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**FOOD AND DRUG ADMINISTRATION PERFORMANCE AND
ACCOUNTABILITY ACT OF 1995**

—————
JUNE 20, 1996.—Ordered to be printed
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Mrs. KASSEBAUM, from the Committee on Labor and Human
Resources, submitted the following

REPORT

together with

ADDITIONAL VIEWS

[To accompany S. 1477]

The Committee on Labor and Human Resources, to which was referred the bill (S. 1477) to amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes, having considered the same, reports favorably thereon with an amendment in the nature of a substitute and recommends that the bill as amended do pass.

CONTENTS

	Page
I. Purpose and summary	1
II. Background and need for the legislation	5
III. Legislative history and votes in committee	9
IV. Explanation of the legislation and committee views	15
V. Cost estimate	66
VI. Regulatory impact statement	66
VII. Section-by-section analysis	66
VIII. Additional views	91
IX. Changes in existing law	104

I. PURPOSE AND SUMMARY

Under the Federal Food, Drug, and Cosmetic Act, the Food and Drug Administration (FDA) has two important functions: (1) the re-

view and approval of important new products that can improve the public health, such as life-saving drugs, biological products, and medical devices; and (2) the prevention of harm to the public from marketed products that are unsafe or ineffective. The Federal Food, Drug, and Cosmetic Act has been amended numerous times in the past 55 years to strengthen the FDA's function of ensuring that unsafe or ineffective products are not marketed but has been changed only once, by the Prescription Drug user Fee Act of 1992 (PDUFA), to strengthen the FDA's function of reviewing and approving important new products that can improve the public health.

The Food and Drug Administration Performance and Accountability Act of 1996, S. 1477, is designed to provide greater balance between these two FDA functions through reforms to expedite new product development, testing, and review. The legislation is designed to ensure the timely availability of safe and effective new products that will benefit the public and to ensure that our Nation continues to lead the world in new product innovation and development.

The legislation builds upon the numerous congressional, FDA, and outside investigations and reports that have identified problems with the current FDA product approval system and have recommended reasonable reforms to streamline and strengthen that system. It includes the following major provisions:

1. THE LEGISLATION ESTABLISHES A CLEARLY DEFINED, BALANCED MISSION FOR THE FDA

Current law contains no mission statement for the FDA. The legislation defined the mission of the FDA as that of protecting and promoting the public health. It further defined protecting and promoting the public health to include not only protecting the public from unsafe or ineffective products but also facilitating the rapid and efficient development and availability of new products that benefit the public.

2. THE LEGISLATION REQUIRES PUBLIC ACCOUNTABILITY BY THE FDA FOR ITS PERFORMANCE

Except as required under PUDFDA, current law provides no form of public accountability by the FDA for its performance of its statutory obligations. The legislation requires the Secretary of Health and Human Services to establish quantifiable performance standards for the FDA. The Secretary is required to publish an annual report in the *Federal Register* measuring in detail the FDA's actual performance against the standards and, if the agency is failing to meet the performance standards, setting forth a plan of corrective action.

3. THE LEGISLATION PROVIDES IMPROVED INTERNAL MANAGEMENT SYSTEMS

Current law is silent on important aspects of FDA management. The legislation requires the Secretary to implement programs and policies to foster collaboration between the FDA, the National Institutes of Health, and other science-based agencies, to establish in-

formation systems, to reform its development and use of policy statements, to improve the scientific review group process, and to establish clear internal appeal mechanisms in order to make existing product regulation requirements more rational, consistent, and efficient.

4. THE LEGISLATION EXPEDITES ACCESS TO PRODUCTS FOR SERIOUSLY ILL PATIENTS

Although FDA's investigational drug and device regulations do allow for some expanded access to investigational drugs and devices, the Federal Food, Drug, and Cosmetic Act has no provisions to ensure that patients who cannot be treated effectively with existing approved therapies may have access to promising new therapies which are the subject of clinical trials or are undergoing FDA review. The legislation establishes a statutory right for individuals, acting through health professionals, to request and manufacturers to provide such therapies, provided certain conditions are met, and requires the FDA to expedite its review of applications for the approval of such therapies.

5. THE LEGISLATION IS DESIGNED TO REVITALIZE THE INVESTIGATION OF NEW PRODUCTS

Current law focuses on the review of new products by the agency but does not currently include requirements that expedite and encourage the investigation of new products. The legislation establishes timely review and reasonable data requirements for initiating clinical investigations and establishes a collaborative relationship between the agency and product sponsors in the design of pre-clinical and clinical testing required for the approval of new products.

6. THE LEGISLATION ESTABLISHES A PROCESS FOR EFFICIENT, ACCOUNTABLE, AND FAIR PRODUCT REVIEW

Current law contains no provisions to ensure that the agency meets statutory time periods for product review. The legislation establishes reasonable data requirements for new product approval applications, petitions, or other submissions, authorizes the agency to contract with outside experts to review all or parts of applications, requires the use of outside experts for some of the simpler applications, establishes procedures and policies to foster a collaborative review process between the agency and the applicant, provides for the use of accredited outside organizations to conduct good manufacturing practice inspections, eliminates environmental impact review except where appropriate, facilitates the consideration of applications for the approval of new uses for already-approved products, and provides an incentive for the sponsors of new drugs and approved drugs to conduct pediatric studies to permit labeling for pediatric uses.

7. THE LEGISLATION STREAMLINES THE DRUG AND BIOLOGICAL PRODUCTS REGULATORY PROCESS

Current law has not kept pace with new technology and scientific knowledge in the development and testing of drugs and biological

products. In addition to reforming the product approval process, the legislation provides the FDA with the statutory flexibility to approve a new drug or biological product on the basis of one adequate and well-controlled clinical trial, permits the approval of drugs and biological products based upon small-scale manufacturing, expands the type of manufacturing changes that may be made without prior agency approval, repeals outdated requirements for agency preapproval of batches of insulin and antibiotics, and reforms the regulation of drugs and biological products.

8. THE LEGISLATION IMPROVES THE REGULATION OF MEDICAL DEVICES

Current law imposes a number of unnecessarily restrictive regulatory requirements on medical devices which require the agency to expend valuable resources reviewing premarket notifications for devices posing minimal risks. These requirements have substantially increased device review and clearance or approval times, delaying the public's access to these products and driving the medical device industry abroad. In addition to reforming the medical device approval process, the legislation eliminates premarket notification for the simplest devices, provides for scientific review group input on whether new devices should be classified as class III devices, provides greater flexibility for device modification without a new premarket notification or approval, establishes reasonable approval standards, requires device tracking and postmarket surveillance only where justified, eliminates distributor reporting requirements, establishes reasonable review requirements specific to devices, and provides the Secretary with authority to recognize appropriate performance standards developed by authoritative standards-setting organizations.

9. THE LEGISLATION REFORMS ANIMAL DRUG APPROVAL REQUIREMENTS

Current law fails to reflect basic differences between animal and human drugs and current practices and scientific knowledge relating to animal drugs. In addition to reforming the new animal drug approval process, the legislation modifies the efficacy standard for new animal drugs to better reflect current scientific knowledge, reduce the regulatory burden on the development of drugs for minor uses and species, and establishes a new system of veterinary feed directive to reflect current and emerging practices in the use of medicated feeds.

10. THE LEGISLATION SIMPLIFIES THE FOOD ADDITIVE APPROVAL PROCESS AND PROVIDES A MORE REASONABLE STANDARDS FOR SOME HEALTH CLAIMS

Current law requires the agency to preapprove indirect food additives, most of which pose little if any risk to human health. In addition to reforming the direct food additive petition process, the legislation replaces the preapproval process for indirect food additive with a simple notification requirement.

The legislation also modifies the current law requirement for FDA preapproval of health claims for foods when claims are based on authoritative recommendations by the National Institutes of

Health, the Centers for Disease Control and Prevention, the National Academy of Sciences, and other, similar bodies.

II. BACKGROUND AND NEED FOR THE LEGISLATION

A. BACKGROUND

Over the years, Congress has dramatically expanded the reach and responsibilities of the FDA. The Federal Food and Drugs Act of 1906, the first national statute enacted by Congress to regulate the American food and drug supply, gave the agency the authority to police the market and remove adulterated or misbranded foods and drugs.

In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act, which expanded the agency's reach to the regulation of cosmetics and medical devices and, for the first time, provided the agency with the authority to review and assure the safety of a product—new drugs—prior to the marketing of that product. The 1938 statute required sponsors of new drugs to file a new drug application notifying the FDA prior to marketing a new human or animal drug. The new drug application became effective after 60 days (which could be extended to 180 days), unless the agency found that it had insufficient information to determine whether the drug was safe for its intended use.

In the ensuing years, Congress enacted a series of statutes further expanding the FDA's regulatory reach. These included the 1944 Pitts Act, which gave the FDA the authority to regulate biological products, and the Miller Pesticide Amendments of 1954, which required FDA premarket approval for pesticides in or on raw or processed foods. The Food Additive Amendment of 1958 required premarket approval of food additives, and the Color Additive Amendments of 1960 required premarket approval of color additives in food, drugs, and cosmetics. The Drug Amendments of 1962 required that drugs be demonstrated to be effective as well as safe prior to marketing. The Animal Drug Amendments of 1968 consolidated the premarket approval requirements for new animal drugs and feed additives. The Medical Device Amendments of 1976 required premarket notification for devices substantially equivalent to those already on the market and premarket approval for new medical devices, and the Safe Medical Devices Act of 1990 required the premarket approval of substantial equivalence notifications.

From 1906 to the present, then, the FDA's role has expanded from one of removing adulterated or misbranded products from the market to one of preapproving the testing and marketing of products.

B. NEED FOR THE LEGISLATION

Over the years, and particularly with the enactment of requirements that the FDA determine that drugs and devices are effective as well as safe, the FDA's requirements for clinical testing and its premarket reviews of new products have grown increasingly complex, time-consuming, and costly. From the 1960s to the 1990s, for example, the time required to complete clinical trials for new drugs has grown from 2.5 to nearly 6 years. Applications for the approval of new drugs typically run to hundreds of thousands of pages in

length. According to the most recent published study, from the beginning of the process to the end, it takes an average of 15 years and costs in the range of \$500 million dollars to bring a new drug to market. [DiMasi, Trends in Drug Development Cost, Times, and Risks, 29 Drug Information Journal 375, 382, April-June 1995.]

By law, the FDA is required to review and act on applications for the approval of new drugs and devices within 180 days. Today, however, it takes the agency on average 606 days to complete its review of new medical devices and 570 days to complete its review of most new drugs. By law, the FDA is required to review and act on petitions for the approval of new food additives within 180 days. However, since 1970, the average time to approval of a direct food additive has been at least 600 days, and some petitions have been pending at the agency since the 1970s. Currently, the FDA reports that it has a backlog of 300 food additive petitions.

These increases in the time, complexity, and cost of bringing new products to market are borne directly by the public, in delayed access to important new products—including lifesaving medical therapies—and in higher costs. They are a growing disincentive to continued investment in the development of innovative new products and a growing incentive for American companies to move research, development, and production abroad, threatening our Nation's continued world leadership in new product development, costing American jobs, and further delaying the public's access in important new products.

Over the past 20 years, a bipartisan consensus has emerged on the need for reforms of the FDA premarket approval process to strike a better balance between the need to ensure that products are safe and effective, on the one hand, and to facilitate the timely availability of new products, on the other.

During 1978 and 1979, Congress considered a wholesale revision of the new drug approval process. This committee led that effort, reporting legislation introduced by Senator Kennedy, the Drug Regulation Reform Act of 1979. That legislation was subsequently approved by the Senate but was not considered by the House of Representatives. A number of the provisions in that legislation are reflected in S. 1477, including provisions to permit new drug sponsors to obtain advice from the agency regarding their investigational plans; to require the FDA to issue written guidelines regarding protocols and methods for conducting drug investigations; to require the FDA to determine within 45 days whether new drug approval applications meet agency filing requirements; to require the FDA to take measures to ensure that reviews are conducted efficiently and expeditiously; and to require the use of advisory committees as part of the dispute resolution mechanism.

Many of these same changes were recommended by the Commission on the Federal Drug Approval Process, convened at the request of then-Representative Albert Gore, Jr., chairman of the House Subcommittee on Investigations and Oversight and then-Representative James Scheuer, chairman of the House Subcommittee on Natural Resources, Agricultural Research and Environment. The Commission's 1982 report recommended such changes as simplification of the investigational new drug requirements; recognition that drug effectiveness could be demonstrated by one study in

appropriate cases; greater utilization of outside expert advice; improving interactions with industry; tracking the review process to ensure timeliness; simplified procedures for the use of investigational drugs for therapeutic purposes; greater reliance upon expert judgment in determining the safety and effectiveness of drugs; concurrent review of portions of new drug applications by FDA; and greater reliance on foreign studies. These recommendations are incorporated in S. 1477.

Concerned about the slow process for the development and approval of AIDS and cancer drugs, in 1988 Vice President Bush requested the President's Cancer Panel to establish a National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS. The Committee's final report, issued in 1990, recommended a national policy to foster the development of new drugs for AIDS and cancer; expediting approval of important new drugs; greater use of scientific judgment of qualified experts in determining the effectiveness of new drugs; the use of surrogate end points to establish drug effectiveness; a more open relationship between the FDA and the regulated industry in order to foster a spirit of mutual cooperation; responsiveness to the needs of patient advocacy groups; a fundamental restructuring of the FDA advisory committee system; more flexible use of investigational drugs for treatment; the right of patients to obtain investigational drugs under expanded access conditions; greater use by the FDA of outside review of new drug applications; and automatic approval of supplemental new drug applications for minor technical changes such as manufacturing modifications. Again, many of these recommendations are incorporated in S. 1477.

In 1989, in response to serious questions that were being raised about the ability of the FDA to perform its job, Secretary of Health and Human Services, Dr. Louis Sullivan, chartered the Advisory Committee on the Food and Drug Administration. The committee was chaired by Dr. Charles Edwards, a former FDA commissioner, and Dr. David Kessler served on the committee until his appointment as FDA commissioner. The charter directed the committee to examine the mission, responsibilities, and structure of the FDA and to make recommendations for improving the agency's operations.

One of the major findings of the committee was the need for the FDA to set forth a clear statement of its mission and goals and a plan for achieving the goals. In formulating a statement of purpose and program goals, the committee found that "the agency should be guided by the principle that expeditious approval of useful and safe new products enhances the health of the American people. Approving such products can be as important as preventing the marketing of harmful or ineffective products. This is especially true for people with life-threatening illnesses and for diseases for which alternative therapies have not been approved." This key recommendation is the informing principle of S. 1477.

In 1991, the Council on Competitiveness, chaired by Vice President Dan Quayle, announced an important Administration initiative to improve the FDA's drug approval process. The initiative was designed to achieve three overarching goals by 1994—a substantial reduction in the average development and approval time for all new drugs; a reduction in FDA approval time for important new

drugs to 6 months; and a reduction in FDA approval time to 12 months for all other drugs.

The Council on Competitiveness also recommended a number of specific reforms, including expanded use of outside reviews; expanded use of advisory committees; flexible interpretation of the efficacy standard; accelerated approval through a reduction in the number of clinical studies required prior to approval and the amount of time FDA requires to grant approval, including reliance on surrogate endpoints; enhanced computerization to track applications and expedite review; and enhanced internal management, including the measurement of progress in application review against statutory deadlines. Many of these recommendations are incorporated in S. 1477.

Most recently, Vice President Gore has pressed for reform of the FDA product approval system as part of President Clinton's Re-inventing Government initiative. The President and Vice President Gore have issued four reports, covering drugs and medical devices, drugs made from biotechnology, food, and cancer drugs, designed to improve the product approval system, eliminate outmoded regulations, and update the Federal Food, Drug, and Cosmetic Act to reflect advances in the science of new product development and testing. Many of the recommendations in these reports are incorporated in S. 1477.

Every administration in the past 20 years has recognized the need for reforms of the FDA's product approval system to bring into better balance the need to ensure the safety and effectiveness of products and the need to facilitate the development, testing, and timely approval of safe and effective products that benefit the public. Until recently, the FDA has been very slow to respond, or has not responded at all, to recommendations for reform made by the distinguished advisory panels that have been convened over the years. At the four hearings that the committee held on FDA reform, witnesses who appeared before the committee—several of whom had served on these advisory panels—testified about the same problems that have been described in the reports summarized above and recommended many of the same solutions.

America's pharmaceutical, biotech, medical device, and food industries are among our most innovative, dynamic, and productive. They contribute significantly to our Nation's high standards of health care and to our unparalleled supply of wholesome, abundant, and affordable food. They hold the promise of further breakthroughs in life-saving and enhancing therapies to combat the diseases and disabling conditions afflicting us today and those which may emerge in the future. They hold the promises of new food technologies that will enhance diets and improve health, provide natural resistance to pests, droughts, and other plagues, and help meet the nutritional needs of a growing world population. They are job-creating industries that contribute positively to our balance of trade.

Formidable challenges must be met, however, if these opportunities are to be realized and America is to continue to lead the world in product innovation. Domestically, our health care system is rapidly reorganizing, consolidating, and moving into managed care, with potentially profound effects on the market for products and

the revenues necessary for continued research and product development. Markets are becoming increasingly competitive, particularly as the European Union moves to adopt a uniform drug and device approval system.

If we are to confront these challenges and realize the opportunities on today's and tomorrow's horizons, we cannot afford an overly complex, bureaucratic, time-consuming, and expensive regulatory system. Nor can we afford an adversarial relationship between the FDA and the industries it regulates or an agency pursuing so many agendas that it lacks a clearcut mission and sphere of responsibility. We must update our food and drug laws and our regulatory practices to reflect the scientific and technological advances that have occurred in the development and testing of new products and to ensure that the FDA is an agency committed to fostering innovation and ensuring timely public access to beneficial new products.

It is no easy feat that Americans ask of the FDA. Americans want it to hold the gate to the market tightly shut against unsafe or ineffective products while opening it wide for the next generation of innovation—with all of its potential promise, but not without its risks. Clear statutory guidance is needed to assist the agency to find this delicate balance and to bring our food and drug laws and regulatory systems into the next century. The FDA Performance and Accountability Act of 1996, S. 1477, embodies many of the bipartisan conclusions and recommendations reached by the expert panels for accomplishing this difficult task of balancing risk and promise.

III. LEGISLATIVE HISTORY AND VOTES IN COMMITTEE

"The Food and Drug Administration Performance and Accountability Act of 1996," S. 1477, was introduced by Senator Kassebaum on December 13, 1995. Prior to the drafting of the legislation, the committee held 2 days of hearings on April 5 and 6, 1995, entitled, "The FDA and the Future of the American Biomedical and Food Industries." These hearings examined the challenges and opportunities facing our Nation's pharmaceutical, biotech, medical device and food industries and ways that the FDA's regulation of these industries might need to be reformed to ensure that these challenges are met and opportunities realized.

Following the introduction of S. 1477, the committee held a hearing on February 21, 1996, entitled "Revitalizing New Product Development—From Clinical Trials Through FDA Review." This hearing focused on the underlying principle informing the provisions of S. 1477—that it is possible through reform to substantially reduce the time it currently takes to develop and test new drugs, biologics, medical devices, and food additives and the time it takes the FDA to review and approve these products.

The committee held a second hearing on S. 1477 on February 22, 1996, entitled "More Information for Better Patient Care." This hearing focused on provisions in S. 1477 reforming the FDA's regulation of the dissemination of information about new uses for approved drugs, biological products, and medical devices.

On March 27 and 28, 1996, the committee held executive sessions to consider S. 1477. Senator Kassebaum brought up and amendment in the nature of a substitute that was considered as

original text for purposes of further amendment. Twelve amendments, including one “sense of the committee” amendment, and two motions were adopted in the executive sessions, and S. 1477 was favorably reported by a roll call vote of 12 yeas to 4 nays.

A. AMENDMENTS AND MOTIONS ADOPTED BY VOICE VOTE DURING
EXECUTIVE SESSIONS

Seven amendments and two motions were adopted in the executive sessions by voice vote:

1. Senator Frist offered an amendment to establish, under a new title of S. 1477, a peer-reviewed grant program to establish and operate three centers for education and research on drugs, devices, and biological products. The amendment provides that the program will be administered by the Secretary, acting through the Commissioner, sets forth mandatory and discretionary activities to be undertaken by the centers, establishes an oversight committee, requires a report to Congress on the impact of the centers on the safe use of drugs, biological products, and medical devices, and authorizes appropriations of \$9 million in fiscal year 1997, \$12 million in fiscal year 1998, \$15 million in fiscal year 1999, and \$15 million in fiscal year 2000.

2. Senators Simon and Frist offered an amendment to extend through fiscal year 1998 the authorization for a clinical pharmacology training pilot program originally authorized under P.L. 102–222. The amendment authorizes an appropriation of \$1.9 million in each fiscal year 1997 and 1998.

3. Senator Kennedy offered an amendment to clarify the Secretary’s authority to determine whether a new device is substantially equivalent to a legally marketed class I or class II device with a more general use than the new device.

