)
 _____ (Name)
 _____ (Agency)
 _____ (Telephone)

SUBJECT: HHS Fact Sheet RE: S1477, Food and Drug Administration Performance and Accountability Act of 1995

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

_____ Concur

_____ No Objection

_____ No Comment

_____ See proposed edits on pages _____

_____ Other: _____

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

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THE IMPACT OF S.1477

The United States Senate is considering S.1477, "The FDA Performance and Accountability Act," which is intended to reform many of processes used by the Food and Drug Administration to regulate the nation's food, drug, biologic, medical device, and animal drug manufacturers. The bill has been approved, with substantial amendments, by the Senate Committee on Labor and Human Resources, and will soon be scheduled for a vote by the full Senate.

Many of the provisions of S.1477 are concepts supported by the FDA. For example, FDA has expressed agreement with such concepts as holding the agency to set performance standards, expediting marketing review of drugs and medical devices for serious medical conditions, having some FDA inspections contracted out to private organizations, reducing the current requirements for environmental impact reviews for new drugs and food additives, enhancing the exportation of unapproved new drugs and devices, repealing outmoded requirements for insulin and antibiotics, exempting most less-dangerous medical devices from FDA premarket review, and many other such provisions. However, the agency has objected to some provisions of S.1477 as radical and inappropriate changes in the safety standards under which FDA has operated for many years to protect the public from unsafe products. Examples of such provisions are listed below.

Much of FDA's Responsibility for Assuring Safety Would be Privatized. The bill requires that FDA contract out safety reviews of new drugs, biologic, medical devices, and food additives if the agency does not meet deadlines established in the

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bill. Because such deadlines are virtually impossible to meet with current resources, FDA would be forced to reduce its work force significantly to free up funds to pay for the private contracts. Of special concern is the private review of medical devices that would be mandated. For devices, medical device companies could hire and pay the reviewer directly. Thus, even potentially dangerous devices such as heart valves and pacemakers would be approved for marketing by reviewers chosen and paid by the companies making the products.

Relies on Foreign Approvals for Approving Products Used by Americans. The bill would force FDA to give approval preference to drugs, devices, animal drugs, or food additives approved in Europe, if the manufacturer requests it. So, for example, a drug approved in Portugal must skip over other drugs being reviewed by FDA, and FDA must make a hasty decision (within 30 days) on whether to approve the drug.

Manufacturers Would be Permitted to Make Dangerous Changes in Their Products.

For drugs and biologics, a manufacturer currently must notify FDA before it changes the way the product is manufactured, a provision that was established to prevent inadvertent or unknowing hazards to be created. This bill would eliminate that requirement for some such changes. For example, a manufacturer of Salk polio vaccine once changed a type of filter used in manufacturing the vaccine without notifying FDA, but the change led to live polio virus in the vaccine. The result was eleven deaths and more than 200 people receiving polio. This bill would permit such changes to occur routinely. For medical devices, similar notification of design changes is now required but would be eliminated under this bill. This enormous "loophole" will prevent FDA

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from protecting Americans from faulty design changes in devices. For example, in the 1980s a heart valve manufacturer (Shiley) made "improvements" in an FDA-approved heart valve; FDA rejected the changes due to inadequate evidence of safety and effectiveness. The company then marketed the "improved" valve overseas, but was forced to cease three years later when thousands of premature, sudden deaths occurred (the new version proved to break easily in real use). If the Senate bill been in effect at the time, Shiley could have marketed the new valve in the U.S. and thousands of deaths might have resulted.

FDA Would Be Prohibited from Ensuring that Patients Get Information About Their Prescription Drugs. FDA is preparing a regulation to encourage pharmacists to give patients leaflets alerting them to important information about their drugs when they pick up a prescription (containing use information, adverse effects, warnings such as avoiding certain foods or other drugs while taking the medicine, what to do if they a side effect, etc.). The program was designed to take effect only if the private sector failed to keep its promise to meet these goals by the turn of the century. The Senate bill prohibits FDA from pursuing the program, even though it could reduce the estimated \$20-100 billion wasted each year on hospitalization and doctor visits resulting from medication errors.

Permits Unsubstantiated Health Claims on Foods. In 1990 Congress cleaned up years of confusing, misleading food labeling with legislation requiring food companies to prove that health claims on foods were valid. Many are now allowed if there is valid

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evidence, such as "foods low in fat can reduce the risk of cancer or heart disease." But the Senate bill would allow a food to make a label claim that it prevents disease based on even the most preliminary conclusions by a Federal agency or the National Academy of Sciences (NAS). For example, beta carotene for years was suspected of having cancer fighting qualities, and NAS publications reflected that emerging belief. However, controlled studies subsequently found no effect in most people and increased cancer in some. If this bill had been law, foods and dietary supplements with beta carotene would have been permitted to make claims that those products lowered the risk of cancer, and millions of Americans would have been lured into either wasting their money or being subjected to increased cancer risk.

Many Animal Drugs Could Be Marketed without Demonstrating Effectiveness.

Currently, all animal drugs must be proven to work as well as be safe. This bill would remove the efficacy requirement for animal drugs used in "minor" species, which includes most animals other than livestock, poultry and dogs and cats. Thus, an outbreak of Ebola virus could occur in this country, with transmission possible to humans, and the drugs used to treat it would not even be required to be effective.

Many Food Additives Would Be Reviewed Under an Unreasonable Time frame.

The bill gives FDA only 90 days to approve an "indirect" food additive, such as a new packaging material. Thus, millions of Americans could be exposed every day to a dangerous food additive that could leach into their foods (and for which FDA had insufficient time to assure could be safely used). For example, in the 1970s FDA was petitioned to approve the plastic acrylonitrile for use in soft drink bottles. The agency had concerns that took years to fully identify (the substance was eventually found to

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be a very potent carcinogen and to cause birth defects). The manufacturer was subsequently able to reduce the levels of impurities 1000-fold and the agency then approved the bottles. If this bill had been in effect, the agency would have either been forced to approve a very hazardous product with limited data or to disapprove a product that was subsequently improved enough to be safely sold by its manufacturer.

Karen ^{J. Callman} ~~Colen~~ 6-19-61

- Call w/ Corporate Contact -

- Jonathan Winer -

- prepared -

WHA / Agency / FDA

- 3 House bills -

- Rhetoric moderate -

- drafting extreme -

- Kessler Skelton

} fall through
point then as
moderate bills

- Testimony

- Sec-by-Sec.

- Kay Hollen asked for document

- Brief tomorrow -

mtg. on Sally's schedule for Monday

- Meet w/ Kennedy, Mon pm

- Four Dem Staff. -

- heads-up that when we're
slamming House - ~~not~~ slamming
FDA reform

- For reform }
{ The Senate bill }
{ ~~is~~ these changes }
is a moderate
bill -

Is testimony

- House Democrats want something
they can circulate -

- House Democrats ~~staff~~ staff need

Conv. w/ Jane Lowerson 4/24

Pilot when Nodd voted for it - had said ~~here~~
was against it. Was willing to
try it as a pilot.

- Positive suggestion on the Coats
language - something we can
show w/ plane,
- Vince Bentaniglia on Coats -

Deadline
Index - Some of the R's are attached

- Manufacturing Changes - FDA working out
- Pharmacy Guides -
Specifics on the language -
- precludes -
↳ negates FDA's

Devote Pilots

- Having only Dem who voted for it -
- Oreg -

12:20-

Tues & Wed - Testifies -

May 1st May 2nd Appropriations

hearing - Should be put down a

~~Ames~~ a marker

- eliminated the ability to regulate
blood safety -

Not shall but Strong — In House

~ We're for reform

~ Lay out good things the Senate does. —

↳ talk moderate / this is an extreme bill [device, food, drugs and biologics]

KESSLER'S TESTIMONY

Review Process

- "demonstrate net benefits that are greater than the risks"
- safe enough (inview of the benefits and cmparative benefits of other availabele treatments)
- review of primary data (pp. 18-19):
 - responses were correctly categorized; judgemental endpoints are supportd by objective data;
 - adverse events are correctly categorized as to severity and causality
 - assess impact of drug on parameters not summarized by sponsors
 - argues: facilitates faster analysis

Proposed Reveiw Times

- compromise existing heath protection
 - no opportunity to obtain clarifications
 - companies ready to manufacture so FDA can start pre-inspection approval
 - compromise effectiveness of advisory committee
- cost
- add'l review cycles
 - decreases work on other functions (e.g. advising on clinical design phase, decrease production and post-approval review)
 - decrease unrelated work (e.g. safety of blood supply, food safety and tampering)

Sec. 407. Sound medical practice (p.28)

Sec. 702. Eliminate approval of devices for specific uses (p.30)

- recognize any use "included within a general use for a predicate device" as an approved use for 510(k) devices
- no assurance of clinical effectiveness, independent review, or accurate labeling

Sec. 703. Require FDA to accept scientifically sound studies

- in lieu of well-controlled clinical trials (p. 31). . . reversing the most significant component of 1962 Act

Sec. 702 and 707. "Eliminate FDA's role in assuring that modifications made to a product do not adversely affect its safety and effectiveness.

-- modification could form the basis for new use claims -- not reviewable

Eliminating comparative effectiveness

Sec. 408 Limits agency review to uses explicitly included as label claims. (p. 35) May preclude FDA requiring info on label about indications for which the drug should not be used.

FDA review bypass provisions

1962 drug amendments and 1990 device amendments eliminated approval by default.

- Sec. 404 -- if FDA fails to meet deadlines, approved if approved in other country.
 - EC program new/untested
 - could provide foreign owned (particularly gov't subsidized) companies w/competitive advantage
- Sec 743 -- third party review if FDA fails to meet deadlines
 - also extends to manufacturing review, and prohibits FDA from inspecting for 2 years.
- Sec. 606 default if FDA misses 30 day reinspection deadline.
- Sec. 902 if FDA fails to review indirect food additives w/in 90 days.

Expanded Access

- Sec. 202 allows company to promote product for any serious disease or condition without "comparable or satisfactory" therapy.
 - no cost recovery req. or req. for enrollment in clinical trials.
 - cites 1995 HHS IG report finding that commercialization of unapproved medical devices shows predatory business practices under today's law

Advisory Cmt's

- increased mtgs.
- tripple advance notice times for mtg.
- increased appeals of first-line decisions

Limiting Flexibility

- sec. 402 -- consider certain products in particular divisions.

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"The FDA Performance and Accountability Act"**SECTION BY SECTION ANALYSIS OF
S.1477 AS REPORTED OUT OF COMMITTEE****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, or any other regulatory action relating to product review; and (2) the scheduling of advisory committee meetings and actions subsequent to committee recommendations. The performance standards must establish objectives to expedite the clinical investigation of drugs, devices and biologics, expedite applications, reduce backlogs, establish a schedule to bring the agency into compliance with the time periods specified in the bill by July 1, 1998, and improve the consistency and fairness of the agency's regulatory process. 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

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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 may increase significantly the number of application 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

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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 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. 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 a chair have X amount of experience).
- 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 would be to require FDA to make a determination within 60 days or to notify the affected persons of the reason why a decision has not been made and the timetable by which a decision will be made.

Sec. 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 or made by the agency.
- 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

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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 should be limited to decisions that have been made -- not issues that are pending.
- The section 907(d) 60 day timetable for final determination is problematic. A better approach would be to require FDA to make a determination within 60 days or to notify the affected persons of the reason why a decision has not been made and the timetable by which a decision will be made.

**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 a codification and 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.

DRAFT**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 a 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 requires FDA to review, within 6 months, applications for (1) drugs or biologics for an immediately life-threatening or serious disease or condition that provide therapy or diagnosis not available or offer 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 provide therapy or diagnosis not available from another approved device or offer a significant improvement over another approved device.

DRAFT**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 a clinical hold within 30 days -- it precludes telephone calls. This would allow less time to review a clinical investigation notification because a letter has to be drafted. A preferable approach would be to require a telephone call within 30 days followed by a letter within an additional 30 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 On 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 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

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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 scientific or clinical need. 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****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(a) authorizes FDA to contract with outside organizations or

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individuals.

- Section 403(b) directs FDA to use this authority (A) for the review of categories of indirect food additive petitions and submissions under section 510(k); (B) to improve the efficiency, timeliness, and quality of the review of applications, petitions, and notifications for the approval and clearance of new drugs, new animal drugs, biologics, food additives, and devices; and (C) to increase the scientific and technical expertise necessary to keep informed of emerging new therapies and technologies. FDA retains full authority to make determinations with respect to approval or disapproval of any product.

Sec. 404. Prompt and Efficient Review ***

- Section 404 requires FDA to establish procedures and policies to facilitate a collaborative review process with the applicant.
- New section 743(b)(2) (requiring certain meetings during the review period unless both sponsor and FDA say unnecessary) will slow down review process. A preferable approach would be to require a meeting prior to the submission, a meeting one half way through the statutory review period, and consultation as appropriate throughout.
- Section 743(b)(4) requires FDA to provide applicants prior to the required meetings with a letter describing the application deficiencies and information necessary to bring the application into a form that would require approval. This essentially cuts the already unrealistic review period in half. One possible fix might be to require FDA to describe deficiencies identified to date and to state what would be required to remedy such deficiencies.
- The bill sets forth unrealistic timeframes without considering resources. It shortens the review times agreed to and funded under the Prescription Drug User Fee Act of 1992. The agency has not and cannot meet the deadlines set forth in the bill using existing resources.
- 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, at the request of the applicant, FDA must within 30 days either approve or disapprove the application.

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- ~~Section 743(d) requires FDA to contract 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 set forth above, the agency has not and cannot meet the timeframes set forth in the bill. Failure to meet the deadline for even one application could trigger the contracting out requirement. Alternatively, if the agency rushes a decision in order to avoid the contracting out hammer, it may have to choose between having more disapprovals or compromising the safety and efficacy by approving products without a thorough review. If contracting out is triggered, the agency will have to significantly reduce its work force in order to pay for the contracting out. This will create an administrative nightmare. The American public will suffer the consequences of a consumer protection agency that has been hollowed out by hammer provisions used to enforce unrealistic and unrealizable performance goals.

Sec. 405. Good Manufacturing Practice Inspection

- Section 405 permits FDA to accredit organizations to conduct inspections to evaluate manufacturers' compliance with requirements for GMP.
- There is no discussion of costs. This is particularly important re: foreign inspections.
- The bill should have 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 of accreditation 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

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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. The provisions that would have allowed 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 were stricken from the bill. A substitute provision, however, is likely to be considered when the bill goes to the floor.

There are major problems with any provision that would allow manufacturers to promote uses that have not been proven safe and effective. Such a provision undercuts the efficacy standard. 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). Off-label use promotion must, at the very least, be tied to submission of an application supporting the off-label use.

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

- Section 408 provides that the determination of effectiveness cannot include the evaluation of cost effectiveness or clinical outcomes, unless the labeling references such.
- Section 408 also provides that the review of an application cannot include the evaluation of any use not included in the labeling. This appears to prohibit FDA from including, in the labeling, warnings about indications for which a product is dangerous or known not to be effective.

DRAFT**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.
- This provision is problematic if it would require FDA to complete its review of a submission within a few days of receiving a substantial amount of new information.

Sec. 410 Alternate Approval of Supplemental Applications

- Section 410, which was replaced during mark up, provides a process for facilitating the submission and review of efficacy supplements.
- It requires FDA to:
 - (1) set performance standards for the prompt review of supplemental applications;
 - (2) provide guidance to industry to clarify the requirements for efficacy supplements and to facilitate the submission of data to support approval of supplemental applications;
 - (3) designate an individual in each Center with responsibility for encouraging the prompt review of supplemental applications and working with sponsors to facilitate the development and submission of data to support supplemental applications; and
 - (4) implement programs and policies to foster collaboration between FDA, NIH, professional medical and scientific societies, and others to identify studies that could support a supplemental application and to encourage sponsors to make such an application or conduct the research to support an application.

DRAFT**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, there are concerns about whether the provision is sufficiently tailored so that it applies to important uses and as to whether a 6 month exclusivity in many cases may be too generous an incentive.