4. Senator Kennedy offered an amendment to strike a provision of S. 1477 that eliminated a requirement for device manufacturers to report to the Secretary, in some circumstances, removals of, or corrections made to, devices already on the market.

5. Senator Kennedy offered an amendment to strike a section of S. 1477 relating to supplemental applications for the approval of new uses of approved drugs and devices and replace that section with alternative provisions to improve the FDA’s supplemental application review process.

6. Senator Gregg offered a sense of the committee amendment encouraging the Secretary of Health and Human Services, in consultation with the Secretary of Commerce, to move toward the acceptance of mutual recognition agreements reached between the European Union and the U.S. Food and Drug Administration.

7. Senators Gregg, Ashcroft, and Frist offered an amendment to clarify the FDA's regulation of radiopharmacological products. The amendment requires the Secretary to issue a proposed and final regulation governing the approval of radiopharmaceuticals, sets forth several issues that must be included in the regulation, and requires that the regulation of radiopharmaceuticals be handled in a single office at the Center for Drug Evaluation and Research.

8. Senator Kassebaum offered a motion to strike provisions in the amendment in the nature of a substitute reforming the FDA's regulation of dissemination of information about new uses for approved drugs, biological product, and devices, with the understanding that the committee would continue to work to come to consensus on this issue before the bill was brought to the Senate floor for consideration.

9. Senator Kassebaum offered a motion to strike provisions in the amendment in the nature of a substitute relating to patient and industry representation on FDA scientific advisory groups with the understanding that the committee would continue to work to come to consensus on this issue before the bill was brought to the Senate floor for consideration.

B. ROLLCALL VOTES TAKEN DURING THE EXECUTIVE SESSIONS

Seven rollcall votes on amendments were taken during the executive session:

1. Senator Coats offered an amendment on accredited-party participation to establish a 3-year pilot program for private sector review of premarket notifications and premarket approval applications for devices. The amendment was adopted by a rollcall vote of 11 yeas to 4 nays.

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

2. Senator Kennedy offered an amendment to strike provisions in the amendment in the nature of a substitute to S. 1477 which would require the Secretary to contract with experts for the review of product approval applications for which the Secretary had failed to meet the statutory period for agency action for at least 95 percent of the applications for approval for that product category. Senator Kennedy's amendment would instead have required that, in the event the Secretary fails to meet either statutory targets or targets set forth in the Prescription Drug User Fee Act for 90 percent of annual actions in a particular product category, then the Secretary must report an action plan to Congress and report every 6 months thereafter on progress toward achieving the plan. The amendment was defeated by a rollcall vote of 7 yeas to 9 nays.

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

3. Senator Coats offered an amendment to limit the Commissioner of the Food and Drug Administration to a term of 5 years and to permit the removal of the Commissioner from office only pursuant to a finding of neglect of duty or malfeasance in office. The amendment was adopted by a rollcall vote of 9 yeas to 7 nays.

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

4. Senator Gregg offered an amendment to permit food manufacturers to make health claims for their products which have not been preapproved by the FDA if those claims are based on published statements, conclusions, or recommendations by a Federal agency with official responsibility for public health protection or research relating directly to human nutrition or the National Academy of Sciences or subdivisions of its scientific body. The amendment requires the manufacturer or distributor to notify the Secretary 90 days in advance of the first introduction of a food bearing such a claim. The amendment was adopted by a rollcall vote of 10 yeas to 6 nays.

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

5. Senator Coats offered an amendment to require the Secretary to call on national organizations to develop a long-range comprehensive action plan to achieve goals consistent with the goals of the FDA's proposed rule on "Prescription Drug Product Labeling: Medication Guide Requirements" relating to the provision of oral and written prescription information to consumers. The amendment prohibits the Secretary from implementing the proposed rule unless the national organizations fail to develop and begin to implement a comprehensive plan within 120 days. The amendment requires the Secretary to review the status of private-sector initiatives and if the goals of the FDA's proposed regulation have not been met, to seek public comment on other initiatives which may be taken to meet such goals. The amendment was adopted by a rollcall vote of 13 yeas to 3 nays.

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

6. Senator Harkin offered an amendment which incorporated the provisions of Senator Coats' amendment on accredited-party participation (see 1 above) but which required the Secretary to approve any compensation agreements reached by the accredited-party and the device manufacturer or sponsor who engages the services of the accredited-party. The amendment was defeated on a rollcall vote of 5 yeas to 11 nays.

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

7. Senator Gregg offered an amendment to prohibit State and local governments from establishing or continuing any requirement relating to the regulation of a nonprescription drug which is different from, or in addition to, or otherwise not identical with Federal requirements. The amendment permits States to apply to the Secretary for an exemption from the prohibition and propose a requirement which is justified by compelling local conditions or protects an important public interest that would otherwise be unprotected, that would not cause the nonprescription drug to be in violation of any applicable requirement or prohibition under Federal law, and that would not unduly burden interstate commerce. The amendment was adopted on a rollcall vote of 10 yeas to 6 nays.

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

C. FOUR AMENDMENTS OFFERED AND SUBSEQUENTLY WITHDRAWN
WITHOUT CONSIDERATION DURING EXECUTIVE SESSION

1. Senator Gregg offered and then withdrew an amendment to replace the Delaney clause, which sets a zero-risk carcinogenic safety standard for food additives, animal drugs, and color additives, with a negligible-risk standard.

2. Senator Wellstone offered an amendment to strike language in the amendment in the nature of a substitute to S. 1477 that required there to be a "nonvoting public representative" on all FDA

scientific advisory groups and instead require there to be a “voting consumer representative, including a patient or patient-nominated individual, who represents the perspective and reports back to the affected community.” This amendment was withdrawn when Senator Kassebaum offered a motion to strike the language in the amendment in the nature of a substitute requiring that scientific advisory groups include a “nonvoting industry representative and a nonvoting public representative.”

3. Senator Harkin offered and then withdrew a second-degree amendment to Senator Coats’ amendment providing for accredited-party participation to establish a 3-year pilot program for the review of medical devices. The second-degree amendment would have prohibited review by accredited third parties of class III devices.

4. Senator Kennedy offered and then withdrew an amendment to substantially revise provisions in the amendment in the nature of a substitute to S. 1477 relating to the responsibilities of manufacturers of drugs and biologics when they make changes in their manufacturing processes. Senator Kassebaum indicated to Senator Kennedy that she would work with him to develop a consensus on this matter before the bill is considered on the Senate floor.

IV. EXPLANATION OF THE LEGISLATION AND COMMITTEE VIEWS

TITLE I—MISSION AND ACCOUNTABILITY

Mission

The first title of S. 1477 establishes in statute that the mission of the FDA is to promote and protect the health of the American public by facilitating the rapid and efficient development and availability of new products, protecting the public from unsafe or ineffective products, and enforcing applicable statutes and regulations in a timely, fair, consistent, and decisive manner.

The committee concurs with the view of the Advisory Committee on the Food and Drug Administration (discussed above) that “the Agency should be guided by the principle that expeditious approval of useful and safe new products enhances the health of the American people. Approving such products can be as important as preventing the marketing of harmful or ineffective products.”

From the 1906 Food and Drugs Act through the 1990 Safe Medical Devices Act, food and drug law has emphasized that the duty of the FDA is to protect the public against unsafe or ineffective products. The purpose of this legislation, as reflected in the mission statement, is to give greater emphasis in the law to ensuring timely access to safe and effective products, while continuing to protect the public against unsafe or ineffective products.

The committee hears often from seriously ill patients and their families who are intensely frustrated by the time that the agency takes to review applications for the approval of promising new therapies. Many must travel abroad to obtain promising new therapies that are still under development or awaiting approval in the United States, or which will never be available here because companies, daunted by the cost, time, and complexity of bringing a new product to market, have opted not to seek FDA approval.

The committee has also received grave expressions of concern by the regulated industries about the impact the increasing complex-

ity and costliness of FDA demands on product development and testing and lengthy delays in new product approval are having on the ability of small, highly innovative start-up companies to continue to pursue new product discovery and development. Stifling innovation is not in the best interests of public health. Nor are overly burdensome requirements which make it increasingly difficult for innovative domestic industries to continue to pursue research, development, and manufacturing in the United States while remaining competitive in international markets.

By making explicit in law that facilitating the rapid and efficient development and availability of new products is a fundamental mission of the FDA, the committee is also hopeful that the FDA will feel more confident in weighing the potential benefits of a product against its potential risks. Because current law places such emphasis on protecting the public from unsafe and ineffective products and Congress has been quick to call the agency on the carpet when unsafe or ineffective products harm consumers, the committee believes the agency may have become overly risk-adverse in its evaluation of promising new products.

The mission statement also reflects the importance the committee places on timely, fair, consistent, and decisive FDA action in enforcing the applicable statutes. The committee, for example, has received numerous reports of fundamental inconsistencies in the enforcement of requirements and regulations from region to region of the country and of field inspectors requiring manufacturing processes that differ from those that the agency has approved under new product approval applications or submissions.

FDA performance standards

Current law contains no provisions designed to ensure that performance standards are set and that the agency is held accountable for adherence to those standards. The legislation requires the Secretary of Health and Human Services to set quantifiable performance standards for the FDA, after broad consultation with experts in the development, clinical testing, and regulation of products subject to the agency's regulation, representatives of patient and consumer advocacy groups, health professionals, and the regulated industries.

The committee intends that the requirement for broad consultation with experts and those affected by FDA's actions be taken very seriously. The FDA regulates approximately 25 percent of the Nation's economy, and its actions—or its failures to act—have profound implications for the lives of all Americans. In setting performance standards for the agency, the Secretary therefore must be as fully informed as possible of the state of the art of product development and regulation and of the potential impact of agency actions and decisions on individuals and the regulated industries.

The legislation also requires the Secretary to publish an annual report in the Federal Register comparing the FDA's actual performance to the standards and if the agency is not in compliance with a standard or standards, setting forth a corrective action plan. The legislation specifically requires that the report include a full statistical presentation relating to applications and petitions for new products approved by the agency during the year. The committee

concluded that requiring the report to be published in the Federal Register, as opposed to submitted to Congress, would result in greater public availability and more widespread consideration.

Some advocates of FDA reform urged the committee to establish an independent review board to oversee the operations of the FDA and to ensure that the reforms in this legislation are implemented. The committee rejected this approach for several reasons. First, the committee believes that it is Congress' responsibility to oversee the FDA and to ensure that reforms are implemented. The committee believes that the performance standards and the annual report will provide Congress with tools for effectively carrying out these oversight responsibilities. Second, the committee was concerned that the logistics of convening an independent review board could well delay the implementation of reforms for a year or more.

The performance standards are required to achieve particular objectives. First, backlogs on all applications must be reduced, with the objective of eliminating all backlogs by January 1, 1998. The performance standards must also establish a schedule to bring the FDA into full compliance with the statutory time deadlines for action on applications by July 1, 1998.

The committee believes that these objectives could be met without compromising the quality of review if the FDA pursues the new policies and procedures established in the legislation. First, and perhaps most importantly, the legislation provides for collaboration between the sponsors of new products and the FDA in the development of protocols for clinical investigation. Such collaboration early in the process should provide the FDA early on with information about the types of studies that are being done, the data that is being collected, and a better sense of whether the investigations are demonstrating that the product is effective. This collaboration through the clinical testing of new products should substantially reduce the burden on the agency once the new product application is filed for agency review. Collaboration on the design and conduct of clinical trials should also substantially reduce the tendency of new product sponsors to conduct many more trials than may be necessary because of their uncertainty about what the FDA will require to demonstrate safety and effectiveness, thereby reducing the number of studies and sheer weight of data submitted to the agency for review.

The committee intends this legislation to encourage the FDA to adopt a team approach, under which the same persons who are working with new product sponsors early in the clinical testing phase would also be the persons responsible for reviewing the new product application once it is filed with the agency.

The committee notes that the agency has implemented this collaborative, team approach to protocol design, clinical investigation, and agency review in its work with sponsors of new drugs for the treatment of AIDS and has achieved, as a result, a very substantial reduction in review times for these drugs.

Second, the legislation requires the Secretary, in consultation with experts in product development and review, consumer and patient advocates, and the regulated industries, to reevaluate the types and amount of data that are required in support of new product applications and publish criteria on this matter in the Federal

Register. The committee has received testimony indicating that advances in the sciences of new product development and statistical analysis would permit the agency to substantially reduce the types and amount of data and information it now requires without compromising its ability to evaluate product safety and effectiveness. Further, the publication of criteria should provide new product sponsors with greater certainty, thus reducing the number of trials and amount of data and information they may feel compelled to file with new product applications.

Third, the legislation substantially reduces the number of applications subject to agency review to allow the agency to focus its review resources on products posing safety and effectiveness issues. For example, under this legislation, applications for FDA preapproval of many drug, biological products, and medical device manufacturing changes would no longer be required. Premarket notifications to the agency would no longer be required for most class I and many class II devices. Similarly, the burden of premarket approval of indirect food additives would be very substantially reduced.

Interagency collaboration and FDA facility consolidation

The legislation requires the Secretary to implement programs and policies that will foster collaboration between the FDA, the National Institutes of Health, and other science-based agencies to enhance the scientific expertise available to the Commissioner for the evaluation of emerging medical therapies, including complementary therapies, and advances in nutrition and food sciences.

The committee includes this provision to help ensure that the FDA has available to it the expertise and assistance it may need to enhance its own capacity for the efficient evaluation of applications for the approval of products that pose substantial new scientific or technical issues.

The committee strongly supports the consolidation of FDA facilities at White Oak, Maryland, as proposed by the FDA in consultation with the General Services Administration (GSA). The consolidation of FDA's facilities into state-of-the-art laboratory space and supporting office space has great significance not only to the FDA, but to the Nation as a whole.

FDA laboratories and facilities are now scattered among 50 buildings at 20 locations in the Washington, D.C., metropolitan area. Many of these facilities are old, poorly maintained, and do not meet accepted standards for laboratory research. These antiquated facilities and fragmentation of agency programs have proven burdensome in many ways. The cost of leasing space for FDA and the difficulty in managing programs that are so widely scattered in the Washington area is a tremendous burden for the FDA. The FDA cannot do its job if it does not have the tools it needs to accomplish its mission. The committee believes that providing the FDA with consolidated, modern, state-of-the-art facilities will enable the FDA to do its job faster and more efficiently, benefiting the taxpayer and the consumer.

Information system

The committee is concerned by reports that it frequently receives from applicants for the approval of new products of the difficulties they encounter in determining the status of the agency's review of the application. In turn, FDA employees often complain that time which could be spent reviewing applications is taken up instead in responding to frequent calls from applicants with questions about the status of their applications. The committee is also concerned about frequent reports it receives from applicants of the FDA asking again for data or information that it has already received, but apparently has misplaced.

To end this frustration and unproductive use of time, the legislation requires the Secretary to establish and maintain an information system to track the status and progress of applications or submissions for FDA approval or clearance of products subject to its regulation and requires that the system permit access by the applicant. Applicants will know the status of their applications and will be able to see where hurdles have been cleared or problems have arisen. The committee intends the product approval system to be collaborative. By opening up communications between the applicant and the agency, the need for formal letters will be reduced, the time and effort involved in review will be reduced, and the entire process will be expedited.

Policy statements

In the past decade, the FDA has relied less on developing its policies and procedures through promulgating substantive regulations and more on the use of informal policy statements, including guidelines, points to consider, and memoranda. This has the advantage of consuming fewer agency resources than the cumbersome process of promulgating substantive regulations and permits the agency to respond more quickly and efficiently to requests for policy guidance.

However, the FDA's increasing reliance on policy statements has also produced several problems. First, the FDA maintains no compilation of these documents. The regulated industries and the public may not be aware that they exist or where they can be found. Second, there is no systematic process for their adoption or amendment. There may or may not be an opportunity for interested outside individuals and organizations to have any input into their formulation or amendment. Third, there is inconsistency among FDA personnel in the use of these documents. Some FDA employees insist upon industry strictly following them, and others do not.

This legislation is intended to ensure the uniform agency use of policy statements. The legislation requires the FDA to establish a clear procedure governing the development and use of informal policy statements that relate to the premarket approval process, requires that affected individuals be given the opportunity to participate in their development or amendment, and requires that the FDA periodically compile and publish all statements of general applicability. The committee wishes to emphasize that it is not the intent of these provisions to make informal policy statements into substantive rules subject to the notice and comment requirements of the Administrative Procedures Act.

Scientific review groups

Scientific review groups have appropriately become an integral element in the FDA product premarket approval process. The FDA often relies on them heavily for expertise and judgment. Although they do not make final decisions, their conclusions and recommendations are followed more than 90 percent of the time.

The current provisions of the Federal Food, Drug, and Cosmetic Act require the use of scientific review groups in implementing the Radiation Control for Health and Safety Act of 1968 and the Medical Device Amendments of 1976, but not in implementing other provisions of the act. This legislation expands the use of advisory committees and establishes requirements for their appointment and use.

The committee agrees that scientific review groups are an important part of the product premarket approval process but has heard some serious concerns about the way they are appointed and used. First, it has been contended that scientific review groups have been too close to the FDA personnel that they advise and therefore have not provided sufficiently independent advice. Second, there has been concern that scientific review groups do not meet sufficiently often to provide timely advice on important matters. Third, many scientific review group members are not experienced with FDA issues and are not given adequate training for their responsibilities. Fourth, members of the public, including the regulated industries, often are not provided with an adequate opportunity for participation in scientific review group meetings. Finally, FDA action following scientific review group recommendations is often delayed substantially.

This legislation builds on the authority provided to the Secretary under section 904 of the Federal Food, Drug, and Cosmetic Act to establish such technical and scientific review groups as are needed to carry out FDA functions. To enhance the independence of the scientific review groups, the legislation provides that the FDA Commissioner may not delegate the appointment and oversight authority relating to scientific review groups and that the FDA will consult with the groups in setting their agendas. The legislation requires that, to the extent feasible, meeting agendas must be publicly announced and published in the Federal Register at least 30 days in advance of meetings. The legislation requires that meetings be held regularly in order to assure that issues ready to come before a scientific review group are handled promptly. Groups are required to meet at least 3 times a year unless there are reasons to meet less frequently.

To assure continuity, the legislation sets a term of 3 years, which may be renewed, for scientific review group members and provides that the chairperson shall have served at least 3 years before assuming that position and therefore may serve a third term. The legislation also requires the FDA to provide adequate training to scientific review group members.

To better ensure the independence of scientific review group conclusions and recommendations, the legislation requires the FDA to provide product sponsors with copies of all documents provided to scientific review groups in preparation for a meeting and to provide product sponsors the opportunity to submit documents to the mem-

bers in response to the FDA's documents. Product sponsors are permitted to submit such documents to the FDA, which is required to provide them to the members immediately.

To better ensure opportunities for public participation at meetings of scientific review groups, the legislation requires that meetings provide adequate time for initial presentations and for response to differing views and requires the encouragement of free and open participation by all interested parties.

To address the concern about lengthy delays between the time that scientific review groups offer conclusions and recommendations and FDA action, the legislation requires the FDA to make a final determination within 60 days of receiving a scientific review group's conclusions or recommendations on a specific issue under review by the group.

Appeals within the FDA

The legislation requires FDA to set forth three types of administrative appeals within the agency and to ensure that individuals are made aware of these appeal mechanisms.

First, the FDA must establish an internal system for administrative appeals of any decision by an FDA employee, except for formal administrative or judicial proceedings. For a significant scientific issue, the final step will involve the right to request evaluation by an appropriate scientific review group.

Second, sponsors of clinical investigations or applications for pre-market product approvals are provided the right to request evaluation by a scientific review group of any significant scientific issue or decision relating to the research, development, investigation, or review of the product involved. The FDA is required to refer the request to the appropriate scientific review group to review the request and determine whether or not the scientific review group should conduct an evaluation. Any such scientific review group review must be conducted expeditiously, at the next meeting of the committee.

The committee recognizes that providing the sponsors of new products the opportunity to request scientific review group review of significant scientific issues in dispute with the agency or decisions made by the agency significantly expands the responsibilities of the scientific review groups. The committee is sensitive to the concern that expanding the responsibilities of scientific review groups may make it more difficult to recruit individuals to serve on them. That is why the committee has included provisions giving the scientific review group the discretion to determine which issues or decisions the group will review. The committee believes that most issues can and should be pursued through the agency's internal appeals process and intends that the option of appealing directly to scientific review groups be used only for very serious scientific disagreements between the sponsors of new products and the agency.

Third, for any scientific dispute, the FDA is authorized to use such additional procedures as may be considered useful. The legislation authorizes but does not require the use of panels of FDA officials or government employees who are not FDA employees and outside mediators and arbitrators. The committee believes that

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

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

Appointment and term of the commissioner of food and drugs

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

TITLE II—EXPEDITED ACCESS TO PRODUCTS FOR SERIOUSLY ILL PATIENTS

Access to unapproved therapies

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

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

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

The person requesting the unapproved therapy must show that there is no comparable or satisfactory alternative, the risk from the investigational product is not greater than the risk from the dis-

ease, there is an investigational protocol in effect under the Federal Food, Drug, and Cosmetic Act, and an expanded access protocol has been approved by the FDA. A manufacturer or distributor may decline to make an investigational product available under such a program.

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

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

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

Expanding humanitarian use of devices

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

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

Expediting approval of new drugs, biological products, and medical devices for serious illnesses

The legislation provides that, for a new drug, biological product, or device that is intended for use for a life-threatening or serious disease or condition and that provides therapy or diagnosis not available from another approved product or offers significant improvement over another approved product, the Secretary must approve or deny the application within 180 days after receipt. It is the committee's intention that applications for the approval of breakthrough products be given priority within the agency.

TITLE III—REVITALIZING THE INVESTIGATION OF NEW PRODUCTS

Timely review and reasonable data requirements for clinical research on drugs and biological products

The scientific process of discovery, research, development, investigation, and ultimate approval, is lengthy and costly for any new product subject to FDA premarket approval. It is essential to keep the discovery and investigational pipeline full of new products, because for every 5,000 drugs that enter the process, only one emerges as an approved new product. It is thus critical to facilitate and encourage the investigation of as many new products as possible, in order to enhance the likelihood of ultimate success. The public health is greatly benefitted by a vital and robust drug development and investigation system.

The law governing the investigation of new drugs (which has always been applied to investigational biological products as well) has not been changed significantly since it was enacted in 1938. The FDA has imposed numerous administrative changes by regulation in the intervening years. This legislation codifies the FDA approach into the Federal Food, Drug, and Cosmetic Act and sets reasonable requirements to make the process work efficiently and expeditiously.

As is true under current FDA regulations, under this legislation a clinical investigation of a new drug may begin 30 days after the date the FDA receives an investigational new drug notification unless the Secretary informs the sponsor in writing that the investigation may not begin and specifies the basis for the decision and the information needed in order for the clinical investigation to begin. Over the years, the FDA has at times issued clinical holds by telephone or by informal correspondence rather than by a formal determination meeting the requirements of this provision, leaving the sponsor uncertain about what is required for the removal of the hold and when and if the FDA will allow the investigation to proceed. The legislation will end these informal practices and require strict adherence to the procedure specified to ensure full and open communication.

Within 1 year after the date of enactment, the legislation requires the Secretary to consult with outside individuals and organizations and, based upon that collaborative process, publish in the Federal Register criteria for the type and amount of information relating to the safety of an investigational drug to be included in an investigational new drug notification under the legislation. These

criteria must be periodically reviewed and may be revised to reflect the most recent agency experience.

This provision has been adopted by the committee because of concern that excessive agency demands for information in an investigational new drug notification are discouraging sponsors from conducting research in the United States and making it more difficult for smaller, innovative sponsors to begin investigations. The committee commends the FDA for its recent publication of guidance on the requirements for initiating clinical investigations that substantially reduced the burden on investigators. However, the committee remains concerned that this burden could again increase and also believes that the collaborative process for reviewing and, the committee hopes, coming to consensus on reasonable data requirements could result in further reductions in requirements.

The legislation permits the Secretary to place a clinical hold on any ongoing clinical investigation if the Secretary determines that such action is necessary for the protection of human subjects. The committee recognizes that the Secretary may well have concerns about the design of research protocols or other aspects of the investigation which do not put human subjects at risk. This legislation does not prevent the Secretary from communicating these concerns to investigators and sponsors and working collaboratively with investigators and sponsors on changes to address such concerns.

The legislation establishes a specific procedure for the FDA to impose a clinical hold on a drug investigation. There must be an opportunity for a meeting within 10 days, and a written list of conditions for the withdrawal of the clinical hold within 10 days after that. Within 20 days after the FDA receives a written request from the sponsor requesting that the clinical hold be removed, the FDA must reply. These provisions are designed to ensure that the FDA promptly conveys the concerns that prompted it to place a hold on a drug investigation, that the investigators are informed of the steps necessary to resume investigations, and that the FDA responds promptly to requests to resume investigations.

Timely review and reasonable data requirements for clinical research on devices

The legislation adopts an approach for the investigation of medical devices that is consistent with that for drugs. The Secretary is required to amend current regulations, within 120 days of the date of enactment, to incorporate the new provisions.

It is rare that a new chemical entity would be changed in the course of an investigation, but medical devices are constantly modified throughout their investigation as part of the developmental process. To reflect this fundamental difference between drugs and devices, the legislation provides that the investigational device regulations permit insignificant developmental changes in devices, including manufacturing changes, during an investigation without requiring a supplement to or an additional approval of an investigational device notification. The legislation provides that the regulations also permit changes or modifications to clinical protocols for an investigational device that do not affect the validity of data or patient protection.

Current law establishes two types of investigations for medical devices: those that may be conducted on the basis of institutional review board approval and those for which a notification of an investigational device exemption must be submitted to the FDA. This legislation does not change this basic approach.

Collaborative research design

The committee strongly believes that the time it takes for the development and testing and for the FDA's review of applications for the premarket approval of new drugs and devices can be substantially reduced and the development, testing, and review processes made far more efficient if there is greater collaboration between the FDA and new product sponsors early in the investigational phase for drugs and devices to mutually determine the protocols for clinical testing. Such collaboration will provide new drug and device sponsors with a clearer understanding early in the process of what the FDA believes will be necessary to demonstrate safety and effectiveness and will familiarize FDA personnel with the new product and with the types of clinical investigations that are being undertaken and the results being obtained in the course of those investigations.

Accordingly, the legislation permits a sponsor to request a meeting with the FDA to review one or more protocols. The request must be in writing and include the proposed protocol. The FDA must then meet with the sponsor within 30 days and provide a written review, including any deficiencies in the protocol. The FDA is required to provide a written summary of the meeting, including a written review of the protocol, which, upon the mutual agreement of the agency and the sponsor, then becomes a part of the FDA product review file.

As a matter of sound science and patient protection, the legislation requires protocols to be designed to limit the number of patients and procedures to the number necessary to permit a determination of the safety and effectiveness of new products. The committee does not intend this requirement to conflict with the objective of including diversity within the patient population selected for clinical testing. The committee is aware of the need to include women, children, the elderly, and minorities in clinical testing, in order to provide adequate experience with a new drug or device on a wide range of patients.

Sponsors of clinical trials often complain that, after receiving approval from one FDA employee for a clinical trial protocol and completing a study on that basis, a new or different FDA employee will conclude that the protocol is nonetheless inadequate or in any event insufficient for product approval. To address this problem, the committee has incorporated in the legislation a specific prohibition against any FDA modification of an agreement reached on a protocol between FDA and the sponsor of an investigation except by the director of the FDA office responsible for the regulation of the drug or device and only for a documented scientific or clinical need or patient safety. The committee intends that the FDA be held to its word on these matters unless there are sound reasons for changing its position. A written scientific explanation, setting forth a rationale that was not available at the time the original de-

cision was made, or new scientific knowledge that has come to light, would ordinarily be required.

It is essential that agreements of this type be made through a formal process, in writing, and become part of the established administrative record. Informal agreements that cannot be documented will not suffice. Neither the FDA nor sponsors of clinical investigations can be held accountable for undocumented recollections of oral statements months or even years after they were made.

The FDA is required to issue guidelines to implement this provision. Repeated failure by a sponsor to follow the guidelines may be grounds for an FDA refusal to schedule a meeting under this provision.

TITLE IV—EFFICIENT, ACCOUNTABLE, AND FAIR PRODUCT REVIEW

Content and review of an application

The legislation establishes requirements that apply to all product premarket approval applications, including those for food additives, new drugs, medical devices, biological products, new animal drugs, animal feed bearing or containing a new animal drug, and color additives. It encompasses all forms of product applications, including petitions and notifications. The intent of the committee is to establish broad requirements for all of these forms of applications.

Consistency in the FDA's handling of filing requirements for applications is extremely important. Differing requirements for competing products would undermine the FDA's credibility and the integrity of the premarket approval process itself. For that reason, the legislation requires the Commissioner within 60 days of enactment to establish and publish in the *Federal Register* a mechanism to ensure the fair and consistent application of filing requirements. The FDA may establish one mechanism for all application, or separate mechanisms for separate centers within FDA, or even separate mechanisms for each type of product application. This is left to the discretion of the agency, as long as applications for similar products receive the same consistent handling.

It is often difficult for an applicant to determine the proper classification of a product as a drug, biological product, or device. Even where the classification of the product is known, the proper organizational center in the FDA where the application will be handled can be uncertain. The legislation therefore provides that, within 60 days of receipt of a written request, the FDA must provide an applicant with a written determination regarding the classification of the product or the component of FDA within which it will be handled, or both. This determination is binding. If the FDA fails to meet this requirement, the applicant's designation shall be final and binding.

For the same reason that the legislation requires the FDA to establish criteria for the type and amount of information to be included in investigational applications, the legislation also requires within 1 year after the date of enactment that the agency publish criteria for the type and amount of information to be included in product approval applications. These criteria will be determined after a consultative process with individuals and organizations

with knowledge, experience, and an interest in this matter. Different criteria will unquestionably be required for each of the product categories involved, to reflect the differences among them. The committee intends that the amount of safety and effectiveness data will be the minimum necessary to provide an adequate assurance that the statutory requirement for safety, and where appropriate effectiveness, will be satisfied. In developing these criteria, international experience will undoubtedly be relevant. For drugs, the FDA is required specifically to consider the recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The FDA participates in the international conference and in the development of these recommendations.

For the reasons that have been discussed throughout this report, it is important to recognize the impact that the ultimate requirements for approval of a new product have upon the total research and development process. The approval criteria cannot be considered in isolation. Much research and development is driven by the final approval requirements. To the extent that those criteria and requirements are excessively onerous and stringent, the investment required for research and development will escalate, the time during which the products are unavailable to consumers will lengthen, and the resulting cost to the public will increase dramatically.

On the other hand, the committee does not intend to reduce the safety or effectiveness of products subject to FDA regulation. It is important that there be adequate assurance that new products are safe and work as intended, but not that there be overwhelming or excessive assurance. No amount of testing can provide complete assurance of either safety or effectiveness, because this ultimately can only be determined through widespread use after marketing begins.

Contracts for expert review

For many years, the FDA has contracted with outside individuals and organizations to review part or all of product applications or agency decisions respecting the safety and effectiveness of marketed products. The FDA contracted with the National Academy of Sciences (NAS) to review the effectiveness of all new drugs for which new drug applications were made effective during 1938–1962 and with the Federation of American Societies for Experimental Biology (FASEB) to review the safety of all food substances that the agency had earlier determined to be generally recognized as safe for their intended use in food. The FDA has contracted with individual experts to review aspects of new drug applications and recently contracted with the Mitre Corporation (now incorporated as Mitretek Corporation) to review supplements to new drug applications. Finally, the FDA has developed a pilot program for third-party review of class I and class II medical device submissions a step beyond traditional agency contracting out activities.

There are sound reasons for using outside individuals and organizations to review, evaluate, and make conclusions and recommendations to the FDA with respect to applications submitted to the FDA. In some instances, individuals outside the FDA have unique expertise not available to the agency. In other instances,

the FDA's internal resources are inadequate to handle surges in the workload. In still other instances, internal FDA resources must be focused on priority matters and cannot be diverted to more routine matters that become backlogged. The FDA has in the past used outside individuals and organizations for these reasons.

The legislation explicitly authorizes the FDA to contract with outside individuals and organizations with expertise in relevant disciplines to review, evaluate, and make conclusions and recommendations to the FDA on any form of submission made to the agency. Under this legislation, the FDA retains full authority to make any determinations with respect to the classification, approval, or disapproval of any product. Thus, although outside experts will assist and advise the FDA, they cannot commit or make any final decision for the agency. Final action must be a function solely within the power of the FDA. However, the FDA is advised not to arbitrarily or systematically disregard the recommendations of the reviewers it has accredited and qualified or to redo without cause the work completed by such reviewers.

The legislation requires the FDA to use its authority to use outside experts under contract (on a basis other than a "pilot" or "demonstration" basis) to ensure the efficiency, timeliness, and quality of the review of premarket approval applications, to ensure that the agency has the requisite scientific and technical expertise with respect to new therapies and technologies, and to assist the agency in managing its workload in the review of the large numbers of indirect food additive petitions and premarket notifications for medical devices under section 510(k) of the Federal Food, Drug, and Cosmetic Act filed with the agency every year. The FDA will determine which types of 510(k) notifications and indirect food additive petitions are reviewed by outside experts. Even where use of outside experts under contract is required, however, the FDA retains full authority to make any final decision regarding approval or disapproval. Accordingly, the process will be made more efficient and cost-effective without in any way undermining the credibility and integrity of the final FDA decision or public health and safety.

The legislation requires the FDA to establish eligibility requirements through the promulgation of a regulation before any individual or organization can be included for consideration for a contract under this provision. The regulation must provide for the protection of confidential or proprietary information and prevent conflicts of interest. Any outside contracts of this nature would also be subject to the requirements of section 708 of the Federal Food, Drug, and Cosmetic Act, which similarly protects confidential information from disclosure by a person under contract with the agency.

The committee expects the agency to quickly accredit and use expert outside individuals and organizations to improve the quality, timeliness, and efficiency of the review process. The committee recognizes, however, that in certain limited instances eligible contractors may not be immediately available.

A continuing problem at the FDA has been its failure to respond in a timely manner to the recommendations of an outside evaluation. Some NAS and FASEB reports still remain unimplemented. Accordingly, the legislation requires that, upon receipt of any such evaluation, the responsible FDA official must personally review the

matter and make a final decision within 60 days or such shorter period prescribed by the Federal Food, Drug, and Cosmetic Act for review of a submission. This will assure that expert conclusions and recommendations do not languish for months or years without an FDA decision.

Within 2 years of the date of enactment, the FDA is required to provide Congress with a report on the use of this new authority. The report must evaluate the extent to which use of contracts with outside experts improves the efficiency of review and the expertise available to the FDA. The committee strongly recommends that this evaluation and report be conducted and prepared by an independent research organization. It is important that this new authority be approached openly and fairly by the FDA, that successes and failures be identified, that means of improving the approach be sought, and that the entire process be refined and improved in order better to serve the American public.

Prompt and efficient review

Perhaps no other issue has generated as much consternation on the part of the public and the regulated industries as the long delays and uncertainties in the FDA's review of premarket notification and approval applications. To address these concerns, the legislation includes new procedures and requirements designed to assure a more efficient, predictable, and timely review without jeopardizing safety or effectiveness. These requirements apply to all premarket notification and approval submissions for products subject to FDA regulation.

The legislation requires the FDA to establish procedures and policies to facilitate a truly collaborative review process that encourages open, informal, and prompt communications to resolve questions or problems that may arise during the review of a premarket approval submission. After observing the success of the collaborative review process the FDA has established for new AIDS drugs, the committee strongly believes that a collaborative review process will significantly improve the efficiency, timeliness, and quality of the review of other important new products, as well.

To foster such collaboration between the FDA and applicants in promptly identifying and resolving potential problems or questions about an application for the premarket approval of a new product, the legislation requires periodic meetings throughout the FDA review process. Meetings must be held before the expiration of half the statutory time period for review and before three-quarters of such period, or within 15 days after an advisory committee has reviewed the application, unless both parties agree that such a meeting is unnecessary. By mutual consent, the two parties may establish a different schedule that might make better use of their time. Prior to the required meetings, the FDA must present to the applicant in writing a description of any deficiencies and the information necessary to make the application approvable. This provision is intended to encourage the FDA to focus on the real substantive issues involved and to require the applicant to respond with appropriate information.

As discussed previously in this report, the committee understands the frustration and desperation of individuals who are seri-

ously ill who must either do without promising new therapies or go abroad where such therapies have been approved in other countries, because the therapies are still under review by the FDA. The legislation provides that, beginning July 1, 1998, if the FDA fails to meet a statutory deadline for action on a premarket approval application for a product that offers a significant improvement over existing approved products or has the potential to make foods more wholesome and contribute to a healthier diet, and the product has already been approved for marketing in the European Union or the United Kingdom, then, at the request of the applicant, the FDA must within 30 days either approve or disapprove the application. Thus, this provision is only triggered by the failure of the agency to meet its statutory review obligations. Further, although the approval of certain products in England or Europe can trigger the requirement for a prompt FDA decision once the agency fails to meet a statutory deadline, the ultimate decision on approval or disapproval remains with FDA itself. Under the legislation, a foreign approval does not create a presumption of approvability. There is no provision for "deemed approval" if the agency fails to act in a timely manner either to disapprove or approve a product. No product subject to premarket approval or clearance can reach the market without an affirmative FDA decision.

If the FDA disapproves an application, the agency must notify the applicant of the reasons for the disapproval. The applicant may then appeal the disapproval as any other disapproval decision may be appealed under current law.

The European Union has recently established a European Medicines Evaluation Agency (EMA) and has adopted directives for determining the regulatory requirements for marketing other products subject to FDA jurisdiction. Although these regulatory systems are new, they build on long-standing, sophisticated systems and are responsible for regulating the safety and effectiveness of products for use by a larger population than in the United States. Accordingly, the committee recognizes that a European Union approval is also an appropriate trigger for requiring prompt FDA decision on an application once the agency has been unable to meet a statutory deadline.

The FDA has itself recognized the validity of relying on foreign approval of important new drugs. As part of the FDA policies for implementing a Reinventing Government initiative to assist cancer patients, the FDA will encourage the manufacturers of cancer drugs which have been approved abroad and are under study in the United States to apply for expanded access protocols to make these drugs available to all appropriate American patients. The committee believes that this recognition should be expanded to all products that offer a significant improvement over a current therapy, whether for cancer or for other serious diseases or conditions.

In addition, this committee gave recognition to the quality and sophistication of the European Union's and United Kingdom's regulatory systems, as well as those of several other countries, in its unanimous support of S. 593, the FDA Export Reform and Enhancement Act, which was recently signed into law by the President as P.L. 104-134.

The legislation also requires the FDA, with the consent of the applicants, to contract for outside expert review of categories of applications when the FDA has in the immediate past fiscal year failed to meet the statutory deadline for action on at least 95 percent of the applications in a particular product category. This provision is intended to provide much-needed help to the agency in precisely those areas where it most needs resources. There may well be reasons why the FDA cannot meet the 95 percent compliance level, such as surge in applications in a particular product category or a lack of agency expertise in evaluating applications which pose new scientific or technical issues. This provision will help remedy such situations.

It is important to note that under this provision, it is the FDA that selects and pays the outside reviewer. The committee expects that the FDA would select only highly qualified reviewers in whom it has full confidence to perform a high-quality confidential, thorough, and independent evaluation of an application.

It is also important to note that the FDA “starts” the review clock itself when it accepts an application for filing. It is the committee’s understanding that one reason the agency fails to meet statutory deadlines for action on applications is its acceptance of applications which are not complete or are not well-presented. The committee believes that applicants must bear the responsibility of submitting the best possible applications to the agency and that this provision will also serve to improve the applications coming into the agency for review.

Finally, it is important to note that the FDA retains full and final authority either to approve or disapprove a product under this provision. A recommendation by an outside reviewer does not trigger a “deemed approval.” The provision requires the FDA to review the determination of the outside reviewer within 60 days of receiving it and either approve or disapprove the application. If the FDA disapproves it, the agency must notify the applicant in writing of the basis for disapproval. The applicant then has the right to appeal that disapproval as any other approval or disapproval decision may be appealed under current law.

The committee emphasizes that it will monitor the statistical and regulatory practices that the FDA may use in complying with and measuring its compliance with statutory deadlines for new product reviews.

Good manufacturing practice inspection

The Federal Food, Drug, and Cosmetic Act requires the manufacturers of drugs and devices to comply with good manufacturing practices (GMP), and the FDA has also promulgated GMP regulations for the food industry. When companies are under court order for failing to comply with GMP, it is routine practice for the FDA to suggest that they hire outside independent GMP consultants to work with them and to conduct inspections in order to bring them into compliance.

The legislation reflects this background by authorizing the FDA to accredit outside organizations to conduct GMP inspections under the Federal Food, Drug, and Cosmetic Act. If the FDA decides to exercise this authority, the FDA is required to establish, by regula-

tion, the requirements that an organization must meet to be eligible to be accredited as qualified to conduct GMP inspections for FDA. Like accreditation for outside expert review, the regulations must provide for the protection of confidential or proprietary information and protection against conflicts of interest.

The legislation establishes a procedure for accreditation. The FDA must act upon an application for accreditation within 90 days of receipt. The FDA may also revoke accreditation at any time for failure of an organization to comply with the applicable requirements.

An accredited organization that conducts an inspection at the request to the FDA is required to apply the same GMP principles that the FDA applies. A report of the inspection must be provided to the FDA within 30 days, and must be provided immediately in the event of any observation that could cause or contribute to a significant threat to the public health.