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**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 adequate well-controlled studies to requiring, at most, one well-controlled study. The provision is extremely problematic if it would prohibit FDA from requiring more than one adequate and well-controlled trial when necessary. Ordinarily, replicated evidence is expected, but FDA, in particular circumstances, may rely on a single adequate and 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. In addition, the phrase "adequate and" does not appear in section 602. The phrase is important because studies may be flawed for reasons other than the control group.

DRAFT**Sec. 603. Pilot and Small Scale Manufacture**

- Section 603 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 ***

- Section 604 permits manufacturers of drugs and most biologics to make many changes in manufacturing without prior approval as long as there is not a resulting change in formulation or release specifications and the changes are validated and records are made available to FDA during inspections.
- Changes that do not affect formulations or release specifications, however, can still change the safety and effectiveness of a product. For example, in the infamous "Cutter" incident with Salk polio vaccine, the company simply changed the type of filter used during manufacturing of the vaccine. No change in formulation or release specifications resulted, but the change in filter led to live virus in the product. Eleven people died and about two hundred more got polio. This provision also would allow a company to change the strain of a virus used for a vaccine or to change the detergent used to cleanse a

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blood derivative of HIV virus, both of which raise serious safety concerns.

- FDA already has undertaken to reduce the number of manufacturing changes that require pre-approval.
- CDER is working diligently with industry to delineate a series of science-based recommendations for the tests and filing requirements when change occurs in the manufacture of an approved new drug. The first of this series is a guidance termed SUPAC-IR, which is intended to provide guidance for immediate release (IR) solid oral dosage forms. Further guidance documents are planned for other types of new drug dosage forms, including extended release solid oral dosage forms, liquids and semisolids, and 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 a substantial risk of adverse effects on product purity, potency, or safety.
- CVM is taking steps towards revising its regulations to ease the process of submitting and reviewing manufacturing changes by better categorizing the types of manufacturing changes, better characterizing the procedures for handling changes, and more appropriately correlating submission and review procedures with the particular categories of changes.

Sec. 605. Insulin and Antibiotics

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

Sec. 606. Modernization of Regulation of Biological Products

- Section 606 amends the Act so that a single license application (rather than separate product and establishment license applications) will be required for all biologics. The amendment gives FDA authority to require establishment information for those biological products for which it is necessary. The language is drafted in a way that provides FDA flexibility to deal with new technologies.

DRAFT**Sec. 607. Effective Medication Guides *****

- Section 607 (an amendment agreed to by the Committee) precludes FDA from implementing its proposed MedGuide program. The MedGuide program would ensure that patients receive useful written information when they get a new prescription (including information about how to take the drug, side effects, and dangerous interactions with foods or other drugs).
- FDA's proposal would have deferred a mandatory program until the year 2000 to give the industry time to implement the voluntary program they have promised since 1980. The amendment prohibits FDA from even providing guidance on the development of the voluntary program.
- Misuse of prescription drugs accounts for many injuries and deaths and costs about \$20 billion in health care costs per year. Since drug companies are permitted to promote prescription drugs, FDA should be permitted to help insure that consumers receive accurate information.

Sec. 608. Requirements For Radiopharmaceuticals

- Section 608 (an amendment agreed to by the Committee), requires FDA to establish regulations governing the approval of certain radiopharmaceuticals. It requires CDER to expedite review of all such applications.

Sec. 608. State and Local Requirements Respecting Nonprescription Drugs Intended for Human Use (Two of the Gregg amendments added a section 608)

- Section 608 prohibits States from imposing requirements for over the counter drugs that are different from or in addition to FDA requirements. FDA may, by regulation, provide for an exemption from the requirements of this provision if it is justified by compelling local conditions or protects an important public interest that would otherwise be unprotected and it would not cause the OTC drug to be in violation of a Federal law, and it would not unduly burden interstate commerce.

DRAFT**Title VII. DEVICE REGULATORY REFORM****Sec. 701. Short Title****Sec. 702. Premarket Notification (see notations on individual provisions)**

- Section 702(a) exempts from FDA review all class I devices except those that FDA determines require a 510(k) to protect the public health and that the FDA lists in the Federal Register within 15 days of enactment. 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 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.
- ** ● Section 702(b) would permit a 510(k) submitter to request advisory committee review of classification decisions prior to final classification. This is a workload issue. In addition, many 510(k) submissions do not contain adequate or sufficient information to warrant advisory committee review. The timeframes for panel meetings are unrealistic.
- Section 702(c), the substantial equivalence provision, would specify that each use reasonably included within a general use for a predicate device "as determined by the Secretary" shall be deemed a legally marketed use for purposes of premarket notification. The phrase in quotations was added during mark up to address concerns that, as originally drafted, the provision would require FDA to accept any general use as a predicate for more specific uses of the same device.
- ** ● Section 702(d) -- the device modification provision -- was amended to address concerns that device manufacturers would be able to make significant and potentially dangerous modifications without submitting any data to FDA. Although the provision is improved, it still fails to address the need for manufacturers to submit 510(k)s when they make significant manufacturing changes or modifications.

DRAFT**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.

Sec. 704. Tracking *

- Section 704 amends the device tracking provision to require a regulation for imposing a tracking requirement, limits tracking to class II and III devices, changes the criteria for a tracking requirement, and eliminates FDA's discretion to apply the provision to "any other device."
- 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 was made more acceptable by adding "would be reasonably likely to be" before "life threatening." It would be preferable if the "permanently implantable" language was changed to "implanted for more than 30 days."

Sec. 705. Postmarket Surveillance

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

DRAFT**Sec. 706. Device Distributor Reporting**

- Section 706 would eliminate distributor reporting.

Sec. 707. Premarket Approval **

- Section 707 includes unrealistic timeframes. By requiring FDA to meet with companies within 90 days and to present a description of deficiencies in the application and "what information is required to bring the application into a form that would require approval," the bill actually requires FDA to do a comprehensive review in one half the current statutory timeframe. It also would require FDA to use advisory panels more often than is currently necessary. The provision would require panels to convene more often than is possible, thus creating a disincentive for qualified experts to take on this government service.
- 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 organizations. The provision requires FDA to recognize all standards adopted by a designated standard setting organization, but FDA may revoke recognition of a performance standard if it determines that the standard is insufficient to provide a reasonable assurance of safety and effectiveness. Manufacturers would certify compliance with the standards.
- 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, 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. In addition, companies should not be permitted to self-certify compliance with recognized standards. Even the EU requires third party certification.

DRAFT**Sec. 709. Accredited Party Participation *****

- Section 709 (an amendment adopted by the Committee) would require FDA, within one year, to allow third party review of any device marketing application, at the request of applicants. It would allow medical device companies to pay private companies to review applications to market devices.
- This provision leaves no discretion to the agency to retain for review even the most complicated or potentially dangerous devices. It permits third party review of devices ranging from heart valves to products used to test the blood supply. It allows the party whose product is being reviewed to choose and directly compensate the third party reviewer. This financial arrangement creates serious conflict of interest potential.

Title VIII. ANIMAL DRUG APPROVAL STANDARDS**Sec. 801. Short Title****Sec. 802. Evidence of Effectiveness ****

- Section 802(a) amends Section 512(d) of the FDC Act to redefine the "substantial evidence" criteria that currently must be met to establish efficacy. The provision changes the substantial evidence requirement from adequate and well-controlled studies to scientifically sound studies. The requirement that the studies fairly and reasonably show effectiveness has been changed to a requirement of a reasonable assurance of efficacy. The provision also eliminates the requirement for field investigations.
- Section 802(b) lists factors to be considered by CVM when approving combination drugs. It does not require sponsors of combination animal drugs to demonstrate effectiveness for their products; they would be permitted to include in a combination animal drug two or more drugs that are targeted to the same indication without having to show that each drug provides some additional benefit.
- Section 802(d) eliminates the requirement that sponsors establish the effectiveness of a drug intended for use in a minor species or intended for a minor use.

DRAFT**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 the manufacture of drugs 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.

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The Following REGO Related Provisions Not Currently in the Bill 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.

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. FDA may not simply permit a "notified substance to go on the market; it is required to act by regulation to "approve" a notification. 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.