Like outside expert review of applications, GMP inspections by accredited organizations are intended to extend the resources available to the FDA to enforce the Federal Food, Drug, and Cosmetic Act. As with all government agencies, the future budget for the FDA remains in doubt. Resources may well be curtailed rather than extended. GMP inspections by qualified accredited organizations may therefore be a very efficient and effective way to assure that the regulated industries meet GMP standards even during a time of Federal Government budget constraints.

The committee also directs the FDA to ensure that inspections provide maximum protection of public health by expanding product-specific training of inspectors and utilizing inspectors with product-specific expertise.

An additional benefit from this approach is that utilizing third party inspections provides another step toward shaping a regulatory system in the United States that is more familiar to other industrialized nations. This, along with the amendment of the FDA's medical device GMP regulations to include pre-production design validation and other quality system concepts from the International Standards Organization (ISO) standards, will increase the opportunity to obtain mutual recognition of inspection authorities and cooperative inspections. To the extent that countries rely on each other to inspect facilities, and trust the findings of such inspections, significant savings will accrue to governments and industry by avoiding duplicative foreign and domestic inspections. Although small steps, the United States' acceptance of inspections by accredited third parties and ISO quality system concepts is important in advancing the cause of international harmonization of regulatory systems.

The committee encourages the FDA to take steps toward establishing global GMP inspection standards in a cooperative effort with foreign regulatory bodies.

Environmental impact review

The National Environmental Policy Act requires that all Federal action be subject to environmental consideration. Some State laws also require a similar analysis. In only one instance, however, has the FDA ever determined that action on a new drug application

might potentially have a significant environmental impact. Even in that instance, the importance of the drug involved to human health outweighed the environmental impact and the drug was therefore approved. In the meantime, new product sponsors are generally required to file environmental impact assessments and statements with new product approval applications, adding substantially to the cost of new product development, adding time to the development and approval process, and consuming valuable FDA review resources.

The legislation ends the automatic requirement for filing environmental assessments, environmental impact statements, or other environmental considerations. New product sponsors would be required to conduct such assessments only if the director of the FDA office responsible for reviewing a product demonstrates, in writing and specifying the basis therefor, that there is a reasonable probability that the environmental impact of the action is sufficiently substantial and within the factors that the FDA is authorized to consider under the Federal Food, Drug, and Cosmetic Act and that consideration of that impact will directly affect the decision on the matter. This assures that, whenever environmental considerations are in fact significant, they will be fully analyzed and taken into account and that industry and agency resources will be focused on considering issues related to the safety and effectiveness of products.

Effectiveness, outcome, and cost-effectiveness standards

The Federal Food, Drug, and Cosmetic Act requires applicants for premarket approval or clearance of a new product to submit adequate data and information to demonstrate the safety and effectiveness of a new drug, biological product, new animal drug, animal feed bearing or containing a new animal drug, or medical device. The proof of effectiveness under the Federal Food, Drug, and Cosmetic Act is directed to the labeling claims for the product. In some instances, however, FDA has required applicants to submit proof beyond that required to justify the requested labeling.

First, the FDA has at times been concerned that a drug or device could be used for unapproved purposes and has required studies to support potential uses not included in the proposed product labeling. Second, the FDA has expressed concern about the potential cost of a new product, in comparison with existing therapy, and has required cost-effectiveness studies. Third, for some diagnostic devices, the FDA has required proof not only that the product performs as labeled but also that it results in a favorable clinical outcome. This legislation makes clear that these policies extend beyond the requirements of law and cannot be required by FDA employees.

The FDA has no authority to require the regulated industry to investigate unapproved uses or to analyze the cost-effectiveness of a product, unless explicit claims are made. The FDA's authority with respect to diagnostic devices resides only in determining whether the device performs as labeled. The clinical outcomes resulting from the use of the device properly fall within the realm of medical practice.

The committee's effectiveness definition is not intended to diminish the scientific rigor with which the FDA will evaluate devices. Instead, it is intended to promote a common understanding between the agency and persons who make premarket submissions of product claims that require effectiveness information. By avoiding the evaluation of unstated clinical outcomes, or other claims not included in proposed labeling, the committee believes the premarket review process will work better by eliminating the guess work now associated with the scope of FDA's effectiveness review.

Definition of a day

Because the legislation is designed to hold the FDA accountable for meeting statutory time deadlines for taking action on product premarket approval applications, it is important to define a "day" for purposes of those deadlines. The legislation defines the term "day" to mean a calendar day other than those days during which the applicant is responding to written questions from the FDA. Thus, the time between the day that the applicant receives a written request for information from the FDA, and the day on which the FDA receives the written response, is not included within the period established for the statutory deadline. Only the time for which the FDA is responsible is counted within the statutory period.

Approval of supplemental applications for approved products

Once the FDA approves a new drug, biological product, or medical device for a particular use, the medical profession may lawfully prescribe it for other uses as well. Unapproved uses of approved new drugs account for perhaps half of the use of drugs in this country today. In some specialty areas, such as cancer, "off-label" uses can be 60 percent or higher.

In order to place a new use of an approved drug or device on the product label, sponsors must file supplemental new drug or device applications for FDA review. Studies relating to the FDA's process for reviewing these applications have shown that it takes as long or longer for the FDA to review supplemental applications as the agency takes to review applications for initial product approvals. These lengthy review times serve as a disincentive to drug and device manufacturers to file supplemental applications. Thus, many drug and device labels do not reflect up-to-date information on new uses for approved products.

The legislation addresses this problem in several ways. The FDA is required to establish performance standards for the review of supplemental applications and to issue guidelines clarifying the requirements and facilitating the submission of data. The guidelines must specify when the submission of a compilation of peer-reviewed studies on the new use of an approved product (a "paper" new drug or device application) can be sufficient to demonstrate safety and effectiveness.

The legislation also requires the FDA to designate an individual in each of its centers (with the exception of the Center for Food Safety and Applied Nutrition) who is responsible for encouraging the prompt review of supplemental applications and working di-

rectly with the regulated industries to facilitate the development and submission of data in support of supplemental applications.

Finally, the legislation requires the Secretary to implement programs and policies that will foster collaboration between the FDA, the NIH, professional medical and scientific societies, and others to identify published and unpublished studies that could support a supplemental application, and to encourage product sponsors to make application or conduct further research in support of an application based in whole or in part on such studies.

Pediatric studies for new drug applications

When it comes to pharmaceuticals, our Nation's children are "therapeutic orphans." Currently, fewer than 30 percent of the prescription medications on the United States market are approved for use in the pediatric population and labeled for pediatric use. Pediatricians using drugs developed with adults in mind but which may also be effective or be the only option for treating the same illnesses and diseases in children must estimate dosages from dosages found to be safe and effective in adults. Such estimates are uncertain because children, and particularly those under 2 years of age, often metabolize drugs differently than do adults. Further, some drugs have different side effects and/or toxicities in children than in adults even when appropriate doses are used.

For these reasons, pediatricians have long had an active interest in promoting clinical studies of drugs in pediatric populations so that the drugs may be labeled for pediatric use. However, there is little incentive for drug sponsors to perform studies for medications which they intend to market primarily for adults and whose use in children is expected to generate little additional revenue. Pediatric studies pose ethical and moral issues relating to using new unapproved drugs on young patients. Second, there are substantial product liability and medical malpractice issues. Third, pediatric patients are more difficult to attract into studies. Fourth, for some drugs, pediatric use represents more difficult issues of drug administration and patient compliance than adult use.

The FDA has sought to address this problem by using its authority to approve labeling based upon the known pharmacokinetics of the drug, as opposed to requiring pediatric clinical trials for efficacy. The FDA has also issued regulations that embody this policy in an attempt to encourage pediatric labeling. These are clearly steps in the right direction, and the committee commends the FDA's initiatives in this area.

The legislation takes a modest further step toward a better resolution of this problem by providing an additional 6 months of market exclusivity when a drug manufacturer, at the request of the FDA, conducts pediatric studies to support pediatric labeling for a drug, either before the new drug approval application is submitted or later.

Notifications for device market clearance

The current language in section 510(k) refers to a "report" to FDA with respect to the marketing of medical devices whereas the same submission is described in section 513(i) as a "notification." To conform these two provisions, a technical amendment is made

in section 510(k) to replace the word “report” with the word “notify.”

Pharmacoeconomic information dissemination

While the committee did not address the dissemination of information by companies about the “off label” use of drugs and devices in the legislation reported by the committee, the committee believes that the FDA should allow companies to freely share pharmacoeconomic and comparative information about approved “on label” uses for products. This information is needed by managed care experts and other health care providers responsible for evaluating the benefits and costs of competing therapies. These health care experts use this information to significantly improve the quality of care by developing comprehensive protocols that teach physicians the best approach to treating a particular disease or condition. Health care providers also rely on companies to conduct studies in the providers’ own populations to help the providers predict the specific benefits and costs of FDA-approved products for their particular organizations.

Companies typically have the best and most information about the cost, effectiveness, and safety of their products. The FDA should not prevent the flow of that information to experts who need it. The competitive marketplace and other regulatory and legal controls over “on label” advertising safeguard the integrity of the information communicated in this sophisticated segment of the market. Restrictions on the ability of companies to make comparative claims on the basis of cost, effectiveness, or safety of approved uses of products actually encourage the sale and use of inferior products.

The FDA Export Reform and Enhancement Act, P.L. 104–134

On August 22, 1995, the committee considered and approved S. 593, the FDA Export Reform and Enhancement Act, which was introduced by Senators Hatch and Gregg. A modified version of S. 593 developed by Senators Gregg and Kennedy was then included in the amendment in the nature of a substitute to S. 1477. Subsequent to the committee’s consideration and approval of the amendment in the nature of a substitute to S. 1477, the FDA export reform provisions were included in the conference report on H.R. 3019, the Balanced Budget Down Payment Act, II, and signed into law by the President on April 26, 1996, as P.L. 104–134. As a conforming amendment, the FDA export reform provisions included in this legislation were eliminated.

It should be noted, however, that the provisions of section 801(e)(1) and section 802 of P.L. 104–134 represent separate and distinct alternative methods for exporting drugs. Pharmaceutical companies may opt to export drugs under section 801(e)(1) if the drug meets the four criteria under that section and has been approved under section 505 for marketing in the United States. This is true even if the manufacturer adds labeling that complies with the requirements of the destination country and that new labeling differs from the FDA-approved labeling. In that event, under section 801(f) the exporter must be sure to include the U.S. labeling and identify in the labeling any differences in the approved conditions for use. The section 801(f) labeling requirements only apply

to products exported under section 801(e)(1). Through a drafting error, these labeling requirements were inadvertently applied to exports of insulin and antibiotics because these products fall within section 801(e)(1) as explained elsewhere in this report.

TITLE V—DRUG AND BIOLOGICAL PRODUCTS REGULATORY REFORM

New drug approval standard

The drug amendments of 1962 added to the Federal Food, Drug, and Cosmetic Act the requirement that the effectiveness of a drug be established by “substantial evidence,” which is defined as adequate and well-controlled investigations, including clinical investigations, by qualified experts on the basis of which such experts could fairly and responsibly conclude that the drug will have the labeled effect.

The FDA usually interprets the requirement to demonstrate substantial evidence of effectiveness to require two adequate and well-controlled clinical studies, but has shown flexibility and approved some drugs on the basis of one adequate and well-controlled clinical study. The legislation confirms the current FDA interpretation that substantial evidence may, as appropriate, consist of data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained before or after the investigation).

Pilot and small-scale manufacture

An important part of applications for new drugs and biological products consists of the information on chemistry, manufacturing, and controls (CMC). During the investigation of a new product, only a relatively small amount of the drug is needed to support the preclinical and clinical trials. It is only after marketing approval is obtained from the FDA that large-scale manufacturing is justified.

For some drugs, where the evidence of effectiveness is overwhelming, companies are prepared to scale up to large manufacturing facilities even before FDA approval is obtained. For small companies with modest capitalization, however, it is common practice to wait for FDA approval of the premarket approval application before scaling up to larger processes. This is particularly characteristic of startup biotechnology companies.

In the past, the FDA has for some drugs required CMC data relating to large-scale manufacture before approval will be granted. This penalizes small companies and especially the biotechnology industry. The legislation therefore requires the FDA to review and approve new drugs and biological products on the basis of pilot and small-scale manufacturing, and to permit the company to scale up to a larger facility after the product has been approved. Scaling up can readily be undertaken on the basis of process validation, without additional clinical trials. Only in the very rare case where full-scale production is essential to ensure the validity of the CMC data prior to approval is the FDA given the authority to require such manufacture as a condition of approval. This is the approach that has been announced in the Reinventing Government initiative relating to drug and medical device regulations. The need for supplemental approval of the manufacturing changes needed to scale up

to larger facilities is subject to the new requirements in section 604 of the legislation.

Manufacturing changes

The manufacturing processes and facilities used to produce a new drug or biological product are under change throughout the investigation of the product and after marketing approval is obtained from the FDA. Innovations are sought to reduce impurities, increase yield, reduce the complexity and time required for manufacture, eliminate equipment, automate procedures, increase stability, and otherwise to improve the drug and reduce its cost. The benefits of these innovations are passed on to the consumer in the form of improved products and lower prices.

In the past, the FDA has imposed very stringent limitations on the ability of the pharmaceutical industry to adopt new manufacturing procedures. For most manufacturing changes, FDA approval of a supplemental application is required. For only a few has the FDA permitted the change to be made immediately and simply reported to the FDA by a simultaneous supplement or in the annual report submitted to the FDA for the drug. For biological products, FDA has been even more stringent, requiring clinical trials to support new manufacturing processes in many situations. Supplemental applications for manufacturing changes have, moreover, traditionally been given a very low priority within the FDA. As a result, it can be years before a new manufacturing process can be used, even if it results in a substantial improvement in the drug.

The impact of past FDA policy in this area on the pharmaceutical industry has been substantial. First, many companies have established manufacturing facilities abroad, where they can use a modern process to supply a drug to the rest of the world long before they can use the same process to supply the United States. Second, some companies have simply given up on important drug manufacturing improvements because of the cost and lengthy process required for approval. Third, drug prices have remained unnecessarily high because of the use of older technology and cannot be reduced even after new technology is approved because of the artificial regulatory cost imposed by the supplemental application process. Both technology and the public health and pocketbook have suffered.

To address these problems, the legislation considered by the committee included a new approach to manufacturing changes for new drugs (including new animal drugs) and biological products. It was the intent of the committee in designing this new approach to permit manufacturers to make minor manufacturing changes without waiting for agency approval when those changes would not adversely affect safety and effectiveness. During the committee's consideration of the legislation, however, there was concern expressed that the approach needed further refinement to better define the types of changes that could affect safety and effectiveness and ensure that such changes were subject to FDA oversight or review and approval. The committee agreed that such refinements would be made before the legislation was brought to the Senate floor for consideration.

Insulin and antibiotics

Separate provisions were added to the Food, Drug, and Cosmetic Act in 1941 to require the approval and certification of batches of insulin and in 1945 to provide for the approval and certification of the antibiotic drug, penicillin. Thereafter, two additional antibiotic drugs were added to this second provision, and in 1961 it was amended to apply to all antibiotic drugs. These separate provisions were thought appropriate because of the inherent variability of insulin and antibiotic products as they were made at that time and because it was thought that they could not adequately be characterized other than through individual batch certification to assure compliance with standards established by the FDA for safety and effectiveness.

Pharmaceutical science has now changed dramatically. Both insulin and antibiotics can now be adequately characterized by chemical, physical, and biological means. Experience by the regulated industry of consistent compliance with insulin and antibiotic standards has led the FDA to exempt these categories of drugs from the requirement of batch certification. The legislation repeals both of these statutory provisions, with the result that insulin and antibiotics will in the future be subject to regulation as new drugs.

There is only one exception to the regulation of insulin and antibiotics as new drugs. Previously, because they were regulated under the adulteration and misbranding provisions of the Food, Drug, and Cosmetic Act rather than under the new drug provisions, antibiotics and insulin were manufactured in the United States and exported for sale to countries throughout the world in compliance with section 801(e)(1) of the Federal Food, Drug, and Cosmetic Act rather than under section 802, which permits only limited exports. The legislation preserves that distinction. Otherwise, manufacturers of insulin and antibiotic who currently have their manufacturing plants in the United States would be forced immediately to build plants abroad in order to supply their products to other countries.

Modernization of regulation of biological products

The provisions of section 351 of the Public Health Service Act that govern the FDA regulation of biological products were initially enacted by Congress in 1902 and were recodified in 1944. Responsibility for implementing these provisions was initially in other parts of the Public Health Service until it was transferred to the FDA in 1972. The basic concept of the statutory requirements has not been revised in more than 90 years.

When FDA assumed responsibility for regulating biological products in 1972, it made two important policy decisions. First, it retained a separate organizational structure and regulatory focus for biological products, rather than combining these products with new drugs. Even when the two organizational structures were temporarily combined, the separate regulatory focus was maintained. Second, because biological products are also drugs, more recent regulatory concepts that were applied to new drugs, (e.g., compliance with drug GMP regulations) were incorporated into the older system for biological products. In the past 25 years, the two regulatory

systems have become similar, although each retains its separate identity.

The legislation takes this logical progression one step further. It substantially revises section 351 of the Public Health Service Act to make it much closer to the current approach for new drugs. Since 1902, the law has required that the applicant for a new biological product ordinarily obtain both a product license and an establishment license. In contrast, the applicant for approval of a new drug is required to submit only a single application, which covers both the product and the manufacturing processes in the establishment. The legislation adopts the same approach for biological products as for new drugs.

The FDA is required to establish, by regulations, the requirements that an applicant must meet in order to obtain approval of a biological product license application. The biological product must meet the same standards for safety and effectiveness as a new drug as well as appropriate GMP requirements. Preapproval inspection for compliance with GMP is included.

One of the most important biological products subject to FDA regulation is blood and products derived from blood. There are two basic categories of these products: (1) blood and blood components, and (2) products that are derived from blood and blood components. For blood and its components, the FDA has established appropriate standards to assure safety, purity, and where appropriate, potency. The legislation requires that blood and its components meet these standards, but there is no need for any additional product-specific license for this category of products. Blood and its components must also be obtained, held, processed, and utilized in accordance with GMP regulations that are specific to this type of product.

In addition to blood and its components, and ever-increasing number of products are derived from blood. For these biological products, the same requirements apply as for any other type of biological product. The safety and effectiveness of these products is subject to demonstration by appropriate scientific evidence.

Establishments that collect, process, and use blood and its components are uniquely located at the local community level. There are more than a thousand of these blood establishments, located throughout the country, in contrast with the usual situation with other pharmaceutical establishments. This legislation intends that regulatory requirements be streamlined and made as efficient as possible so that the fewest number of license applications will be required to cover all of the individual locations under a single management. For example, a single application should be sufficient to permit all facilities under one management to utilize particular types of products or methods of processing, as long as all facilities are required to meet applicable requirements and standards for each separate facility is wasteful of both industry and government resources and achieves no useful public health purpose.

In contrast, it is important that, when a problem is found at a particular facility, the FDA has adequate power to revoke whatever licenses are applicable with respect to that specific location. If ten facilities are under one management and the FDA discovers that two fail to meet GMP requirements, or two are not properly using products or processes for which all of the facilities are licensed, the

proper remedy is for FDA to revoke the applicable license with respect to those two facilities but not to interfere with the activities of the other eight.

The legislative includes specific procedures for the approval and revocation of biological product licenses. The FDA may at any time propose to revoke and approved license after an opportunity for a hearing on the record in accordance with section 554 of the Administrative Procedure Act. Before initiating such a proceeding, the FDA must review any written submission by the licensee responding to a notice of inspectional findings if received within 30 days after the inspection. If the licensee requests another inspection to demonstrate that it has now achieved compliance with applicable standards, the FDA must conduct an inspection within 30 days to determine the current status of the matter. If compliance is still not achieved, however, the licensee cannot again invoke this requirement.

Special provisions are included in the legislation where there is not only a lack of compliance with regulatory requirements but also a determination that there a danger to health. Under those circumstances, the FDA is required to immediately suspend the license and then initiate the hearing process.

Even before the FDA was delegated responsibility for the regulation of biological products, the FDA regulations governing investigational new drugs were used as the applicable requirements for the investigation of biological products as well. This practice is retained under the legislation. For biological products, the investigational drug notification will be submitted to the center responsible for regulating biologics rather than to the center responsible for drugs within FDA.

To simplify the statutory language, the legislation incorporates a definition of "biological product" to encompass all of the products that are presently included within the Public Health Service Act provisions governing this category of products. That defined term is then used throughout the new provision as well as in sections of the Food, Drug, Cosmetic Act that apply to both new drugs and biological products.

In accordance with customary practice for the past 25 years, the requirements regarding labeling and advertising for drugs are applied to biological products and the provisions governing advisory committees are also applied to biological product advisory committees.

Regulation of human tissue

The committee is aware that there is considerable debate between the FDA and the biotechnology industry about the appropriate level of regulation for an emerging and promising new technology, known as tissue engineering. Tissue engineering, which uses either a patient's own cells or compatible donor cells to repair and reconstruct injured or diseased tissue, is already being used to grow replacement skin for burn victims and replacement cartilage for injuries that result from accidents or athletics.