Sec. 903. Health Claims of Food Products **

- The committee adopted this amendment that would permit companies to include in the labeling of food products claims that have been recommended by NIH, CDC, or the National Academy of Science.
- This provision fundamentally alters the criteria for health claims that were so carefully worked out in the Nutrition Labeling and Education Act of 1990.

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Under the bill, there would be no single body to make decisions on health claims, and the result could be inconsistent decisions by different organizations using different standards. Companies would be allowed to pick and choose among government bodies.

**Title X. ESTABLISHMENT IF CENTERS OF EDUCATION AND
RESEARCH ON DRUGS, DEVICES, AND BIOLOGICAL
PRODUCTS**

Sec. 1001. Centers for Education and Research on Drugs, Devices, and Biological Products

- Section 1001 (an amendment agreed to by the Committee) directs the Secretary, acting through the Commissioner, to establish a consortium of 3 or more centers for research and education on drugs, devices, and biological products and to make grants to 3 or more private entities to assist in the establishment and operation of a center for research and education.
- This amendment was agreed to subject to appropriations being provided.

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1477.SBS

Incorporating Comments from GC (Ann Wion, Seth Ray, Linda Kahan, and Gail Schmerfeld)

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

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TO: washfax

FROM: washfax

SUBJECT: Life Science April 12, 1996

Life Science
April 12, 1996

COMPARING PROPOSALS FOR FOOD AND DRUG ADMINISTRATION REFORM

Whether by "reinventing" the Food and Drug Administration (FDA) or simply by clarifying the agency's mission, both the administration and Congress are bent on reforming the agency that oversees the development and approval of our nation's drugs and medical devices.

A Senate bill introduced last fall was joined recently by a Republican sponsored House effort. Both the House and Senate bills include proposals to clarify the agency's mission.

The Senate bill, introduced by Nancy Kassebaum, R-KS, would establish that FDA's mission includes the "rapid and efficient development and availability of safe and effective products." The House bill also has language for "prompt and efficient review," but goes on to require that FDA "harmonize" its regulatory criteria with those of other countries.

The Kassebaum bill would require FDA to develop and publish standards for the review of drugs and new medical devices that would expedite investigation of new biologics through closer collaboration with product sponsors, expedite breakthrough drugs for conditions for which alternative therapies are not effective, eliminate application backlogs, and establish performance goals that bring FDA into compliance by 1998.

The House bill would also encourage greater collaboration between the FDA and investigators, establish "pre-research ground rules," that detail the information the agency needs to consider an application, and clarify the agency's standards for effectiveness of new products.

While current law requires one or more clinical investigations to establish efficacy, authors of the House bill say FDA often interprets this requirement to mean "at least two" studies, and their bill is meant to remedy that misconception.

The Kassebaum bill would require FDA to report annually on its compliance with performance standards. If any of the agency's divisions demonstrated an inability to complete at least 95% of its reviews within its deadlines, FDA would be required to contract with outside reviewers for the backlog and for new applications.

The House bill claims to strike a "middle ground" on third party reviewers by giving applicants the option of requesting FDA-accredited independent third party reviewers from the beginning. Third party reviews, the cost of which would be borne by applicants, would be carried out using standards "virtually identical" to those of the agency and would be subject ultimately to agency approval.

Sponsors of new drugs or medical devices could provide unapproved products to physicians and their patients under the Senate bill. The measure would also require expedited review of drugs and devices--in as few as four months--for conditions for which there are no satisfactory alternative therapies.

If a product had already been approved by the European Union and FDA was unable to complete its review within target time periods, the agency would be required to approve or disapprove the product and, in the case of a disapproval, explain its reasoning in writing.

The House bill would also create a "fast track" for the approval of applications for new drugs for serious or life-threatening conditions, would streamline the approval process for "off-label" uses of existing drugs, and allow greater use of experimental medical devices "when the risks posed by not using the device exceed the risks of doing so."

It would also bring FDA's review standards closer to "nationally-or internationally recognized consensus standards in addressing safety and effectiveness questions."

But patient advocacy groups and other consumer organizations say they are concerned about the potential consequences of the congressional reform proposals.

The American Association of Retired Persons (AARP) said it approves of expediting potentially life-saving drugs and devices to patients, but opposes any measures that would weaken FDA's protective role.

"While there have been legitimate complaints about the FDA's delay in approving some drugs and devices, the agency has greatly improved its approval process in recent years," AARP Executive Director Horace Deets said in a letter to Kassebaum.

"AARP supports efforts to continue to improve the FDA's performance, provided such efforts do not jeopardize the health and safety of consumers," Deets added.

The reform initiative announced by the administration last week, which is pursued under the aegis of Reinventing Government (RIGO), is specifically tailored to cancer drugs. The proposals include a change in FDA's drug approval process that would allow it to cut review time for cancer drugs in half, from 12.4 months to 6 months.

According to the administration, cancer patients would also have access to drugs approved as safe and efficient abroad, even while the drugs are undergoing tests for approval in the United States.

The proposal would also allow companies to market treatments that are still being tested, cutting several years off the time needed to get a drug to market, President Clinton told a White House audience.

"We're sending a message loud and clear," Health and Human Services Secretary Donna Shalala added. "When it comes to approving cancer drugs, we can honor the public trust and maintain the public health."

NOTICE

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Statement

PRMA

The Need for FDA Reform

Problems with Current FDA Practices

Pharmaceutical Research and Manufacturers of America

April 17, 1996

Pharmaceutical Research and Manufacturers of America

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INTRODUCTION

H.R. 3199, the Drug and Biological Products Reform Act, would greatly streamline and improve outdated FDA processes. It would shorten the too-long drug development and approval process and make it more efficient. Patients would have more timely access to needed therapies and manufacturers would work with a more responsive and efficient agency on the common goal of helping those patients who need pharmaceuticals. H.R. 3199 is a moderate bill which provides for needed reform of the FDA while carefully maintaining the agency's focus on safety and efficacy.

The following papers explain how each provision of H.R. 3199 would solve an existing problem at the FDA. Although PhRMA has proposed several changes, including technical amendments, we fully support H.R. 3199. Taken as a whole, the provisions in the legislation offer a blueprint for creating an agency that is able to meet the challenge of the 21st century: making the most sophisticated therapies available to patients as soon as possible without compromising safety or efficacy.

FDA MISSION AND ANNUAL REPORT TO CONGRESSProblem

Currently, the Food and Drug Administration has no statutorily defined mission statement. As a result, the agency's perception of its mission is often ambiguous and subject to change as agency personnel and Administration priorities change. The agency must have a defined mission which reflects the equally important goals of promoting the public health (through approval of safe and effective products) and protecting the public health (through preventing unsafe and ineffective products from reaching the market).

Solution

H.R. 3199 defines a mission for the agency. The mission statement includes promoting and protecting the public health without impeding innovation or product availability. The mission statement also requires that FDA work with the regulatory agencies of other countries to reduce the burden of regulation, harmonize regulatory requirements and achieve appropriate reciprocal arrangements.

H.R. 3199 also requires the agency to submit an annual performance report to Congress. Congressional Committees currently investigate the FDA, but the review is always on an ad hoc basis regarding specific products and problems. H.R. 3199 remedies this lack of day-to-day accountability by requiring the FDA to report on its progress in meeting performance standards and deadlines, its staffing and resource levels, its accreditation of third parties to conduct reviews and inspections, and its goals and activities with international organizations. The agency would also be required to benchmark its performance against comparable agencies in other countries.

These provisions will help improve agency accountability and ensure adequate performance data to allow effective oversight, but the bill should be amended to include clear performance measures. Improved performance can be better achieved and measured by adding a permanent panel of outside experts to oversee the agency's policy and performance, and/or requiring that FDA publish quantifiable standards relating to its performance. (H.R. 3199, §2)

STREAMLINING CLINICAL RESEARCH: IND REFORM

Problem

FDA's IND process is far more burdensome than that required in Europe. The agency currently requires that all clinical investigations (tests on human volunteers) be conducted only after submission of an IND (Investigational New Drug Application) that contains detailed information about the drug and the results of prior studies (usually in animals). Numerous blue-ribbon groups have found that FDA's burdensome requirements discourage early clinical research on new drugs. As a result, an increasing amount of this research is being transferred to Europe -- causing the loss of research funds in the U.S. -- particularly to universities and non-profit research centers -- and the loss by clinical investigators in the U.S. of early experience with new drugs.