The committee considered various options for addressing this issue but ultimately determined that it would be premature, given the emerging and changing nature of this new technology and the

unanticipated issues which may arise in the future, to put into statute a particular regulatory scheme at this time.

The Commissioner of the FDA has provided this committee with some guidance on this issue. Commenting on S. 1477 as introduced in testimony before the committee on February 21, 1996, the Commissioner stated that the bill “would dramatically limit the agency’s ability to manage its resources efficiently.” Specifically, the Commissioner stated, the bill “forces us to keep biologic product licenses, even when we are willing to eliminate them for some types of biologics . . . conversely, it eliminates establishment licenses, even for products that could be most simply and effectively regulated using ELAs [establishment license applications] . . . In addition, certain technologies may actually be more flexibly regulated by the use of the ELA, for example, cellular and gene therapies, and xenotransplantation (tissues and organs transplanted from animals to humans). GMP’s alone would not be adequate to assure that proper controls are maintained to prevent the spread of infectious diseases.”

The reported bill addresses the Commissioner’s concerns by providing a very flexible approach to biological product regulation. Section 606 of the legislation explicitly authorizes the Secretary to issue a single license for biological products. The license may cover the product, the facility in which the product is manufactured, or both the product and the facility. This would provide, for example, the flexibility to regulate human tissue and similar cellular therapies in a manner consistent with the regulation of blood, for which regulation focuses on the facility rather than the particular product.

The Committee anticipates that the Commissioner would use this flexibility to regulate the facilities in which a product is manufactured, as opposed to the product itself, for types of tissue that are used to provide structural support and/or maintain their original cellular function, particularly when the tissue is not transported from a donor but rather is grown from the patient’s own tissue. The FDA has acknowledged that this type of tissue—known as autologous tissue—presents a very low level of patient risk and can properly be presumed effective to repair, reconstruct, augment, or replace native tissue when it has been processed to retain the native structure or function.

Effective medication guides

The committee believes that it is essential that consumers receive useful oral and written information about prescription medications. Current, voluntary, private-sector initiatives between health care professionals (physicians, pharmacists, nurses), the pharmaceutical industry, patient drug information database companies, and consumer organizations, subject to State Board of Pharmacy regulation, are working well to provide the majority of consumers with useful oral and written information about their prescription medications.

However, the FDA has issued a medication guide regulation that would centralize in the agency control of the distribution of written information and mandate rigid standards for the content and format of such information. The committee is concerned that this pro-

posed regulation would divert attention from the real need for effective health professional-patient communication by disproportionately focusing on written information, by engendering a false impression that the goal of ensuring that as many consumers as possible receive information about their prescription medications has been obtained solely by providing written information, and by diverting FDA resources from more critical agency activities. Moreover, the FDA's proposed Medication Guide requirements fail to recognize the success of the private sector in addressing this issue, add liability and costs on health care providers and the pharmaceutical industry, and stifle innovation in the delivery of written patient information.

The language adopted by the committee would prohibit the Secretary from finalizing this regulation or developing any type of standard format in the form of a policy statement or guidance document specifying a uniform content for written information provided to consumers about their prescription medications. Instead, the legislation directs the Secretary, within 30 days of enactment, to request a broad-based coalition of private-sector organizations to develop an action plan consistent with the goals specified in the proposed Medguide rule, namely the distribution of patient information to 75 percent of individuals receiving new prescriptions by the year 2000 and 95 percent by the year 2006. The committee believes the National Council on Patient Information and Education (NCPPIE) is such an organization. In comments submitted in response to the FDS-proposed rule, NCPPIE has outlined such a private-sector action plan. The American Medical Association is also developing such a plan.

Within 120 days of enactment, if the private-sector action plan is not developed and implementation of such a plan commenced, the prohibition on the Secretary's authority to take further action relative to this issue is lifted.

This provision should not be construed as prohibiting the FDA from using its existing statutory or regulatory authority to require as part of the manufacturer's approved product labeling the dispensing of written information inserts to consumers on a case-by-case basis with select prescription drugs to meet certain patient safety requirements.

This provision should not be construed to prohibit the FDA from conducting a voluntary, informational, nonregulatory workshop in conjunction with the review of private-sector initiatives authorized under this provision.

Requirement of radiopharmaceuticals

Radiopharmaceutical products are used for both diagnostic and therapeutic purposes. It is essential that the individuals in the FDA who regulate these products have knowledge and expertise in the field of nuclear medicine. It is also important that the review of radiopharmaceuticals take into account differences between these drugs and nonradioactive drugs with respect to their safety profiles, pharmacological activity, and clinical uses. The legislation therefore requires consolidation of review in a separate office within the Center for Drug Evaluation and Research, and the promulgation of separate regulations governing the review and approval

of all radiopharmaceutical products and the development of FDA policy relating to these products. In addition, since diagnostic radiopharmaceuticals are frequently used to provide images of processes in the body that may be caused by a number of different disorders, the legislation requires the FDA to permit the labeling of radiopharmaceuticals in such cases to provide information on this manner of use rather than limiting label information to specific underlying disorders.

State and local requirements respecting nonprescription drugs intended for human use

Under the Federal Food, Drug, and Cosmetic Act and the Fair Packaging and Labeling Act (FPLA), Congress has required national uniformity with respect to most food labeling requirements but not with respect to other aspects of FDA regulation, such as its regulation of nonprescription drugs. Nonprescription drugs are subject to intense and comprehensive regulation by the FDA. Their labeling is controlled either by regulations that set forth nonprescription drug monographs or by new drug applications. The formulation is also subject to the requirements of detailed regulations that establish which active ingredients may be used and the permitted dosage. Additional warnings, limitations on active ingredients, or other regulatory requirements should therefore be imposed on a Federal level by FDA, not by individual State and local governments throughout the country. The committee voted in favor of national uniformity for nonprescription drugs. In doing so, the committee recognized that there should be a single, nationwide system for regulating the safety and labeling of nonprescription drugs and noted a willingness to consider other FDA-regulated products, such as foods, cosmetics and prescription drugs, that may also lend themselves to such a comprehensive system.

The legislation therefore adopts, as a general rule, the requirement of national uniformity in the regulation of nonprescription drugs. No State or local government is permitted to impose different requirements, whether by labeling, advertising, or any other form of communication.

On the other hand, the committee recognizes that importance of States in regulating the food and drug supply in the United States. This legislation specifically provides that national uniformity does not affect the traditional authority of the States to place a nonprescription drug on prescription. It also authorizes States to petition for an exemption from the general rule of national uniformity where the State can demonstrate a compelling and unique local need that is different from the rest of the country. Under these circumstances, the FDA is authorized to grant an exemption by regulation, after thorough consideration of the matter, if the State can also show that the local requirement would not cause any nonprescription drug to be in violation of any applicable provision of Federal law and would not unduly burden interstate commerce. This assures adequate balance. The primary jurisdiction of the FDA is clearly recognized, but the partnership role of the States is also given adequate attention. All States may, of course, vigorously enforce requirements for nonprescription drugs that are identical to the Federal requirements.

Regulation of nonprescription drugs

The committee notes the importance of nonprescription drugs in the Nation's health care system. While consumers spend less than 2 cents of their health care dollar on nonprescription drugs, such drugs produce substantial savings to the individual and the health care system in reductions in physician visits, prescription drug costs, insurance costs, lost time from work, and travel. The committee notes that products switched from prescription to nonprescription status contribute significantly to these savings. For example, consumers saved over \$1 billion in the first 3 years after the FDA switched the skin treatment 0.5 percent hydrocortisone in 1979. Similarly, consumers save up to \$750 million a year—and 110,000 doctors visits—from the switch of cough-cold medicines from prescription to nonprescription status.

The committee therefore expects that the FDA, as part of its mission set forth in section 102 of this legislation of “facilitating the rapid and efficient development and availability of products subject to its regulation,” will establish appropriate procedures and policies, including performance standards, to expedite the review of applications to switch prescription drugs to nonprescription status. The committee encourages the FDA to give strong consideration to establishing a separate office for nonprescription drugs and conferring on that office primary review and sign-off authority for applications to switch drugs from prescription to nonprescription status. At a minimum, the committee recommends that an individual or individuals within the Center for Drug Evaluation and Research be designated to ensure timely and efficient agency review and action on such applications and that the agency consider using the explicit authority granted to it to contract for outside expert review when such contracts would achieve more timely and efficient reviews.

TITLE VI—DEVICE REGULATORY REFORM

Premarket notification

Under the medical device provisions of the law that were enacted as part of the Medical Device Amendments of 1976 and amended under the Safe Medical Devices Act of 1990, approximately 97 percent of all devices were cleared for marketing through FDA's premarket notification program. When a device is found to be substantially equivalent to a legally marketed device, it may likewise be marketed after the FDA issues an order making that finding.

After the enactment of the Safe Medical Devices Act of 1990, severe backlogs of premarket notifications and premarket approval applications developed at the FDA. Recognizing that part of the problem was the sheer number of notifications the agency was receiving for class I or II products that posed very little risk, President Clinton announced a Reinventing Government initiative to eliminate the notification requirement for some devices posing a minimal risk, and the FDA has now acted to exempt a substantial number of such devices. By eliminating premarket notification reviews for some low-risk devices, agency resources could instead be used on more critical devices, including those subject to premarket approval applications.

Building on the President's initiative, the legislation exempts all class I devices from premarket notification requirements, except those identified by the Secretary within 15 days of the enactment of this legislation as requiring premarket notification to protect the public health. In addition, the FDA is required to review all class II products to determine those that should and should not be exempt from the section 510(k) process. The FDA is provided 30 days to complete this exemption process. Because the agency on its own initiative has already had this matter under review for several years, and because the committee put the agency on notice through multiple requests over the last several months for a list of any class I devices which the agency determines should continue to require premarket notification to protect the public health and any class II devices that the agency believes should be exempt from premarket notification, this is a reasonable time within which to complete the job.

Finally, at any time, an interested person may petition the FDA to exempt a type of class II device from the section 510(k) process. The FDA is required to respond to any such petition within 120 days. By eliminating low-risk devices from the FDA's premarket review responsibility, FDA personnel will be better able to handle within the statutory deadlines the remaining section 510(k) notifications and premarket approval applications for devices that may pose a risk to public health and safety or provide health benefits to patients.

It has become FDA practice to decline to take action on a section 510(k) notification when the agency has made an administrative determination that a company is not in compliance with a GMP requirement or other provision of the Federal Food, Drug, and Cosmetic Act. There is no statutory basis for this practice. If a violation of the Federal Food, Drug, and Cosmetic Act occurs that is in fact related to a substantial equivalence decision, that clearly provides a ground for an adverse FDA action on a section 510(k) notification. However, if there is a violation that is not related to the substantial equivalence decision, the FDA should proceed with the substantial equivalence decision on the merits and use its extensive existing remedies to correct the violation. The committee has acted to ensure that when a device is violative of the Federal Food, Drug, and Cosmetic Act, and it is substantially equivalent to a lawful predicate device, the agency shall issue a substantial equivalence order and use its existing statutory remedies to correct the violation.

Currently under the Federal Food, Drug, and Cosmetic Act, when a new device is found to be not substantially equivalent to a legally marketed predicate device, it remains automatically classified into class III and requires premarket approval before marketing. The premarket approval process is the most expensive and resource-intensive device review process at the FDA. When devices that could be regulated by lesser means than product-by-product premarket approval reviews are nonetheless classified into class III because of their uniqueness and not their risk, there is substantial harm to the public health by needlessly diverting FDA resources into an intensive and lengthy premarket approval review.

The Medical Device Amendments of 1976 included automatic classification into class III as an efficient means of classifying new devices that were not substantially equivalent to a device on the market prior to the 1976 amendments. Pre-1976 amendment devices were classified by rulemaking after expert panel reviews and recommendations. Congress believed that such new devices would be reclassified to their appropriate level of regulation because manufacturers of such devices would have appropriate incentives to pursue a reclassification based on the Federal Food, Drug, and Cosmetic Act's risk-based classification definitions. However, reclassification has proven to be an extremely burdensome process for the FDA and an uncertain vehicle to achieve appropriate classifications for new, not substantially equivalent devices.

The committee therefore determined that 20 years of device classification experience permits a mechanism to ensure that all devices are classified and regulated based on the risk-based classification definitions in the Federal Food, Drug, and Cosmetic Act. The legislation permits a premarket notification submitter to request an advisory panel review and an initial risk-based classification by the FDA within 30 days of receiving a not-substantially-equivalent order from the agency. Once such a request is made, the device is not deemed to be classified until an advisory committee makes its classification recommendation to the FDA and the agency issues its order classifying the device. Both the advisory committee and the FDA will rely on the act's classification definitions to establish a classification for a device. The advisory committee will have 60 days to formulate a recommendation, and the FDA will have 10 days to act on that recommendation and classify the device.

This approach will avoid a misallocation of agency resources on premarket application reviews and will also help facilitate the FDA's premarket notification decision-making because a not-substantially-equivalent decision will no longer necessarily commit FDA to a premarket approval application review. Moreover, this procedure will allow devices to be classified by risk without resorting to the costly and uncertain reclassification process. The committee expects that this provision should permit the FDA to be more efficient in classifying devices, and this, in turn, should permit the agency to better handle its large premarket device review responsibilities.

The committee believes that this provision should also help address concerns it has received about the appropriate classification of in vitro diagnostic tests. In vitro diagnostic test systems accomplish their intended use by physiochemical action on a specimen outside of the body and are not intended for therapeutic purposes. The committee understands that in vitro diagnostic tests are distinctly different from other medical devices, in that they do not pose concerns about safety, they are not life-sustaining or life-supporting, they do not introduce energy into the patient, and they are not injected or implanted in the body. The committee urges the FDA to consider these factors when determining the appropriate classification for these devices.

Another concern addressed by this legislation is the apparent inconsistency with which the FDA interprets the intended use of predicate devices with general labeling. The FDA often will not

permit a device with a general intended use to be used as a predicate for purposes of establishing the substantial equivalence of a device for a more specific use even when medical literature demonstrates the use of the device for specific applications is subsumed within the general use.

However, at times the FDA will interpret a general predicate to include specific uses even when such uses could not have been included within the predicate device's preamendment uses. For example, the FDA cleared condoms through the premarket notification process with labeling including reference to AIDS and the HIV virus, even though AIDS and HIV were not known prior to the Medical Device Amendments of 1976. The FDA reasoned that preamendment condoms were intended for the prevention of sexually transmitted diseases and, therefore, the device was a suitable predicate for condoms intended for use to prevent the transmission of the HIV virus. In short, it appears that no standard exists regarding when the FDA should permit reliance on a general predicate for a newer device with a specific use, and when the agency should refuse to allow such reliance.

Accordingly, the legislation identifies such a standard. When the FDA determines that a specific use is "reasonably included within the general use" of a predicate device, that use of the predicate device should be available for a substantial-equivalence comparison. Each person relying upon this provision must demonstrate the substantial equivalence of the newer device and the marketed device.

The FDA's regulation governing when a change or modification in a marketed device requires a new premarket notification has provided uncertain guidance to manufacturers and has led to much confusion over the years. To respond to this continuing uncertainty, the committee has identified the two instances in which a new premarket notification will be required for a change or modification.

Specifically, the legislation requires a new premarket notification for a marketed device when the person responsible for the device has made a major change or modification in the device's intended use or a significant change or modification in device design that has a significant effect on safety or effectiveness. Otherwise, the person responsible for the marketed device need not file a new premarket notification if that person possesses data or information that shows that the change or modification does not adversely affect safety or effectiveness.

The committee considers a significant design change that has a significant effect on safety or effectiveness to be a change which alters the identity of a marketed device such that the modified device utilizes a new operating principle or technological characteristic. Design changes related to power source or product composition materials and components are only considered significant if they result in a new product line or a major redesign of a product, or the effect on safety and effectiveness cannot be readily demonstrated by bench testing.

Importantly, the committee requires that data or information relied upon not to file a premarket notification for a device change or modification must be maintained for the expected life of a device or for 2 years, whichever is longer. The committee requires that such data will be available to the FDA upon request. The commit-

tee expects that if the FDA disagrees with the conclusion that the data or information demonstrates that the change will not adversely affect safety or effectiveness, the agency will use its extensive enforcement authorities to take appropriate regulatory action.

Once again, the committee has adopted an approach that will assure continued emphasis on the safety and effectiveness of medical devices, but that will save FDA resources and focus them on the most important device review issues. FDA personnel who previously reviewed premarket notifications relating to device modifications that do not affect safety or effectiveness will now become available to spend their time and effort on those devices where questions about safety and effectiveness remain uncertain.

Medical device approval standards

The statutory standard for proof of effectiveness of a medical device was purposely chosen in the Medical Device Amendments of 1976 to be different from that for new drugs. Different language was used for the express purpose of emphasizing this difference. As the Cooper Committee emphasized in its 1969 report, drugs and devices are different in nature and present different issues when considering safety and effectiveness. For medical devices, for example, the skill of the person using the device is often of paramount importance, in contrast with the use of new drugs. Accordingly, the committee confirms the legislative intent of the 1976 amendments that the standard of proof of effectiveness for medical devices must be viewed as separate and distinct from that for new drugs.

Indeed, the committee is informed that the amount of clinical evidence of safety and effectiveness for a device is often much less than that required for a new drug. Devices can be extensively evaluated by in vitro testing which can be used to assess virtually every aspect of device performance. This testing, in conjunction with a well-controlled clinical study, has been deemed adequate by the FDA in the past to demonstrate a reasonable assurance of effectiveness, and the agency should take care to maintain the distinction between the evaluation of device and new drug effectiveness. An important distinction that the FDA should keep in mind is that the method of control in a device study often can be historically based, and double blinding in new studies is typically unnecessary for devices.

Specifically, device investigations often cannot be blinded, because the effect of the device is often immediately apparent. A "phantom" device is not often a realistic alternative. Further, requiring the use of a previous generation of a device to establish the effectiveness of a newer generation of the device raises ethical issues when the newer generation of the device may offer a substantial improvement in effectiveness or safety. Moreover, if an historical control is available, blinding is needlessly costly and without obvious benefit.

The use of retrospective or historical data for purposes of a control, as the FDA does now in some cases, but inconsistently, is therefore desirable. The legislation provides that such historical data shall be adequate for that purpose if there are sufficient valid data to constitute a control, the effects of the device on the disease are clearly defined and well understood, and there is no compelling

public health reason that would require concurrent controls. Additionally, historical data also can be used to demonstrate safety and effectiveness under the legislation.

Tracking

The Safe Medical Devices Act of 1990 added a new provision to require device tracking for every device the failure of which would be reasonably likely to have serious adverse health consequences and which is a permanently implanted device or a life-sustaining device that is used outside a device user facility, as well as any other device designated by the FDA.

This statutory mandate has proven to be uncertain with regard to which devices require mandatory tracking. The FDA's regulation for tracking identifies an illustrative list of devices subject to mandatory tracking, suggesting that the list is comprehensive, yet not complete.

To address these problems, the legislation repeals mandatory tracking and instead provides the Secretary with the discretion to require by regulation the tracking of class II or class III devices the failure of which would be life threatening or have serious adverse health consequences and which are permanently implanted or life-sustaining and used outside a device user facility.

The committee expects that the FDA, prior to promulgating such a regulation, will consult with the affected parties as part of the determination of the most efficient method for tracking.

Postmarket surveillance

The Safe Medical Devices Act of 1990 also included a provision requiring a manufacturer to conduct postmarket surveillance for any device first marketed after January 1, 1991, that is a permanent implant the failure of which may cause serious adverse health consequences or death, is intended for use in supporting or sustaining human life, or potentially presents a serious risk to human health. In addition to this mandatory surveillance, FDA was authorized to require postmarket surveillance for any device when the agency determined that surveillance is necessary to protect the public health or to provide safety or effectiveness data. All manufacturers subject to mandatory postmarket surveillance were required to submit protocols for FDA approval within 30 days of first marketing the device. The FDA was required to determine the adequacy of the principal investigator and the protocol and to approve the protocol after review by an appropriately qualified advisory committee.

In practice, the provision for mandatory surveillance, like the one for mandatory tracking, is so broadly worded that it is causing a good deal of uncertainty about those devices which are subject to this requirement. The committee legislation repeals mandatory surveillance and provides the Secretary with broad discretion to implement postmarket surveillance requirements through regulations. Under current law, required surveillance is limited to devices first introduced into commerce after January 1, 1991. Under the legislation, subject to the Secretary's discretion, any device may be subject to surveillance if it is a permanent implant the failure of which may cause serious, adverse health consequences or death, or is in-

tended for a use in supporting or sustaining life, or potentially presents a serious risk to human health or creates public health concerns.

The legislation retains the requirement that, before a manufacturer who is required to conduct postmarket surveillance implements a surveillance protocol, it must be submitted to the FDA, subjected to review by a qualified scientific review committee, and approved by the FDA. This will continue to assure that any requirement of postmarket surveillance effort will be worthwhile.