In addition, the clinical hold procedure, by which the FDA stops the conducting of trials, has become unpredictable and arbitrary, and there is no deadline for the removal of a hold.

Solution

H.R. 3199 would allow clinical research to begin 21 days after a manufacturer notifies the FDA, unless the FDA affirmatively disapproves the IND. The notification would contain adequate information to assess the safety of the compound. The FDA would be allowed to request additional information if needed to protect the public health.

H.R. 3199 also clarifies the clinical hold procedure. A clinical hold could be put on any trial if the Secretary had information that the drug represented an unreasonable risk to the safety of the trial subjects. The reasons would have to be specified in writing and the FDA would have to respond to a request to remove a hold within 15 days.

Because of concerns about Phase I research moving to Europe, the FDA issued an IND Guidance on November 20, 1995, essentially deregulating much of early clinical research. The Guidance eliminated many manufacturing requirements irrelevant to "first in man" studies, streamlined clinical hold procedures, and improved pharmacological toxicology requirements. H.R. 3199 codifies the FDA's administrative improvements and further reforms this important process. (*H.R. 3199, §3*)

Example

A drug company wishes to begin testing a promising new compound on humans. Animal tests have not shown any toxicity. The company submits an IND that details the safety profile of the drug and how it will be tested. Twenty-one days after notifying the agency, the company begins clinical tests.

THE CONTENT AND REVIEW OF A NEW DRUG APPLICATION

Problem

A new drug application contains several hundred thousand pages of raw data. FDA staff review and often reanalyze the data. This data includes thousands of pages of individual clinical patient data. FDA reviewers do not, and could not, use all of this data in their reviews -- nor do they need it all to evaluate the safety and effectiveness of a new drug. The use of accurate reports and tables of relevant data would enable FDA reviewers to operate more efficiently and still appropriately decide whether a new drug is safe and effective.

The FDA has never adopted a single set of procedures for reviewing an NDA. FDA officials frequently change advice on appropriate testing procedures for new drugs, leaving applicants at the mercy of a succession of reviewers.

Solution

H.R. 3199 eliminates the need to submit raw data. Instead, an NDA sponsor would submit adequate reports of clinical and preclinical investigations, confirming safety and efficacy. The sponsor would certify the accuracy of the reports and would make the full data available at the request of an FDA office director. Drug approval agencies in Europe -- and most other sophisticated countries worldwide -- use reports of certified clinical data to evaluate product applications.

The legislation would also establish standards for reviewing an NDA. The FDA and a sponsor would have to meet within 30 days of sponsor request to agree on the design and size of clinical trials, which generate the information contained in an NDA. The agreement could not be changed unless the sponsor agrees in writing or the agency demonstrates a pressing need to protect the public health. Standards for NDA review would apply to both agency personnel and third parties. (*H.R. 3199, §4*)

Examples

- A company meets with FDA after submitting an IND to agree on the size and number of clinical trials. After completion of the trials, the company compiles the information into report form, rather than submitting the raw data to FDA. The agency reviewer studies the reports, and requests any data needed in order to answer questions about efficacy. The manufacturer provides the data that are the basis of the conclusion reached in the report.
- After a manufacturer submits an NDA, the agency sends a letter stating the need for an additional clinical trial. The company responds that the data is complete and that the NDA adheres to the agreement worked out before trials began. FDA acknowledges this fact and withdraws the request for an additional trial.

EFFECTIVENESS DETERMINATION

Problem

FDA currently requires two duplicative, ritualistic, large-scale clinical trials to prove efficacy. The second trial in this method ignores what is learned in the first trial and greatly increases the time to bring new drugs to patients. This requirement was *administratively* imposed by FDA following enactment of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act to ensure that information was collected in accordance with the scientific standards of that time. This requirement must often be satisfied by large, expensive, uninformative trials that confirm what is already known from earlier, smaller, and less costly trials.

Valid scientific principles require that results observed in a single study be confirmed, but there are better and more meaningful ways of validating results than by rote large-scale repetition of the initial study. Instead, information learned in a pivotal, or primary, study can be used to generate scientifically valid data in an efficient confirmatory follow-up study. This up-to-date scientific practice should be the rule at FDA -- not the exception -- so that safe and effective new medicines can be made available more quickly to patients.

Carl Peck, former Director of the Center for Drug Evaluation and Research, estimates that the need for two large trials means that approximately 25,000 people per year are in clinical trials that they do not need in order to prove efficacy. The result of this efficacy standard is two-fold: patients are undergoing unnecessary trials, and access to new therapies is delayed, even though the products have been proven safe and effective.

Solution

H.R. 3199 clarifies that the determination of effectiveness can be made using one or more clinical trials, rather than requiring two. The bill recognizes the improvements that have been made in science during the past three decades.

H.R. 3199 also defines the evidence needed to prove efficacy for a drug that would treat a serious or life-threatening condition. In these cases, effectiveness is proved if experts can reasonably and fairly conclude that the drug will be effective in a significant number of patients, and if the benefits of the drug outweigh the risks.

This new paradigm for proving efficacy would not impact the safety data base in any way. Safety experience would be collected and reported as it is now. The re-engineered process described above provides high-quality scientific information to answer the key safety and efficacy questions prior to marketing approval. (H.R. 3199, §5)

H.R. 3199 also states what substantial evidence is required to prove efficacy for a new usage of an already-approved drug. This provision should be improved to note that efficacy can be proven in such a case using published studies and confirmatory information, including inclusion in a recognized compendium.

Examples

A manufacturer conducts a large-scale, double-blind, well-controlled clinical trial of a new neurological drug. The trial shows that the drug is more effective than the placebo in reducing the tremors associated with Parkinson's disease. Rather than repeating the ~~same~~ size and type of trial again, a smaller and more focused trial is conducted. The results of the second trial confirm the first, and effectiveness is shown. The total safety database has experience from about 1500 patients.

A large placebo-controlled study of a new cancer drug is conducted. The drug is more effective than the placebo in shrinking tumors and has few side effects. Based on the drug's performance in shrinking tumors, agency and company scientists agree that the drug has demonstrated effectiveness and that the benefits outweigh the risks.

SCIENTIFIC ADVISORY PANELS

Problem

FDA began significant use of advisory committees to review issues relating to new drugs during the early 1970s. The use of advisory committees has grown without statutory structure, resulting in a number of problems. First, many groups have been appointed by the division they advise, and are thus not truly independent. Second, the members of committees often lack the relevant expertise and necessary training, are poorly compensated, and have a short tenure. The agency often tightly controls the flow of information to and from the group. There is also no deadline for FDA action on advisory group recommendations.

Solution

H.R. 3199 strengthens the quality, independence and efficiency of FDA scientific advisory panels. The groups would be located within the office of a center director, and the members would be selected on the basis of technical expertise. Panel members must disclose conflicts of interest, which can be waived by the FDA. Industry would be allowed a non-voting representative on the panel, as would the general public. The FDA would be required to provide adequate training to the panel members. (H.R. 3199, §6)

Example

A new advisory group for arthritis drugs is assembled by the agency. The members are: one general practitioner, two rheumatology specialists, an orthopedic surgeon, a gerontologist, a representative from the American Arthritis Foundation, and a pharmaceutical company researcher who has spent 20 years working on arthritis medications. The AAF and industry representatives may not vote in the group's decisions, and the industry representative recuses himself from a discussion of his company's product because his role is to serve as an information resource. The group meets six times a year to review NDAs for arthritis drugs. Each time the group makes a recommendation, the FDA must act within 30 days on the recommendation.

USE OF THIRD PARTIES

Problem

For more than 20 years, FDA has experimented with the use of outside individuals and organizations to review portions of NDAs, but has not adopted a systematic approach to outside review. In an FDA pilot project five years ago, the MITRE Corporation reviewed five efficacy supplements in a highly professional and timely manner.

The expanded use of external expert reviewers has been recommended by 14 blue-ribbon groups that have studied the FDA over the years.

Solution

H.R. 3199 requires the Secretary of Health and Human Services to establish procedures for accrediting third parties. Accredited parties would have to be fully independent of the regulated industries and would be subject to stringent requirements for data collection and disclosure of activities.

The expanded use of outside review organizations would enhance the quality of FDA's reviews by capitalizing on the country's rich reservoir of private-sector scientific and technological talent. This also would give the agency more flexibility to meet variable workloads and the means to use the diverse resources and expertise of the private-sector in a cost-effective way. Under H.R. 3199, the FDA would retain the ultimate decision to approve or disapprove the NDA, based on the recommendation of the third-party reviewer. (*H.R. 3199, §5, §8*)

PhRMA would suggest several changes to H.R. 3199's sections on use of outside reviewers. First, the language should be clarified to ensure that third parties adhere to the same standard of safety and efficacy as the agency. Second, PhRMA does not believe that applicants should pay third parties to conduct reviews. Third, PhRMA does not support the use of third parties to conduct GMP inspections for drugs.

Example

A University has a nationally-recognized medical center. The faculty believes they can conduct reviews of NDAs and supplemental NDAs in the area of arthritis drugs. The FDA recognizes that it has a gap in its staffing with respect to understanding the biology of arthritis and drugs to treat this disease. Rather than substantially expanding the agency, FDA decides to contract out reviews for some of the NDAs for arthritis drugs. Once the Secretary establishes the procedures, the University applies for accreditation. The faculty demonstrates a clear ability to review pending applications and conflict of interest is vetted. The University is accredited as an outside-review organization and begins to conduct reviews.

DISPUTE RESOLUTION: APPEALS PROCESS AND JUDICIAL REVIEW**Problem**

The FD&C Act provides for formal appeals at the end of the NDA process, but contains no provisions for appeal within the agency when disputes arise during the rest of the development and approval process.

Appeals through the current system are difficult for two reasons. Companies often fear that appeals of a reviewer's or Director's decision will lead to retribution in the form of delay or a negative ruling on a future application. Another difficulty is that a manager must "go on the record" to overrule a subordinate. This means that a supervisor must justify his actions to his superiors and, often, Congress and the public. Because the decision being appealed invariably is to keep a product or indication off the market, a supervisor has to overrule another expert and personally accept the risk of determining that the product or indication should be allowed to be marketed.

Solution

H.R. 3199 establishes a system for appeals within the agency. The system would allow the appeal of any decision by any agency employee. FDA would be required to make this system and its procedures known.

Sponsors could request an evaluation by a scientific advisory group, a special government employee hired to handle dispute resolution or a non-governmental expert on the issue in question. A report on the appeal would have to be filed within 60 days, although 30 extra days may be granted in special circumstances. After receiving a report, the FDA would have 30 days to act; if the agency failed to act, the recommendation would be deemed the decision of the FDA.

H.R. 3199 also provides for judicial review of NDA approval decisions contested by the sponsor. Within 30 days of the denial of marketing approval, the sponsor may file a petition for judicial review with the U.S. Court of Appeals. The court may rule to allow marketing of a product, and the Court's decision is subject to review by the Supreme Court. (H.R. 3199, §9, §24)

Example

A sponsor is told by the FDA that a clinical trial must contain 2,000 patients. The sponsor believes that it will be difficult to find 2,000 patient volunteers, because the condition being treated is uncommon, and suggests 1,000 might be a more realistic number. The agency denies this request, and the sponsor decides to appeal. Both the agency and the sponsor present their views to a scientific advisory group, and the group decides that 1,200 patients is the proper number. The FDA accepts this recommendation and the clinical trial proceeds.

GOOD MANUFACTURING PRACTICES

Problem

During the past few years, the FDA has increasingly delayed the marketing of drugs by citing failure to comply with technical aspects of the agency's good manufacturing practice (GMP) regulations. Often, FDA field personnel question or do not rely upon the chemistry, manufacturing and controls approved in a New Drug Application or by officials at FDA headquarters. GMP regulations frequently are broad and general, inviting constant re-interpretation by different agency personnel. It often takes several months on the part of the industry sponsor, the FDA headquarters reviewer, and/or the FDA staff at the District level to successfully resolve scientific issues that ultimately turn out to be based on individual interpretations of an FDA investigator.

GMPs assure that all drugs are manufactured according to strict specifications and that every batch of a product is safe, effective, and fit for use. An NDA includes the specifications for the product's manufacture, called the chemistry, manufacturing and controls section.

Solution

H.R. 3199 would achieve greater regulatory certainty and consistency in interpreting compliance with GMPs. All chemistry, manufacturing and controls that are part of an approved NDA or comply with a decision by the responsible FDA official and are part of the official written administrative record are deemed in compliance with GMPs. Unless there is evidence of immediate threat to the public health, marketing approval may not be delayed solely for GMP issues. (H.R. 3199, §10, §11)

Examples

- During a pre-approval inspection, the FDA investigator questions the drug dissolution specification for a solid dosage form, even though the Headquarters reviewer has approved the specifications as part of the Chemistry, Manufacturing and Controls section of the NDA. This inappropriate action requires several days of negotiations to resolve, and would be prevented under H.R. 3199.
- A GMP inspection results in a delay in marketing of a product for several months because the FDA District Office questions the use by the firm of a chemical sterilization process that was specifically approved in the NDA. Again, H.R. 3199 would prohibit a delay of marketing if the process in question were specified in the NDA.

MANUFACTURING CHANGES AND SMALL SCALE MANUFACTURE

Problem

Once a new drug is approved, the manufacturer almost always finds new methods of manufacturing that are more efficient, less expensive and often result in a safer and improved-quality drug. Under current FDA policy, no new method of manufacture can be implemented without prior FDA approval. Approval often takes years and is extremely expensive.

The FDA sometimes requires that a manufacturer produce batches of a new drug in a full-scale manufacturing plant even if only small amounts are needed for research. This full-scale requirement can be prohibitively expensive, and represents a major investment for a drug that may not receive approval.

Solution

H.R. 3199 eliminates the FDA case-by-case prior approval of small changes in manufacturing by establishing reporting categories. The first category includes drugs, certain biologics and animal drugs. Changes to these products require validation, and if the changes to these products do not alter the formulation or release specifications, the manufacturer need only report them to FDA annually. Other changes may be made as long as the manufacturer demonstrates bioequivalence and reports the changes to FDA immediately.

Other biologics, those which cannot be well-characterized or which are not the subject of a monograph in an official compendium, are in a second category. If the changes are made in the facility itself, or the changes do not alter the manufacturing process or release specifications, they can be made at any time and reported annually to FDA. Any other changes require completion of a study demonstrating bioequivalence.

H.R. 3199 also eliminates the requirement that a drug be made in a full-scale manufacturing plant in order to demonstrate safety and efficacy. A new drug could be made in a small-scale or pilot facility unless the Secretary specifies in writing, after an informal hearing, that only full-scale manufacture will ensure safety and efficacy.

On November 30, 1995 FDA issued the SUPAC (scale up and post-approval changes) Guidance for immediate release and solid dosage forms. This is a good first step, but does not achieve what needs to be codified in law. H.R. 3199 will rationalize the process by which companies notify the Agency of validated changes to its manufacturing and controls for approved products. (H.R. 3199, §12, §13) FDA's traditional compliance and enforcement programs will continue to assure the quality of marketed drug products.

Example

A company manufactures a prescription anti-histamine. In addition to the active ingredient, each tablet contains inert ingredients which have no effect on the drug's efficacy. The

company decides to change one of the inactive ingredients, which will not change the drug's potency or release in the body. Under H.R. 3199, this change can be made and reported to the FDA in an annual report.

PRODUCT-SPECIFIC CHANGES: INSULIN, ANTIBIOTICS, NONPRESCRIPTION DRUGSProblem

The FDA currently requires batch certification of insulin and certain antibiotics. This provision reflects outdated scientific standards and is burdensome to manufacturers. The FDA also does not address issues related to nonprescription drugs in an orderly manner. To respond to past inefficiencies, the agency created the Office of Nonprescription Drugs in the early 1990s, which has increased the focus on dealing with OTC issues and problems.