Device distributor reporting

Since 1976, and reinforced in 1990, the Federal Food, Drug, and Cosmetic Act has required medical device reporting by distributors as well as manufacturers. The Safe Medical Devices Act of 1990 added this requirement for device user facilities. As a result, there has been a substantial increase in reporting for medical devices, including much duplication. Further, the FDA, after request by the committee, has been unable to confirm that it either tracks distributor reports or acts on the basis of such reports. To avoid duplication and the costs associated with it, the legislation continues to require manufacturers and user facilities to report adverse events to the FDA but eliminates distributor reporting. Since user facilities and manufacturers submit medical device reports to the FDA, there is no need for additional reporting by distributors.

Premarket approval

The committee has been concerned that class III devices that require approvals before marketing are not reviewed in a timely manner and that the data requirements for such approvals are uncertain and often too difficult to satisfy in a reasonable timeframe. To respond to this situation, the committee has set forth procedures and rules that will result in one 180-day review cycle with milestone events to help ensure the timely progression of reviews of premarket approval applications (PMAs). The committee has also included provisions that parallel those in the investigational device exemption section of this bill which require the Secretary to consider certain data resulting from studies in which immaterial changes to devices occurred. The amendments to section 515 of the Federal Food, Drug, and Cosmetic Act governing premarket approval application reviews are intended to promote prompt and efficient FDA consideration of devices, many of which make the largest contributions to the public health.

The committee recognizes that devices are often changed during or after investigations based on information learned from investigational experience. When such changes occur, the committee believes that the data generated in the investigation, under certain circumstances, should be relied upon by the FDA in evaluating the safety and effectiveness of the modified device. Accordingly, the legislation requires the Secretary to accept and review such data if the modification of the device “does not constitute a significant change in the design or the basic principles of operation of the device that would invalidate the data or information [from the investigation].” This provision allows reliance on earlier versions of devices when the next generation is not significantly different from

its predecessor. In this way, reviews can be made more efficient by avoiding duplication of data that remains applicable to a modified PMA device. Consistent with this theme, data and information supporting the approval of a device under section 515 will be available for use in subsequent PMA reviews, if the data are relevant to the design and intended use of the device subject to a pending PMA review.

The committee receives frequent reports that FDA reviewers raise major new questions and concerns about a pending PMA late in the 180-day statutory review to “stop the clock.” Significant information requests result from these concerns, thus resetting the 180-day clock when a “major” amendment is submitted.

The committee believes that a collaborative review process would help to address these problems. The legislation creates a new, more device-specific collaborative procedure under which premarket approval applications are to be reviewed. The legislation continues to require that the FDA take action on a medical device premarket approval application within 180 days of receipt. To facilitate the review by identifying potential problems with and questions regarding an application early in the review process, the FDA is required to meet with the applicant within 90 days of receipt of the application that has been filed for review. If the application is not in a form that would require approval, the FDA must provide in writing a description of the information required to bring the PMA into such a form.

The FDA is then required to submit the application to an advisory committee, unless a referral is not needed, within 30 days of that meeting or at the next scheduled advisory committee meeting, whichever is later. Within 15 days after the advisory committee meeting, the FDA and the applicant must again meet to discuss the status of the application and any action needed to bring it into a form that would require approval. The applicant may decline any such meeting if it concludes that a meeting is unnecessary.

If no advisory committee review is required, the FDA must meet with the applicant, at the discretion of the applicant, not later than 135 days after the application is received and inform the applicant of whether or not the application is in a form that would require approval. If the application is in such a form, the FDA must present in writing to the applicant, at or before the meeting, a description of all additional information necessary for the application’s approval. If the application is not in a form that would require approval, the FDA is required to deny the application, and prior to the meeting present in writing to the applicant each basis for denying approval and the additional information required to bring the application into a form that would require approval.

Within 180 days of the receipt of an application that has been accepted for substantive review, the legislation requires the FDA either to approve or deny it. The 180-day period may not be enlarged by a PMA amendment.

To implement these new, collaborative-review procedures, the FDA is required to revise its current regulations governing premarket approval.

The committee recognizes that many are concerned that the agency will be unable to meet the 180-day statutory review time

without user fees or another source of significant new revenues. However, the committee believes that this concern fails to take into account several important factors.

First, the FDA controls the clock. The FDA determines whether or not to accept an application for review, thereby starting the clock. If reviewers are raising substantial questions and concerns well into the review process, the review probably has been wasteful because the application's deficiencies should have been identified early in the review process, as provided for under this legislation.

Second, the legislation puts in place a collaborative process for designing clinical protocols. It encourages a team approach from the planning and initiation of clinical investigations through the review of the application. When such a process is in place, FDA reviewers should already be relatively familiar with the type of data and other information to be derived from the clinical investigation of the device and/or comfortable with the clinical investigation protocol. Hence, when an application comes into the agency, the reviewers should be more comfortable with it.

Third, the legislation simply requires decisiveness. If at the end of the 180-day period the FDA is not satisfied that an application should be approved, it must deny it. This places pressure on the FDA, but also requires PMA applicants to submit meritorious, high-quality applications.

Fourth, the legislation reduces the workload of the FDA's Center for Devices and Radiological Health substantially. Most class I and many class II devices will be exempt from review. The number of new 510(k) notifications and premarket approval applications being filed because minor changes have been made in an investigational or approved device will be sharply reduced. The FDA has the discretion under this legislation to determine just how sharply reduced its workload will be. The agency will determine, for example, how many class I devices should remain subject to premarket notification and how many class II devices will be exempted from premarket notification.

The legislation also contains new provisions relating to supplemental applications for PMA devices. Supplemental applications that relate to manufacturing changes or product changes will not be required when data or information show the changes do not adversely affect safety or effectiveness. PMA holders must notify the FDA of significant changes and maintain data supporting changes in a device master file for the expected life of the device or 2 years, whichever is later. For the reasons discussed above, this will streamline the product premarket approval process and conserve FDA resources while continuing to assure the safety and effectiveness of the products involved.

Device performance standards

Since before the enactment of the Medical Device Amendments of 1976, voluntary standards-setting organizations in the United States and abroad have established performance standards for categories and characteristics related to medical device products. These organizations include the American National Standards Institute (ANSI), the International Standards Organization (ISO), and the International Electrotechnical Commission (IEC), as well

as others. Although standards from these organizations are recognized as authoritative, and are therefore followed throughout the world, the FDA has failed to establish any policy regarding their recognition and use under the Federal Food, Drug, and Cosmetic Act in this country. This legislation remedies that problem.

The legislation requires the FDA to recognize appropriate medical device performance standards developed by organizations such as ANSI, ISO, IEC, and any other standards-setting organization certified by the agency. The legislation requires the FDA to establish a procedure governing certification of such organizations, which shall be based on specified criteria.

It is important that all medical device performance standards recognized by the FDA under this new procedure be publicly listed, so that any interested person will know the regulatory status of the standard. Accordingly, the legislation requires FDA to publish in the Federal Register the name of all standards to which recognition has been given. Any standard not on the published list would not be accepted as recognized by the FDA under this provision.

Just as the FDA may certify standard-setting organizations, it may revoke certification if the organization no longer meets certification requirements. In the event that the certification of an organization is revoked, the FDA is required to address the effect of this revocation on the agency's prior recognition of the organization's standards.

Other provisions in the Federal Food, Drug, and Cosmetic Act authorize FDA to promulgate performance standards for medical devices using the procedures set forth in the law. This legislation does not in any way change the authority of FDA to promulgate such standards, which may differ from the standards established by certified organizations and recognized under this new provision.

The FDA may not require conformity with any such standard as a condition for approving any type of medical device application if the applicant demonstrates that the device is substantially equivalent to a legally marketed predicate device or otherwise provides reasonable assurance of safety and effectiveness.

The FDA may revoke a particular performance standard recognized under this legislation upon a determination that it is insufficient to provide reasonable assurance of safety and effectiveness. Upon revocation, the FDA must notify the certified organization and provide the basis for the action.

The legislation requires that a recognized performance standard must include provisions that will provide reasonable assurance of the safe and effective performance of the device. Where necessary to provide such assurance, the standard must include provisions with respect to such elements as construction and components and such requirements as testing and performance measurement and results. Where appropriate, labeling may also be prescribed. These required elements are designed to assure that a recognized performance standard will provide sound public health protection.

Accredited-party participation

In recent years, the FDA has consumed substantially more time for the review of medical devices. For example, FDA's average review time for premarket classifications has increased over the last

6 years by well over 200 percent (from 82 days to 178 days for total review time; from 66 days to 137 days for time in the FDA's hands), while the number of applications has generally held steady. In addition, premarket approval times have increased from 348 to 773 total days (247 to 606 days in FDA's hands) on average, while submissions in the same 6-year period dropped from 84 to 43 (almost in half). It is important to note that by statute, premarket classifications are expected within 90 days and premarket approvals must be granted or denied within 180 days.

This delay is in part a consequence of the agency's difficulty in maintaining the technological expertise and capability necessary to review applications within the statutory time frame. Also contributing to this delay is the FDA's management of its resources. The FDA has regularly made this committee and others aware of its desire to have more resources in order to address its inability to review products within the statutory time frame. In past years, Congress has responded with increasing appropriations. However, as resources available to the Federal Government have tightened, Congress has been pressed to find alternative sources of revenue.

As a result, the committee decided to test, through a pilot program and a follow-up study, whether supplementing FDA resources with fees paid by a product sponsor to FDA-accredited reviewers and by supplementing FDA expertise with that of private parties would reduce delays in medical device approvals and improve the technical sophistication of those reviews. The legislation includes a provision under which accredited individuals and organizations with relevant expertise will, at the option of a product sponsor, be used to provide recommendations to the FDA regarding premarket notifications and premarket approval applications. The FDA will then review those recommendations and make final decision with respect to classification or approval or disapproval of the premarket approval application.

This provision is consistent with the approach taken throughout this legislation: the FDA retains all of the authority it has under current law to make final product review decisions. This legislation does not authorize any other person or organization outside the agency to make such a final decision. Thus, in numerous respects, the provision maintains a strong, continued role for the FDA in the device approval process. For example, the FDA alone accredits the pool of qualified private parties to conduct the reviews and selects from that pool two or more accredited parties from whom the product sponsor may select. Although a product sponsor has the option to select an accredited party, it does so only from a list pre-selected and accredited by the FDA, thus limiting if not eliminating potential "forum shopping." The FDA also establishes rules protecting the confidentiality and the proprietary nature of information contained in the review. The FDA promulgates the rules to prevent conflict of interest. The FDA has authority to ensure compliance by the accrediting party and has the ability to withdraw or suspend accreditation of parties not in compliance. In short, the FDA will have full control over the individuals and organizations eligible for selection.

The FDA's role is not limited to accredited-party selection. In addition, the FDA alone will continue to set product review stand-

ards. Most significantly, the FDA conducts both an initial filing review to confirm completeness and basis for review and retains authority to make the final decision with respect to the classification or approval or disapproval of application. The FDA has no less than a total of 30 days (of the 90 days allotted under the statute) to review a submission under section 510(k) and 75 days (of the 180 days under the statute) to review premarket approval applications. Further, the FDA is not bound by an accredited party's determination—there is no presumption given to the accredited party's recommendation of approvability or classification of a product.

The program established under this provision would apply to all types of medical devices, including premarket approval applications and premarket notifications. The committee intends that a rule of reason be applied by the FDA so that the FDA does not unnecessarily accredit two or more organizations capable of reviewing only one type of product for which one or no applications will be filed during the course of the pilot program.

To adequately supplement the resources available to the FDA, the product sponsor will directly contract with and pay the accredited party at the sponsor's own expense. This mechanism is similar to that proposed by the FDA in its own pilot project at the Center for Devices and Radiological Health.

The program established under this provision will be subject to review within 3 years following the accreditation of the first party. A full analysis of the strengths and weaknesses of the program will be conducted and provided to Congress and the public, enabling Congress to extend or modify the program at that time.

TITLE VII—ANIMAL DRUG REGULATORY REFORM

The committee is very concerned about the serious shortage of approved drugs for the treatment of both food-producing and companion animals. It is for that reason that the committee supported the approval of legislation in the 103rd Congress to permit veterinarians to legally prescribe animal and human drugs for uses other than their FDA-approved, labeled uses, recognizing, however, the need for further legislation to address the problems creating the shortage.

Two of these problems are lengthy delays in the FDA Center for Veterinary Medicine's (CVM) review and approval process and the daunting cost of bringing a new animal drug to market or obtaining approval for additional uses of approved drugs (i.e., approval of a drug approved for use in horses to be used in dogs). The CVM's own internal study in 1993 found that it was taking the agency an average of 58 months to approve a new chemical entity for use in animals. Industry research indicates that the cost of bringing a new animal drug to market can at times approach \$200 million. These delays and costs are discouraging research on and development of new animal drugs and additional uses for approved drugs.

The committee is heartened by the much-needed recent steps the Center for Veterinary Medicine is taking to better ensure the timely review and approval of new animal drugs and by the commitment the Commissioner of the FDA gave in his February 21 testimony before this committee to addressing the serious problems in the animal drug review process.

This legislation incorporates a number of statutory and regulatory reforms that the committee believes are necessary to support the efforts of the Center for Veterinary Medicine and the commitment given by the Commissioner.

Evidence of effectiveness

The committee found that much of the delay in new animal drug approvals and the cost of bringing a new animal drug to market can be tied to costly, duplicative requirements for demonstrating the effectiveness of new animal drugs. The Federal Food, Drug, and Cosmetic Act currently requires efficacy to be demonstrated through “adequate and well-controlled investigations, including field investigation.” The FDA has interpreted this language to routinely require three field investigations, each in a different region of the Nation. The committee finds that this requirement has led to duplicative tests that are expensive and time-consuming for new drug sponsors but that often yield information of little benefit to the agency, veterinarians, and animal drug sponsors.

The legislation amends the statutory definition of what constitutes evidence of effectiveness to allow the FDA to accept one or more scientifically sound studies, including in vitro studies, studies in laboratory animals, bioequivalence studies, and any other similar studies, that, taken together, provide reasonable assurance that the drug will have the claimed or intended effect. This is a far more flexible definition, permitting the FDA to adapt the types of studies it requires to demonstrate the effectiveness of the particular characteristics and proposed uses of the new animal drug. The legislation removes the statutory requirement for “field investigation” but provides the authority to the FDA to require field investigation when necessary.

In reviewing the approval procedures for animal drugs used in combination with one another, the committee recognizes that the FDA needs greater flexibility in its approval requirements. Currently, the FDA treats all animal drug combinations as never-before-approved products, even when the drugs used in combination have each been approved by the FDA. The FDA requires that for combinations of approved animal drugs, all laboratory and field investigations be conducted again to determine the effectiveness of the combination. The FDA also requires that, if the combined products make the same claim, the combined effect must be greater than the effect of either product used alone. Further, the FDA requires that, if the combined products treat unique claims, sponsors must show that both products remain effective when they are combined. The committee finds these requirements to be redundant and unnecessarily time-consuming and expensive.

The legislation reflects the committee’s view that the primary concern raised by combination drugs is whether they will in combination exceed the tolerance levels set for human safety. Under the legislation, the FDA is limited in its evaluation of a combination drug comprised of two previously approved drugs or a drug that bears labeling that recommends use with another animal drug to the consideration of whether the drugs in combination affect human safety (i.e., whether the longest withdrawal time of any of

the active ingredients is above its safe concentration) or interferes with a method of analysis of an ingredient.

Both the FDA and the regulated industry have long struggled with the difficult problems raised by the use of new animal drugs in a minor species or for a limited use. The FDA has long recognized that some drugs have extraordinarily small markets because they are either used in a minor species or otherwise have very limited use. The FDA has attempted to encourage the development of these drugs by streamlining several of the effectiveness requirements for these drugs. For example, when a manufacturer seeks approval for a use in a minor species of a drug already being used in a major species, the FDA does not always require original effectiveness testing for the minor species use. It allows the sponsor to extrapolate from tests done of the drug in a major species.

The committee commends the FDA for its efforts to encourage the development and availability of drugs for minor species and limited uses. The committee believes that the provisions in the legislation are consistent with these efforts. The legislation exempts drugs for minor species and limited uses from the usual requirements for demonstrating substantial evidence of effectiveness if there is a previously approved animal drug application for the drug.

The legislation requires that, when the FDA issues its revised regulations defining the requirement of "substantial evidence" of effectiveness, it must take into account the need to encourage the submission of new animal drug applications for three types of products for which there is a strong public policy justification: drugs that conserve food resources; drugs designed for use by veterinary practitioners in order to establish effective doses; and drugs for use in minor species, for limited uses, and for permitted unlabeled uses. In addition to providing an incentive for these three categories of drugs, the FDA is required to take into account a citizen petition submitted to the agency in October 1991 requesting the agency to adopt flexible labeling for veterinary prescription drugs that will recognize a range of safe and effective dosages within which veterinarians may use their training and experience to prescribe a particular dose for a specific animal. The labeling for many human drugs provides a dosage range rather than one particular dose and relies on the physician to exercise professional judgment in making a prescription. Regulation pertaining to animal drugs should follow this precedent.

In addition to the applicable provisions requiring a collaborative process for the review of all new premarket approval applications contained in title IV of this act, the legislation provides specific requirements for applications relating to new animal drugs. The FDA is required to provide a new animal drug sponsor an opportunity for a conference prior to the submission of an application, in order to provide advice regarding the requirements that must be satisfied for approval of the product. That advice is binding unless FDA subsequently determines that a new documented scientific requirement essential to determination of the safety or effectiveness of the drug has appeared after the meeting. Within 10 days after any such meeting, if the FDA requires any type of study other than those specified in the new definition of substantial evidence of ef-

fectiveness, the agency must provide a written justification for that requirement, specific to the animal drug and its intended uses. This will assure both that the FDA has the flexibility to require whatever evidence of safety and effectiveness is scientifically justified for a particular drug and its intended uses and that the applicant will receive a full and detailed scientific justification for any requirement for a study other than those specified in the definition of substantial evidence, such as a well-controlled field trial.

Once again, the legislation streamlines the premarket approval process and assures that a reasonable amount of scientific evidence will be required to establish safety and effectiveness, but at the same time provides adequate authority for the FDA to require whatever type of evidence is scientifically justified to establish that the drug is safe and effective for its intended uses. As is true throughout the legislation, efficiency is imposed but not at the expense of public protection.

Limitation of residues

Under present law, the FDA may deny approval of a new animal drug application if the proposed tolerance limitation exceeds what is reasonably required to accomplish the physical or other technical effect for which the drug is intended. In practice, the FDA has interpreted the law to require that new animal drug sponsors identify the “optimal” dose for a drug—the least amount of the drug necessary for the drug to be effective. This requirement adds greatly to the time and expense of developing and testing new animal drugs.

The legislation would instead require the FDA to deny approval of a new animal drug if any use prescribed, recommended, or suggested in the proposed labeling for the drug would result in a residue in excess of a tolerance set by the FDA to be safe for the drug. It would in effect permit the sponsor to identify a dosage range for the drug which would not exceed tolerances set by the FDA.

Adulterated drugs

As amended by the Drug Amendments of 1962, the law presently requires all drugs to be manufactured, processed, packed, and held in conformity with good manufacturing practices (GMP). The FDA has, in turn, promulgated GMP regulations for the preparation of all drug products, including both human and animal drugs.

There are, however, differences between human and animal drugs that justify separate and distinct GMP regulations for these two different categories of products. The legislation therefore includes a revision of the drug adulteration provisions of the Food, Drug, and Cosmetic Act to require separate GMP regulations that are appropriate for animal drugs.

Veterinary feed directives

Current provisions of the Federal Food, Drug, and Cosmetic Act provide for nonprescription animal drugs and prescription animal drugs. To date, nearly all drugs used in feed have been approved as nonprescription drugs. Requiring prescription status for such drugs would impose a significant burden on distribution. As a result, the animal feed industry has been limited in its ability to in-

corporate prescription veterinary drugs, and the animal husbandry industry has been limited to the use of veterinary prescription drugs in inefficient and costly ways.

The legislation includes provisions reflecting an agreement reached by the FDA and the regulated industries to create a new animal drug category, "veterinary feed directive drugs," which includes all animal drugs intended for use in feed that are limited to use under the supervision of a licensed veterinarian. A veterinary feed directive drug must be fed to animals only upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice. The drugs, their labeling, and the directive under which they are used are all to be regulated by the FDA. Records must be kept as specified by the FDA and must be made available for FDA inspection. Any distributor on animal feed bearing or containing a veterinary feed directive drug must register with the FDA. Failure to follow FDA regulatory requirements will result in the same penalties as any other violation of the Federal Food, Drug, and Cosmetic Act.

Adequate regulatory controls are therefore imposed to assure the safe and effective use of these veterinary prescription drugs while creating a more efficient and effective distribution system. This approach maintains public health protection but incorporates regulatory flexibility to accommodate the changing needs of the animal husbandry industry.

Timeframes for approval

Present law requires FDA action on a new animal drug application within 180 days. With the substantive and procedural changes in the Federal Food, Drug, and Cosmetic Act under this legislation, unimportant submissions will no longer be required, long and complex applications will be replaced by shorter and more focused applications, the requirements for approval will be simplified, and thus the reviews by FDA can be substantially shortened. Particularly for animal drugs, the efficiencies created by this legislation will substantially reduce the time and effort needed to review product premarket approval applications. The committee concludes that 90 days is a reasonable statutory deadline for the future.

TITLE VIII—FOOD REGULATORY REFORM

Indirect food additives

There are two major categories of food additives: direct food additives, which are directly incorporated into food and are intended to be ingested as part of the food supply; and indirect food additives, which are used as processing aids, packaging materials, or other food contact uses and are intended solely for these functional food contact purposes rather than for human ingestion. Residues of indirect food additives are in fact found in the food supply, but that is an incidental result of their use and not their intended purpose.

Under the Food Additives Amendment of 1958, both of these two quite different categories of food additives are subject to the same procedures and requirements. Both require FDA premarket review and the publication of a regulation specifying the conditions under which they are approved for use.

These two categories of food additives also result in distinctly different impacts on the FDA workload. There is an average of only about one new direct food additive approved by the FDA every 5 years. In contrast, there are dozens of indirect food additives under consideration at any time. The current backlog of indirect food additive petitions is substantial.

Because indirect food additives are intended only for food contact rather than for any functional use as a component of the food supply, the risk that they present to the public health and safety is minimal. There is no documented case of human harm caused by an indirect food additive. Although public protection must continue to be assured, the committee concludes that a different procedure should be available for FDA review of indirect food additives than is adopted for direct food additives in title IV of this legislation.

The legislation includes a simplified premarket notification procedure for indirect food additives in order to streamline the process without sacrificing consumer protection against unsafe substances in the food supply. Any person may submit a premarket notification to the FDA for an indirect food additive at least 90 days prior to marketing, with information demonstrating that the labeled use of the product is safe. Within 90 days, the FDA must either approve or disapprove the notification and publish a notice in the Federal Register. If the notification is approved, an appropriate food additive regulation must be promulgated.

This simple procedure will allow the FDA to quickly dispose of its existing inventory. It retains adequate public protection but recognizes that reduced regulatory control is appropriate in light of the lower potential for public health risk. As is the case throughout this act, the FDA retains the authority and responsibility to either approve or disapprove indirect food additive petitions under this simplified approach.

The FDA has recently initiated a "threshold of regulation" process for considering exemptions of indirect food additives from the requirement for premarket approval, after considering this approach for more than 25 years. Under the new FDA procedure, an applicant may submit an application for an exemption in lieu of an application for a regulation. Both approaches require an application and both approaches require an FDA evaluation and response. The savings in FDA time and effort cannot be determined at this time. Since the FDA has, after years of study, set a specific human exposure level that represents no potential safety risk (0.5 ppb in the daily diet), the committee encourages the agency to consider providing manufacturers with data demonstrating a lower exposure an automatic exemption from the need for a regulation on the condition that they maintain the documentation to support their exemption for as long as the product is marketed and make the data available to FDA upon request. It seems to the committee that this would be a more effective and efficient method of handling this matter. The committee will monitor the progress of the new threshold of regulation approach to determine whether legislation is needed to streamline it.

Health claims of food products

Under section 403(r)(3)(a) of the Federal Food, Drug, and Cosmetic Act, adopted under the Nutrition Labeling and Education Act of 1990 (NLEA), health claims can be made for food products only if explicitly approved by the FDA. From the beginning, it has been the concern of Congress that health claims be authorized when they are supported by sound science and are stated in a truthful, nonmisleading manner in the context in which they are presented. Such claims can promote public health by promptly communicating the health benefits of foods as these benefits are discovered. Presenting them at the point of purchase through food labeling can dramatically and positively affect consumer purchasing decisions.

Unfortunately, the promised benefits of the original health claims provisions of the NLEA have not been fully realized. The FDA has established unduly stringent criteria for approving health claims for food, resulting in the approval of very few health claims available for use in only limited circumstances. In addition, as is true with other areas of premarket approval, the health claims process has become a regulatory bottleneck, preventing useful claims from entering the market without undue delay.

The promised benefits of health claims have also not been fully realized because the NLEA failed to give sufficient weight to the determinations of authoritative bodies outside the FDA concerning the validity of diet/disease relationships. There are a number of important federal public health agencies that, along with the National Academy of Sciences (NAS), regularly make authoritative statements concerning diet and disease relationships. The Surgeon General and the NAS have published authoritative books and reports on such relationships. The National Cancer Institute (NCI) publishes pamphlets recommending food choices that can help reduce the risk of cancer. The National Heart, Lung, and Blood Institute (NHLBI) publishes information on diets that will reduce the risk of heart disease. Nonetheless, the diet/disease relationships plainly recognized in these materials may not be communicated through food labeling unless the FDA first issues a rule specifically authorizing claims concerning the particular diet/disease relationship.

The adverse impact this can have on public health came into focus when the Centers for Disease Control and prevention (CDC), recognizing the benefits of adequate folic acid intake among women of childbearing age, issued a recommendation in 1992 stating:

All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other [neural tube defects]. [Centers for Disease Control, 41 *Morbidity and Mortality Weekly Report* (September 11, 1992).]

The CDC estimated that this recommendation could reduce the number of cases of spina bifida and other neural tube defects in the United States by 50 percent.

Despite the substantial evidence supporting the CDC recommendation, manufacturers were prohibited from making claims about the folic acid/neural tube defect relationship until the FDA

approved the claim. The FDA did not accept the CDC's position, issuing a rule in January, 1993, prohibiting folic acid/neural tube defect claims within months after the CDC's recommendation was issued. Several months later, despite any change in the scientific evidence, the agency reversed itself. It proposed to authorize such claims in October, 1993, and published a final authorizing regulation in March, 1996.

There is no telling how many children were born with preventable neural tube defects as a result of the FDA's initial refusal to accept the CDC's recommendation and subsequent delay in promulgating a final regulation.

The amendments the legislation makes to section 403(r) of the Federal Food, Drug, and Cosmetic Act would help to prevent problems such as the one witnessed with folic acid from occurring with respect to other diet/disease relationships. The legislation recognizes that authoritative scientific organizations within the Federal Government, as well as the NAS, represent a unique and important source of health information for the American public. Under the legislation, authoritative publications of these organizations can properly be used as the basis for a health claim in food labeling without the need for further FDA approval or the promulgation of a regulation. If this provision had been in effect, the information linking inadequate dietary folic acid to an increased risk of neural tube defects could have been made broadly available to the American public through food labeling more than 3 years earlier.

While this legislation eliminates the need for FDA approval of information contained in authoritative publications issued by Federal public health agencies and the NAS, it retains the NLEA requirement that all health claims satisfy the "disqualifying nutrient levels" established by the FDA. In addition, nothing in this legislation is intended to limit the FDA's power to prohibit false or misleading claims under sections 403(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act. The agency may take action against a claim that is stated in such a manner as to mischaracterize the authoritative statement, conclusion, or recommendation upon which it is based, or that otherwise misleads.

The legislation requires that, at least 90 days prior to introducing a food bearing a new health claim authorized under this section, a manufacturer or distributor notify the FDA of the basis for the claim. This notification requirement will enable the FDA to identify misleading claims and notify manufacturers or distributors where such claims may merit enforcement action. The FDA retains the full panoply of enforcement powers the agency has historically possessed to remedy misleading claims, including the powers of seizure, injunction, and criminal penalties. In addition, the FDA may initiate a rulemaking to define a health claim if the agency determines that such regulations are necessary to assure that specific claims are made in a truthful, nonmisleading manner.

Delaney clause reform

During its consideration of S. 1477, the committee discussed a proposed amendment to reform the Delaney clause. Because there was inadequate time to consider the matter fully, the proposed amendment was withdrawn. The committee recognizes; however,

the importance of this issue. Every recent FDA Commissioner, has supported a reevaluation and revision of the Delaney clause to reflect more recent scientific and technical advances. The Delaney clause made sound policy sense when it was enacted almost 40 years ago, but scientific advances in the intervening years have made it obsolete. Both the FDA and the EPA now rely on quantitative risk assessment and other forms of scientific analysis to regulate carcinogenic substances and have administratively adopted the approach of accepting insignificant or negligible risk rather than imposing a zero tolerance for potential carcinogens.

Incentive for research and development of new food and color additives

The committee briefly discussed market exclusivity as an incentive for research and development of new food and color additive products. The provision would be similar to the existing law that applies to new prescription drugs. Due to time constraints, the matter was not formally presented to the committee. However, several members indicated an interest in pursuing this matter further.

TITLE IX—ESTABLISHMENT FOR CENTERS FOR EDUCATION AND RESEARCH ON DRUGS, DEVICES, AND BIOLOGICAL PRODUCTS

Centers for education and research on drugs, devices, and biological products

As this report has noted, there are many not-yet-approved uses for new drugs, biological products, medical devices, and animal drugs, for which there is no economic incentive for the pharmaceutical industry to undertake research. To fill this gap, the legislation authorizes the appropriation of funds to establish a grant program administered by the FDA to establish, through awarding peer-reviewed grants, a consortium of at least three centers for research and education. It is expected that grants for these centers will be made to academic medical centers having programs, for example, in clinical pharmacology, with the requisite expertise to conduct appropriate educational and research programs. These centers will become responsible for conducting needed clinical and laboratory research on matters that otherwise would not receive adequate medical and scientific attention.

It is the intention of the committee that this research not duplicate privately funded research or be conducted in areas where there are already incentives for such private research. The funds granted under this provision should be used to fill in the gaps of scientific and medical knowledge where information is now lacking and private research is unlikely. No organization has been established to conduct this type of research, and these funds will provide a modest beginning. In addition, coordinated educational programs will be conducted for health care providers, pharmacists, and the public on topics such as recognition and anticipation of adverse drug reactions and drug interactions, individualized dosage in the elderly, children, women, or patients with abnormal kidney, liver, or heart function and other areas not likely to be adequately addressed by currently available programs. The committee intends to

review the progress made under this program in the coming years to determine whether it should be retained, modified, or revoked.

TITLE X—PROGRAM IN CLINICAL PHARMACOLOGY

The legislation extends the authority and authorization of appropriations through fiscal year 1998 for a clinical pharmacology training program originally authorized under section 2(b) of Public Law 102–222.

V. COST ESTIMATE

A Letter From Congressional Budget Office requested March, 1996, has not been received to date, June 20, 1996. Due to time constraints, the CBO Report will be added to this report at a later date, when it is received.

VI. REGULATORY IMPACT STATEMENT

The committee has determined that this legislation will reduce the regulatory burden of paperwork that currently exists in the FDA premarket approval of new products.

VII. SECTION-BY-SECTION ANALYSIS

Sec. 1. Short title

Section 1 provides that the act be cited as the “Food and Drug Administration Performance and Accountability Act of 1996.”

Sec. 2. Table of contents

Section 2 contains the table of contents.

Sec. 3. References

Section 3 provides that all references are to the Federal Food, Drug, and Cosmetic Act (FFDCA) unless otherwise expressly provided.

TITLE I—MISSION AND ACCOUNTABILITY

Sec. 101. Short title

Section 101 provides that the title be cited as the “Food and Drug Administration Regulatory Reform Act of 1996.”

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

Section 102 amends section 903(a) of the FFDCA to provide that the mission of the FDA is to promote and protect the health of the American public by facilitating the rapid and efficient development and availability of products, protecting the public from unsafe or ineffective products, and enforcing the law in a timely, fair, consistent, and decisive manner.

Sec. 103. Performance standards and review

Section 103 amends section 903(b) of the FFDCA to require the FDA within 180 days of enactment, after consultation with outside individuals and organizations, to establish quantifiable performance standards for action on certain submissions and applications and the scheduling of advisory committee meetings and action

taken following those meetings. The performance standards shall be reviewed annually by the FDA and, after further consultation with outside individuals and organizations, may be revised. The performance standards shall establish objectives that expedite clinical investigation and applications for new products for an immediately life-threatening disease or condition or for any other serious condition if the product provides therapy or a tool for diagnosis or monitoring such a disease or condition not available from other approved products or significant improvement over other approved products; reduce backlogs on all applications with the objective of eliminating backlogs by January 1, 1998; establish a schedule to bring the FDA into full compliance with statutory time periods by July 1, 1998, and improve the consistency and fairness of the FDA regulatory process. The FDA is required to prepare and publish in the Federal Register an annual report providing detailed data on the actual performance relating to each of the types of actions subject to a performance standard, comparing the actual performance with the standard, describing priorities, analyzing any failure to achieve a standard, identifying regulatory policies that have a significant impact on performance and analyzing how they could be modified in order to achieve compliance with the standards, and setting forth a plan to achieve compliance with the standards that have not been met. The report must include a full statistical presentation relating to all applications and petitions for product approval.

Sec. 104. Interagency collaboration

Section 104 amends section 903(b) of the FFDCA to require the Secretary to foster collaboration with the National Institutes of Health and other science-based agencies to enhance the scientific expertise available to the FDA for the evaluation of emerging medical therapies and advancement in nutrition and food science.

Sec. 105. Information system

Section 105 adds a new section 906 to the FFDCA to require the FDA to establish and maintain an information system to track the status and progress of all applications for product approval. The system must permit access by the applicant.

Sec. 106. Policy statements

Section 106 amends section 701(a) of the FFDCA to provide that the FDA must establish a procedure governing the development and use of all policy statements of general applicability that provide guidance relating to the conduct of testing or the content of applications for product approval. The procedure must provide an opportunity for public participation prior to FDA adoption of a policy statement unless there is a public health need to issue the document immediately. The FDA is required to establish a procedure for the compilation and publication of all policy statements.

Sec. 107. Scientific review groups

Section 107 amends section 904 of the FFDCA to establish requirements for scientific review groups that are used as advisory committees.

Section 904(b) provides that the FDA Commissioner may not delegate the appointment and oversight authority for advisory committees.

Section 904(c) provides membership and meeting requirements for advisory committees. The Commissioner is required to consult with an advisory committee in determining the matters that the committee will consider and in establishing an appropriate agenda. The specific matters and questions to be discussed in an advisory committee meeting shall, if feasible, be publicly announced in the Federal Register at least 30 days prior to the date of the meeting. Advisory committee members serve for a term of 3 years, which may be renewed for a second term. The chairperson must have served at least 3 years before becoming chairperson and may be renewed for a third term. Advisory committee members shall be given adequate education and training. Advisory committees shall have regular meetings, at appropriate intervals and for a sufficient length of time necessary to handle all matters that come before them. The meetings shall occur not less than 3 times each year unless there are reasons for fewer meetings.

Section 904(d) provides for access information and participation by interested persons in advisory committee meetings. When an advisory committee reviews a product application, the FDA must provide the applicant with copies of all documents relating to the applicant's submission provided to the advisory committee, at the same time that they are given to the advisory committee. The applicant shall have an opportunity to provide its own documents to the advisory committee, through the FDA. Advisory committee meetings shall provide adequate time for initial presentations and for response to any differing views, and shall encourage free and open participation by all interested persons.

Section 904(e) provides that, within 60 days after an advisory committee makes its conclusions and recommendations on any matter, the FDA official responsible for the matter must review those conclusions and recommendations, make a final determination, and notify the affected persons. If the FDA determination differs from the advisory committee conclusions and recommendations, the reasons for the difference must be specified.

Sec. 108. Appeals within the Food and Drug Administration

Section 108 adds a new section 907 to the FFDC to provide for appeals within FDA.

Section 907(a) provides that the FDA must establish a system for internal appeals from any decision by an employee, except for formal administrative or judicial proceedings. As the final stage in the internal appeals system, the FDA shall provide for the right to request an evaluation by an appropriate advisory committee on a matter involving a significant scientific issue. The FDA must make publicly known the existence of the internal appeal system and the procedures involved.

Section 907(b) provides for appeal by an applicant or sponsor of any significant scientific issue to an advisory committee. The advisory committee shall review the request and determine whether to conduct an evaluation, within 30 days after the FDA receives the request. Significant scientific issues that an advisory committee

may evaluate include, but are not limited to, matters involving an FDA hold on a clinical investigation, an FDA refusal to file a product application, a protocol design, and other decisions relating to pending product applications where the same issue has not previously been reviewed by an advisory committee. If the advisory committee agrees to evaluate an issue, it shall be scheduled for the next meeting.

Section 907(c) provides for additional informal and formal appeal procedures. The FDA is authorized to sue such additional procedures as may be considered useful. These include, but are not limited to, panels of qualified FDA officials, panels of qualified government employees who are not FDA employees, and outside mediators and arbitrators. Such panels are not subject to the Federal Advisory Committee Act.

Section 907(d) provides that, within 60 days after any matter appealed under this section has been the subject of conclusions and recommendations, the FDA official responsible for the matter shall personally review those conclusions and recommendations, make a final determination on the matter, and notify the parties. If the FDA determination differs from the conclusions and recommendations of the group that reviewed the matter, the reasons for the difference must be specified.

Sec. 109. Appointment and term of the Commissioner of Food and Drugs

Section 109 amends section 903(b)(1) of the FFDCA to limit the term of the Commissioner of Food and Drugs to 1 term of 5 years. The commissioner may be removed from office only pursuant to a finding by the President of neglect of duty or malfeasance in office. The present Commissioner is excluded from this provision.

TITLE II—EXPEDITED ACCESS TO PRODUCTS FOR SERIOUSLY ILL PATIENTS

Sec. 201. Short title

Section 201 provides that the title be cited as the “Patient Rights Regulatory Reform Act of 1996.”

Sec. 202. Access to unapproved therapies

Section 202 adds a new section 551 to the FFDCA to provide for expanded access to unapproved therapies and diagnostics.

Section 551(a) provides that any person, through a licensed health care practitioner or professional, may request from a manufacturer or distributor, and the manufacturer or distributor may provide after compliance with the investigational provisions of the FFDCA, an investigational drug (including a biological product) or device for the diagnosis, monitoring, or treatment of a serious disease or condition, an immediately life-threatening or seriously debilitating disease or conditions and any other disease or condition designated by the FDA as appropriate for expanded access. This provision applies only if the person has no comparable or satisfactory alternative therapy, the risk to the person from the investigational product is not greater than the risk from the disease or con-

dition, and the sponsor and investigators comply with the requirements for an investigational drug or device.

Section 551(b) provides that a manufacturer or distributor may submit to the FDA one or more expanded access protocols, subject to the requirements for investigational drugs and devices. The protocols may include any form of use of the drug or device outside a clinical investigation prior to approval for marketing, including protocols for treatment use, parallel track, single patient use, emergency use, and uncontrolled trials.

Section 551(c) provides that a manufacturer or distributor may charge for an investigational drug or device under an expanded access protocol, but the price may not be more than necessary to recover the costs of manufacture and handling. The FDA must be notified in advance of assessing any such charge.

Section 551(d) requires the FDA to inform national, State, and local medical associations and societies, voluntary health associations, and other appropriate persons about the availability of investigational drugs and devices under expanded access protocols.

Sec. 203. Expanding humanitarian use of devices

Section 203 amends section 520(m) of the FFDCA to require the FDA to approve or deny a humanitarian device application within 30 days of receipt and to eliminate limitations upon the term of an expanded access protocol and the requirement for FDA regulations to implement the provision.

Sec. 204. Expediting approval of new drugs, biologics, and medical devices for serious conditions

Section 204(a) amends section 505(c)(1) of the FFDCA to provide that an application for approval for a new drug or biological product that is intended for use for an immediately life-threatening or serious disease or condition and that provides therapy or diagnosis not available for another approved drug or biological product or offers significant improvement over another approved drug or biological product shall be acted upon within 180 days after receipt.

Section 204(b) amends section 515(d)(1)(A) of the FFDCA by similarly providing that applications for the approval of class III devices that meet these criteria shall also be acted upon within 180 days. This amendment is made effective on July 1, 1998.

TITLE III—REVITALIZING THE INVESTIGATION OF NEW PRODUCTS

Sec. 301. Short title

Section 301 provides that the title be cited as the “Investigational Products Regulatory Reform Act of 1996.”

Sec. 302. Timely review and reasonable data requirements for clinical research on drugs and biological products

Section 302 amends section 505(i) of the FFDCA to add two new paragraphs relating to the clinical investigation of new drugs.

Section 505(i)(2) provides that a clinical investigation of a new drug (including a biological product) may begin 30 days after the FDA receives from the sponsor notification of the investigation, unless within the 30-day period the FDA informs the sponsor in writ-

ing that the investigation may not begin and specifies the basis for the decision and the information that is needed in order for the clinical investigation to commence. Within 1 year after the date of enactment, after consultation with individuals and organizations, the FDA is required to publish in the Federal Register criteria for the type and amount of information relating to the safety of an investigational drug that must be included in such a notification. In establishing these criteria, the FDA must take into account the recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The FDA must periodically review, and may revise, these criteria. The FDA must also establish a mechanism to insure the fair and consistent application of safety standards for clinical investigations.