Solution

H.R. 3199 eliminates the requirement for batch certification of insulin and certain antibiotics. The bill also codifies that all applications or petitions to switch a drug from prescription to over-the-counter be reviewed and acted upon by a single office in CDER. A single scientific review group may provide conclusions and recommendations regarding such matters. (H.R. 3199, §14, §15)

Examples

- A company has been manufacturing an antibiotic for more than a decade. Despite the fact that there has never been a problem with any of their products, the company still must certify each batch as pure and potent. After the passage of H.R. 3199, the company no longer has to complete batch certification.
- A company manufactures a prescription analgesic. They decide that the drug would be suitable for use as a non-prescription product. Instead of applying to the office that reviewed the original application, the company sends the application to the Office of Nonprescription Drugs, which efficiently handles the review.

DISSEMINATION OF SCIENTIFIC INFORMATION AND THE PRACTICE OF MEDICINE

Problem

Under current law, pharmaceutical companies may only disseminate information about a product in response to a specific written request. In addition, the FDA must approve all changes to the labeled indications for a drug, which requires the submission of a supplemental NDA.

Drug companies should be able to provide healthcare providers with authoritative, peer-reviewed medical and scientific information about their products so that they can make the most informed choices for their patients. They should be permitted to do so as soon as the information is available, rather than being required to wait for a formal change in labeling. Companies would still have a strong incentive to seek the broadest approved indications for their products because only such indications could be promoted in advertising.

Through regulation of information dissemination, the FDA is interfering with the clinical judgment and practice of healthcare providers.

Solution

H.R. 3199 allows the dissemination of such information unless the manufacturer actively promotes the off-label use. The provision is intended to permit legitimate dissemination of medical and scientific information to ensure that maximum public health benefits would derive from the information. The provision does not encourage promotion or advertising of off-label uses.

H.R. 3199 also states, in confirmation of current law, that nothing in the legislation shall be construed to limit or interfere with the authority of a healthcare practitioner licensed by law to prescribe drugs for on- or off-label uses.

The FDA has announced changes to its policy on dissemination of information, allowing the distribution of medical textbooks and journal reprints if the article reports an original study that was submitted as part of the proof of the drug's efficacy. This new policy essentially limits distribution of materials to those referencing approved uses. Since many drugs are used off-label, this new FDA policy does little to help healthcare professionals learn more about the most up-to-date treatments for their patients. (H.R. 3199, §20, §22)

Example

The journal of a medical specialty society publishes a peer-reviewed article which reports that a drug approved to treat bladder cancer is extremely effective in treating lung cancer. The company that produces the drug sends copies of the article out to the head of oncology at 100 major hospitals. Since the article has been published and is available to anyone who reads the journal, the company is merely facilitating the availability of information that may help patients.

AGENCY PRACTICES: INFORMATION SYSTEM, INFORMAL AGENCY STATEMENTS,
EDUCATION AND RESEARCH

Problem

The efficiency and responsiveness of the agency should be improved. There is no central process for tracking the status of applications. The FDA relies on a wide variety of informal agency statements for establishing agency policy, which creates problems like a lack of certainty, shifting policies and priorities, and a lack of input by affected parties into policy development. The FDA also devotes considerable resources to scientific research unrelated, and sometimes in conflict with, the goal of rapid approval of new practices.

Solution

H.R. 3199 addresses all these problems and thus refocuses FDA on the goal of timely product approval. The bill mandates the establishment of an information system, accessible by applicants, that would track the status and progress of each submission to the agency. H.R. 3199 also prohibits FDA from relying on informal agency statements to enforce regulations or require compliance with existing regulations. The FDA must also publish in the Federal Register the availability of statements and make the statements available electronically. PhRMA suggests that the provision be amended to allow action in accordance with an informal agency statement unless the Secretary determines that doing so puts the public health at risk. Finally, the bill requires that all research undertaken by the agency be directly related to the approval of new products or the general agency mission. (H.R. 3199, §16, §21, §22)

Examples

- A company uses the information system to look up the status of its NDA. The company learns that the NDA has been received and is halfway through review by the appropriate division.

BIOLOGICAL PRODUCTS

Problem

The current system regulates drugs and biologics differently, which is inefficient, redundant, and inconsistent. There are many common characteristics between traditional drugs and biologic drugs, with the exception of blood, tissue, and whole-cell vaccines, which are different and must be treated differently.

The current arrangement, which dates from the beginning of this century, does not regulate biologics any better or worse than drugs, and thus in no way improves the safety of these products. Except for blood, tissue, and whole-cell vaccines, there is no scientific or public-policy reason to regulate drugs and biologics in different ways. Modern analytical methodologies now permit detailed characterization of complex biologics, as has long been the case with traditional drugs.

Solution

The bill creates three categories: biological products, blood and blood products, and tissue. Regulation of these products is moved to the text of the Food, Drug and Cosmetic Act from the Public Health Service Act, simplifying their regulation.

Similar to current regulation, H.R. 3199 establishes the requirement for a product license application (PLA) for biologics. Within two years, the Secretary is required to harmonize the regulation of PLAs with NDAs. If the Secretary fails to do so, all PLA regulations would be eliminated and biologics would be subject to NDA regulations.

Separate requirements are established for blood products. These products must conform to standards for safety, purity and potency. Licenses are required for establishments that produce these products. Licenses can be revoked upon demonstration of immediate harm to the public health. Human tissue will be regulated only if the Secretary demonstrates, in writing, that voluntary regulation is insufficient to protect the public health. If so, standards will be established by regulation.

On November 9 and 30, 1995, FDA issued regulations to eliminate several CBER requirements: ELAs for well-characterized biologics, individual lot release for most products, pre-approval of launch promotional products, and "responsible head" procedure. These proposed regulations are a good first step toward improving FDA processes for biologics, but more must be done, as would be the case under H.R. 3199. (H.R. 3199, §25)

Example

A manufacturer discovers a new biologic product that is well-characterized. Under the new law, they submit a PLA to the FDA. They do not have to submit an ELA.

GLOSSARY OF TERMS

Approval	FDA approval of a new drug. This means that the FDA has reviewed all of the studies and supporting literature, made a determination that the drug is safe and effective, and is allowing the manufacturer to market the drug.
Biotechnology	The collection of industrial processes that involve the use of biological systems. For some of the industries, these processes involve the use of genetically engineered organisms. Other processes use recombinant DNA, monoclonal antibodies/hybridoma, continuous cell lines and gene therapy. Biotechnology yields biologics , used medically as diagnostic or therapeutic agents.
CBER	Center for B iology Evaluation and R esearch This division of the FDA reviews, approves and regulates new biologics -- vaccines, blood and tissue, and biotechnology drugs. The current Director is Dr. Kathryn Zoon.
CDER	Center for D rug Evaluation and R esearch This division has responsibility for reviewing, approving, and regulating new drugs. The current Director is Dr. Janet Woodcock.
Clinical Trials	Tests of a new drug on human subjects, which occur in three phases: In Phase I Clinical Trials , the drug is tested on about 20 to 80 normal healthy volunteers. The tests study a drug's safety profile, including the safe dosage range. The studies also determine how a drug is absorbed, metabolized and excreted and the duration of its action. In Phase II Clinical Trials , controlled studies are conducted with approximately 100 to 300 patient volunteers (people who have the disease) to study the drug's effectiveness. In Phase III Clinical Trials , the drug is given to about 1,000 to 3,000 patients in clinics and hospitals. Physicians closely monitor the patients to determine efficacy and identify adverse reactions.
Commissioner	The head of the FDA, which is part of the Public Health Service, is the Commissioner, who reports to the Secretary of Health and Human Services. The current Commissioner is Dr. David Kessler, appointed by President Bush in 1990.
Drug	As defined in the Food, Drug and Cosmetic Act, a drug is an article "intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals."

ELA	Establishment License Application -- An ELA is the biologic product equivalent of a GMP. The ELA outlines the manufacturing specifications for a biologic and explains how and where it will be produced.
EMA	European Medicines Evaluation Agency -- the drug regulatory agency for the countries of the European Union, located in London.
GMP	Good Manufacturing Practice -- Commonly accepted quality assurance and control practices that are used by drug manufacturers to assure that products meet the required standards and specifications for safety, effectiveness and fitness for use.
IND	Investigational New Drug Application. After completing pre-clinical testing (see below), a manufacturer files an IND with the FDA. The IND allows commencement of tests of a new drug in humans.
MCA	Medicines Control Agency -- the drug regulatory agency in the United Kingdom, located in London.
NME	New Molecular Entity An NME is a drug or biologic submitted for approval that is unique and different from any previously submitted drug or biologic.
NDA	New Drug Application. An NDA is the summary and tabulation of all data relating to the safety and effectiveness of a drug. FDA approval is based on a review of the content of an NDA.
Pivotal	A pivotal study is typically a large-scale clinical study that the FDA and the industry sponsor agree has the scientific power to answer the key question "Does this drug work?" A confirmatory study takes what is learned in the first study and uses this information to design an efficient follow-up study that completes the proof of efficacy.
PLA	Product License Application -- A PLA is the biologic drug equivalent of an NDA. It contains information on safety and efficacy and the data from clinical trials.
Pre-clinical testing	During pre-clinical testing, a pharmaceutical company conducts laboratory and animal studies to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety.

THE U.S. DRUG APPROVAL PROCESS

Introduction:

The U.S. system of new drug approvals is perhaps the most rigorous in the world. On average, it costs a company \$359 million to get one new drug from the laboratory to the pharmacist's shelf, according to a February 1993 report by the Congressional Office of Technology Assessment.

It takes 15 years on average for an experimental drug to travel from lab to medicine chest, according to the Tufts University Center for the Study of Drug Development. Only five in 5,000 compounds that enter pre-clinical testing make it to human testing. And only one of those five is approved.

The Process:

1. **Preclinical -- Discovery & Development**

- **Drug Discovery** -- In ongoing research, in-house pharmaceutical chemists work with new and existing molecules. Once a molecule is discovered, biologists will conduct pharmacological tests: the molecule will be tested in cells from specific organ systems (e.g., kidney or heart) to see if there is drug action that has medical promise.
- **Pre-clinical Testing** -- Once a compound is identified, it is first studied in a test tube. The researcher will add the drug to a few cancer cells or a virus, to see if anything happens, like reduction in the number of cells or neutralization of the virus. If the compound has the desired result in a test tube, testing begins on animals. Animal studies help determine if the new drug is toxic and if there are any side effects. Animal and laboratory studies are the pre-clinical phase of drug development.
- **Investigational New Drug (IND) Application** -- After completing pre-clinical testing, the company files an IND to begin testing the drug in humans. The IND becomes effective if the FDA does not disapprove it in 30 days. The IND shows the results of previous experiments; how, where, and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. In addition, the IND must be reviewed by the Institutional Review Board where the studies will be conducted, and progress reports on clinical trials must be submitted at least annually to FDA.

2. **Clinical -- Testing and Evaluation**

- **Clinical Trials -- Phase I (safety)** -- After filing the IND, clinical trials begin. In Phase I trials, the drug is tested on about 20 to 80 healthy volunteers. These tests study a drug's safety profile, including the safe dosage range. The studies also determine how a drug is absorbed, distributed, metabolized and excreted, and the duration of its action.

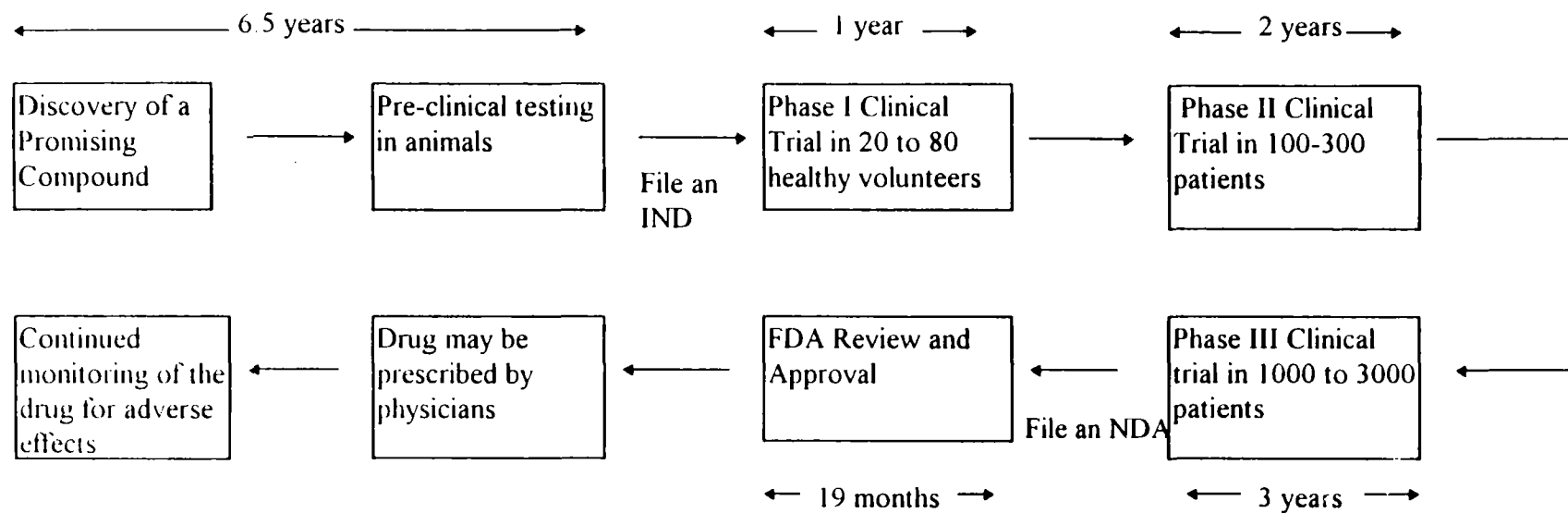
- **Clinical Trials -- Phase II (effectiveness)** -- In Phase II trials, controlled studies of approximately 100 to 300 patient volunteers are conducted. Phase II trials study the effectiveness of the drug on the disease for which it is intended.
- **Clinical Trials -- Phase III** -- In Phase III trials, the drug is given to about 1,000 to 3,000 patients. These trials are conducted in hospitals and clinics, and physicians monitor patients closely to determine efficacy and identify adverse reactions.

3. Review & Approval

- **New Drug Application (NDA)** -- Following the completion of clinical trials, the company analyzes all of the data and files a New Drug Application with the FDA if the data successfully demonstrate safety and effectiveness. The NDA must contain all of the scientific information that the company has gathered, including data on each individual patient. NDAs typically run 200,000 pages or more. By law, the FDA is allowed six months to review an NDA, although their current average time is 19 months.
- **FDA review** -- The process comprises the following steps, all of which are conducted by FDA reviewers who read over submitted data, but do not conduct clinical tests:
 - Chemists focus on how the drug is put together, whether the manufacturing controls and packaging are adequate to ensure the stability of the product, and whether the proposed labeling accurately reflects the effects of the drug.
 - Pharmacologists evaluate the effects of the drug on laboratory animals in short-term and long-term studies.
 - Physicians evaluate the results of the clinical tests--including the drug's adverse as well as therapeutic effects.
 - Statisticians evaluate the designs for each controlled study, the validity of statistical analyses, and the conclusions of safety and effectiveness based on the study data.
 - Microbiologists evaluate the data on anti-infectives (antibiotics, antivirals and antifungals). These drugs differ from others because they're intended to affect the disease-causing microbes themselves.
 - Other staff evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed, metabolized and eliminated. They determine whether the evidence supports the labeling for the recommended dosing regimen.
- **Follow Up** -- Once the FDA approves the NDA, the new medicine becomes available for physicians to prescribe. The company must continue to submit periodic reports to the FDA, including any cases of adverse reactions and appropriate quality-control records. For some medications, FDA requires additional studies (Phase IV) to evaluate long-term effects.

The process is outlined on the chart on the next page.

THE DRUG DEVELOPMENT AND APPROVAL PROCESS



The drug discovery and approval process currently takes an average of 15 years and costs almost \$400 million.