Section 505(i)(3) provides that, in order to place a clinical hold on any ongoing investigation, the FDA must determine that such action is necessary for the protection of human subjects. If the FDA does place a clinical hold on an investigation, the agency must immediately advise the applicant in writing of such action and provide an opportunity to meet within 10 working days. The FDA is required to provide to the sponsor a written list of conditions for the withdrawal of the clinical hold. A written request from the sponsor for the removal of the clinical hold must receive an FDA decision in writing and specifying the reasons therefore within 20 days of the receipt of the request.

Sec. 303. Timely review and reasonable data requirements for clinical research on devices

Section 303 amends section 520(g) of the FFDCFA, which relates to the clinical investigation of medical devices.

Section 520(g)(6) provides that the provisions relating to the amount of information on the safety of an investigational drug, and insuring the fair and consistent application of safety standards for clinical investigations, in new sections 505(i)(2) (B) and (C) shall apply to medical devices.

Section 520(g)(7) provides that the FDA must, within 120 days of enactment, amend its current regulations relating to investigational devices to reflect the new law. The regulations must permit developmental changes in devices in response to information collected during an investigation without the additional approval of an investigational device exemption or supplement if the sponsor determines that the changes do not constitute a significant change in design or basic principles of operation. The new regulations must also permit, without approval of a supplement, changes in clinical protocols that do not affect the validity of the data obtained from the approved protocol, if the changes do not affect patient protection.

Sec. 304. Sense of the committee concerning mutual recognition agreements

This section indicates that it is the sense of the committee that the Secretary of Health and Human Services, in consultation with the Secretary of Commerce, should move toward the acceptance of

mutual recognition agreements reached between the European Union and the Food and Drug Administration.

Sec. 305. Collaborative research design

Section 305 amends Chapter V the FFDCa to add a new section 552 on collaborative research design.

Section 552(a) provides that any person who intends to sponsor a preclinical or clinical investigation of a drug or device may request a meeting with the FDA to review one or more protocols. Such a request must be in writing and include the proposed protocol. The FDA must meet with the person within 30 days and provide a written review of the protocol, including any deficiencies. A written summary shall be made of the meeting, which shall be made part of the FDA product review file.

Section 552(b) provides that agreements reached through meetings with respect to a protocol may be modified only by mutual consent, by the sponsor unilaterally if the change would not require FDA approval, and by the DFA unilaterally only by the director of the responsible FDA office in writing, and specifying the scientific or clinical need.

Section 552(c) provides that appeals from an adverse FDA decision disapproving or modifying a protocol may be made under new section 907 of the FFDCa.

Section 552(d) provides that the FDA must issue guidelines under this provision, which shall address the responsibilities both of the person requesting the meeting and of the FDA. Repeated failure to follow the guidelines may be grounds for a refusal by the FDA to meet with a person.

TITLE IV—EFFICIENT, ACCOUNTABLE, AND FAIR PRODUCT REVIEW

Sec. 401. Short title

Section 401 provides that the title be cited as the “Product Review Regulatory Reform Act of 1996.”

Sec. 402. The content and review of an application

Section 402 amends chapter VII of the FFDCa to add a new subchapter D on review of applications and to add a new section 741 on content and review of an application.

Section 741(a) provides that this section applies to any application or related submission for approval or clearance of a food additive, new drug, device, biological product, new animal drug, animal feed bearing or containing a new animal drug, or color additive.

Section 741(b) requires the FDA to publish in Federal Register within 60 days of enactment a mechanism to insure the fair and consistent application of filing requirements.

Section 741(c) establishes a proceed for determining the classification of a product as a drug, biological product, or device, or the organizational component of the FDA that will regulate the product. The FDA must provide a written statement of the classification of the product or the component of the FDA that will regulate the product upon request. The FDA statement is binding and may not be changed by the FDA except with the written agreement of the person. If the FDA does not provide the statement within 60 days,

the classification and component designated by the person submitting the request shall be final and binding upon the FDA and may not be changed without the written agreement of the person.

Section 741(d) provides that, within 1 year after enactment, the FDA must consult with individuals and organizations and publish in the Federal Register criteria for the type and amount of information relating to safety and effectiveness to be included in a product approval application. The FDA must consider any recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use is establishing the criteria for drugs.

Sec. 403. Contracts for expert review

Section 403 amends chapter VII of the FFDCA to add a new section 742 on contracts for expert review.

Section 742(a) authorizes the FDA to contract with outside organizations and individuals with relevant expertise to review, evaluate, and make conclusions and recommendations to FDA on parts or all of any product application. The FDA retains full authority to make determinations with respect to the approval or disapproval of any product. User fee funds may be used for external review of any drug for which a user fee was paid.

The FDA is required to use this authority to contract for the expert review of categories of indirect food additives and 510(k) submissions. The FDA is also required to use this authority whenever contracts will improve the efficiency, timeliness, and quality of the review of applications, petitions, and notifications for the approval or clearance of new drugs, new animal drugs, biological products, or food additives; and whenever contracts will increase the scientific or technical expertise necessary to keep informed of emerging new therapies and technologies posing significant new scientific and technical issues. In all cases, the FDA retains full authority to make determinations with respect to the approval or disapproval of a product.

Section 742(b) provides that, within 90 days of the date of enactment, the FDA shall by regulation establish the requirements an organization shall meet to be eligible to conduct expert reviews under subsection (a). The regulations are required to provide for the protection of confidential or proprietary information and for protection against conflicts of interest.

Section 742(c) provides that, when expert review is used under this section, the FDA official responsible for the matter shall personally review the conclusions and recommendations of the expert review organization or individual and shall make a final decision regarding the matter within 60 days but not later than the applicable time prescribed for review of an application as set forth in other provisions of the FFDCA.

Section 742(d) requires the FDA to provide a report to Congress on the use of outside individuals and organizations for expert reviews under this section. The report must include an evaluation of the extent to which such contracts improved the efficiency of review and expertise available to the FDA.

Sec. 404. Prompt and efficient review

Section 404 amends chapter VII of the FFDCFA to add a new section 743 on prompt and efficient review of product applications.

Section 743(a) provides that the product review provisions in this section apply to all of the applications and other related submissions for human food additives, animal feed additives, new drugs, new animal drugs, animal feed bearing or containing a new animal drug, premarket notification for medical devices, premarket approval for medical devices, and color additive petitions.

Section 743(b) requires the FDA to establish procedures and policies to facilitate a collaborative review process between the FDA and the applicant. This process must include open, informal, and prompt communications. Except for substantial equivalence determinations for devices, meetings must be held before the expiration of half of the statutory time period for review and before the expiration of three-quarters of such period, or within 15 days after an advisory committee has convened and made recommendations on an application, except for substantial equivalence determinations for medical devices. By mutual consent, the FDA and the applicant may establish a different schedule. Prior to these meetings, the FDA must present to the applicant in writing a description of any deficiencies and the information necessary to bring the application into a form which would require approval. Any agreement between the FDA and the applicant to supersede these procedures and policies must be in writing and specify the changes involved.

Section 743(c) provides that, beginning July 1, 1998, if the FDA fails to meet a time period for action on an application for a new drug, device, biological product, or new animal drug that offers a significant improvement over existing products, or a petition for a direct food additive that has the potential to make foods more wholesome and contribute to a healthier diet, and the product has already been approved for marketing in the European Union or the United Kingdom, upon the request of the applicant the FDA shall within 30 days either approve or disapprove the application and notify the applicant. If the FDA disapproves the application, the notification must set forth the reasons for the disapproval.

A person whose application has been disapproved may obtain judicial review under existing provisions in the FFDCFA relating to judicial review.

Section 743(d) provides that, beginning July 1, 1998, if the FDA in any fiscal year fails to meet the statutory time period for at least 95 percent of the applications in a particular product category, the FDA shall in the following year, with the consent of the applicant, contract with expert individuals and organizations under section 742 to review new applications for that particular product category and any applications already under agency review for that particular product category. Within 60 days of receiving the outside review, but no later than the time period for review set forth in the FFDCFA, the FDA must either approve or disapprove the application and, in the case of a disapproval, notify the applicant in writing of the basis for the disapproval.

Sec. 405. Good manufacturing practice inspection

Section 405 amends chapter VII of the FFDCa to add a new section 744 governing good manufacturing practice (GMP) inspection.

Section 744(a) provides that the FDA may accredit organizations to conduct inspections under section 704 to evaluate compliance with applicable GMP requirements.

Section 744(b) provides that, if the FDA elects to accredit organizations to conduct GMP inspections under section 704, within 90 days of the date of enactment the agency shall establish the requirements that an organization shall meet to be eligible to be accredited. The regulation must provide for the protection of confidential or proprietary information and protection against conflicts of interest.

Section 744(c) provides that, within 90 days after the FDA receives an application for accreditation, the agency shall review it and determine whether it is in compliance with the applicable requirements. The FDA shall grant accreditation, or shall deny accreditation and specify the reasons and the requirements that shall be met to obtain accreditation, within the 90 days.

Section 744(d) authorizes the FDA at any time to revoke accreditation for failure to comply with applicable requirements, after specifying in writing the reasons for the revocation and the requirements that shall be met to retain accreditation and after an informal hearing on the revocation.

Section 744(e) provides that an accredited organization that conducts an inspection under this section at the request of the FDA shall apply all relevant good manufacturing principles establish in the FFDCa and FDA regulations, provide to the FDA and the manufacturer within 30 days after the inspection a report of the findings, and immediately provide the FDA with a notice of any condition that would cause or contribute to a significant threat to the public health.

Sec. 406. Environmental impact review

Section 406 amends chapter VII of the FFDCa to add a new section 745 dealing with environmental impact review.

Section 745 provides that, notwithstanding any provision of other law, no action by the FDA under the FFDCa shall be subject to the requirement of an environmental assessment, environmental impact statement, or other environmental consideration unless the director of the FDA office responsible for the action involved demonstrates, in writing and specifying the basis, that there is a reasonable probability that the environmental impact of the action is sufficiently substantial and within the factors that the FDA is authorized to consider under the FFDCa and that consideration of that impact will directly affect the decision on the action.

Sec. 407. Effectiveness, outcome, and cost-effectiveness standards

Section 407 amends section 741, as added by section 402, to add three limitations with respect to the determination of product effectiveness.

Section 741(e) provides that, in reviewing an application for a new drug, biological products, new animal drug, animal feed bearing or containing a new animal drug, or device, the determination

of effectiveness shall not include evaluation of any potential use not include in the labeling, the cost-effectiveness of the product as compared to the cost-effectiveness of a similar product unless the proposed labeling explicitly includes a representation about cost-effectiveness, and the clinical outcome resulting from the use of a diagnostic device unless the labeling explicitly includes a representation regarding clinical outcome.

Sec. 408. Definition of a day for purposes of product review

Section 408 amends section 201 of the FDCA to add to following definition of a “day” for purposes of reviewing product applications and similar submissions. The term “day” means a calendar day during which FDA has responsibility to review a submission, and excludes those days during which the applicant is responding to requests from the FDA.

Sec. 409. Alternative approval of supplemental new drug applications

Section 409 provides that the FDA shall establish in the Federal Register performance standards for the prompt review of supplemental applications for approved products within 180 days after enactment. The FDA must also issue guidance within 180 days to clarify the requirements and facilitate the submission of data to support approval of such supplemental applications. The guidance shall clarify circumstances in which published studies may be the basis for approval, specify data requirements that will avoid duplication of previously submitted data, and define supplemental applications that are eligible for priority review. The FDA is required to designate an individual in each center (except food) with responsibility for encouraging prompt review of supplemental applications and working with sponsors to facilitate the development and submission of data to support such supplemental applications. The FDA shall implement programs and policies to foster collaboration between the FDA, the National Institutes of Health, and others, to identify published and unpublished studies to support supplemental applications and to encourage sponsors to make application or to conduct further research in support of an application based on such studies.

Sec. 410. Pediatric studies marketing exclusivity

Section 410 amends chapter V of the FDCA to add the following new section 505A regarding pediatric studies for new drug applications.

Section 505A(a) provides for an additional 6 months of market exclusivity for a new drug for which reports of pediatric studies are included in an application after the date of enactment.

Section 505A(b) provides for an additional 6 months of market exclusivity where FDA makes a written request for pediatric studies for a previously approved new drug and such studies are completed and accepted by the FDA.

Section 505A(c) provides the criteria for the pediatric studies that are subject to this section. The FDA may enter into an agreement for specific studies to be conducted by an applicant. If the applicant and the FDA agree upon written protocols for such studies,

the requirement for market exclusivity is satisfied upon the completion of the studies in accordance with the protocols and the submission of the reports of the FDA. Within 60 days after submission of the report of the studies, the FDA must determine if they were conducted in accordance with the written protocols and reported as required, and so notify the applicant. If there is no agreement in writing on the protocols for the studies, the requirement for market exclusivity is satisfied when the studies have been completed and the reports accepted by the FDA. Within 90 days after submission of the reports of the studies, the FDA shall accept or reject the reports and so notify the applicant. The FDA's responsibility in accepting or rejecting the reports shall be limited to determining that the studies fairly respond to the written request, that the studies have been conducted in accordance with commonly accepted scientific principles and protocols, and that they have been reported in accordance with the FDA requirements for filing.

Section 505A(d) provides that, if a section 505(b)(2) new drug application or an abbreviated new drug application for a drug may be made effective after submission of reports of pediatric studies but before the FDA has determined whether the requirements of subsection (c) have been satisfied, the FDA may delay the effective date of any such other approvals until the determination is made under subsection (c), not to exceed 90 days. If the requirements of subsection (c) are satisfied, the 6-month market exclusivity period shall begin on the date that such other approvals would have been permitted absent action under this provision.

Section 505A(e) requires the FDA to publish notice of any determination that the provisions of this section have been met and that additional market exclusivity has been granted.

Section 505A(f) defines "pediatric studies" to mean at least one human clinical investigation in a population of adolescent age or younger. At the discretion of the FDA, pharmacokinetic studies may be considered as clinical investigations.

Sec. 411. Notifications for device market clearance

Section 411 amends section 510(k) of the FFDCA to clarify that the submission to the FDA is a notification and not a report.

TITLE V—DRUG AND BIOLOGICAL PRODUCTS REGULATORY REFORM

Sec. 501. Short title

Section 501 provides that the title be cited as the "Drug and Biological Product Regulatory Reform Act of 1996."

Sec. 502. New drug approval standard

Section 501 amends section 505(d) of the FFDCA to add at the end thereof a new sentence which states that substantial evidence of effectiveness may consist of data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained either before or after such investigation).

Sec. 503. Pilot and small-scale manufacture

Section 503 amends section 505(c) of the FFDCA to provide that a new drug or biological product may be approved by the FDA on

the basis of manufacture in a pilot or other small facility prior to scaling up to a larger facility, unless the FDA demonstrates, in writing and specifying in detail the reasons after an informal hearing, that a full scale production facility is necessary to ensure safety or effectiveness.

Sec. 504. Manufacturing changes

Section 504 amends chapter VII of the FFDCA, as amended by section 406, to add a new section 746 on manufacturing changes.

Section 746(a) provides that the new section applies to new drugs, biological products, and new animal drugs.

Section 746(b) provides that a change in the manufacture of a new drug, a biological product that is the subject of an official monograph or that can be adequately characterized by chemical, physical, or biological means, or a new animal drug, shall require validation. If there is no change in the approved qualitative and quantitative formulation or in the approved release specifications, or if any such change is of a type permitted by FDA regulations, the manufacturing change may be made at any time and shall be reported annually to the secretary. Any other change shall require completion of an appropriate study demonstrating equivalence according to criteria established by the FDA unless that requirement is waived by the FDA, may be made at any time, and shall be reported to the FDA through a supplement or amendment submitted at the time the change is made.

Section 746(c) applies to changes in biological products that are not subject to an official monograph and cannot adequately characterized by chemical, physical, or biological means. These changes also require validation. If the change relates solely to the modification of the manufacturing facility or personnel, with no change in the process or release specifications, it may be made at any time and shall be reported annually to the secretary. Any other change shall require completion of a bioassay or other appropriate study demonstrating equivalence according to criteria established by the FDA unless such requirement is waived by the FDA, may be made at any time, and shall be reported to the FDA through an amendment submitted at the time the change is made.

Section 746(d) provides that, prior to approval of a biological product, a determination shall be made whether the product can be adequately characterized for purposes of this section. Such a determination shall be made with respect to previously approved biological products within 90 days after the date of enactment. Any determination under this subsection is subject to change based upon new scientific information.

Sec. 505. Insulin and antibiotics

Section 505 repeals sections 506 and 507 of the FFDCA, which currently govern the approval and certification of insulin and antibiotics. As a conforming amendment, section 802 is amended to permit the continued exportation of unapproved insulin and antibiotic drugs without regard to the export provisions that otherwise apply to new drugs if they meet the requirements of section 801(e)(1).

Sec. 506. Modernization of regulation of biological products

Section 506 amends section 351 of the Public Health Service Act to revise the provisions under which biological products are regulated.

Section 506(a) revises section 351(a) of the Public Health Service Act to require that no person shall introduce or deliver for introduction into interstate commerce any biological product unless a license is in effect and each package is properly marked. The license shall, as determined by the Secretary, cover the biological product or the facility in which the product is manufactured, or both. The FDA shall establish, by regulation, requirements for license applications. License applications shall be approved based upon a demonstration that the biological product is safe and effective in accordance with sections 505(c) and 505(d); or meets standards designed to ensure that the product is safe, pure, and where appropriate, potent and that the methods, facilities, and controls used for manufacture, processing, packing and holding meet designated standards. A license application that covers a facility shall ensure that the product meets appropriate standards. A license application for blood or a blood component shall be approved based on a demonstration that the product is safe, pure, and where appropriate, potent, and that the facility meets appropriate standards. Requirements for approval of biological products shall include preapproval inspection and agreement to permit facility inspections.

An approved license for a biological product may be revoked after an opportunity for a hearing if the FDA determines that the requirements for approval are no longer met or that other public health reasons, prescribed by regulation, exist. Revocation may not occur prior to an opportunity for a written response submitted by the licensee within 30 days of the date of receipt of inspectional findings. Revocation of a product license shall not prevent the continued use of a licensed biological product unless the product is subject to recall. If the licensee requests an inspection before the FDA has taken final action to revoke a license, the FDA shall conduct an inspection within 30 days. If the inspection confirms that the licensee is not in compliance with applicable standards, the 30-day requirement for inspection shall not apply to any subsequent request. If the inspection confirms that the licensee is in compliance with all applicable requirements, the FDA must withdraw any proposed action. Where the FDA determines that grounds for license revocation exist that constitute a danger to health, the FDA shall suspend the license and initiate the hearing process within 30 days.

An investigational biological product subject to the investigational new drug provisions, including section 505(i) of the FFDCA.

Section 506(b) amends section 351(d) of the Public Health Service Act to repeal the requirement for a separate establishment license.

Section 506(c) amends section 251(b) of the Public Health Service Act to provide that no person shall falsely label any biological product.

Section 506(d) amends section 351(c) of the Public Health Service Act to conform the language to the other changes made in this section.

Section 506(e) amends section 351 of the Public Health Service Act to add a new subsection (i) to define the term “biological product.” The definition conforms to existing provisions of law. Sections 505(i), 903, and 904 of the FFDCA Act, which relate to investigational new drugs and advisory committees, are applicable to biological products. Requirements involving labeling and advertising for biological products are required to be established in accordance with the provisions in sections 201(m) and 502(n) of the FFDCA, which apply to labeling and advertising for drugs.

Sec. 507. Effective medication guides

Section 507 amends chapter IX of the FFDCA, as amended by section 108, to add a new section 908 regarding effective medication guides.

Section 908(a) requires the FDA within 30 days of enactment to request national health care organizations to develop a long-range comprehensive plan relating to the provision of oral and written prescription drug information to consumers. The plan must be consistent with the goals of the recent FDA-proposed regulation governing medication guide requirements for prescription drugs.

Section 908(b) describes the requirements for the plan.

Section 908(c) provides that the FDA shall have no authority to implement its proposed regulation or to develop any similar regulation or policy statement relating to the same subject if, within 120 days after enactment, the national organizations described in subsection (a) meet and begin to develop the plan described in that subsection.

Section 908(d) provides that by January 1, 2001, the Secretary of HHS must review the status of private sector initiatives in this field to determine whether they achieve the goals of the plan described in subsection (a). If those goals are not achieved, the limitation above will no longer apply and the FDA will be free to seek public comment on other initiatives to meet those goals. The Secretary may not delegate this review.

Sec. 508. State and local requirements respecting nonprescription drugs intended for human use

Section 508 amends chapter V of the FFDCA to add a new section 523 regarding State and local requirements for nonprescription drugs intended for human use. Section 523(a) provides that no State or political subdivision may establish or continue in effect any requirement relating to human nonprescription drugs which is different from or in addition to, or otherwise not identical with, a requirement of the FFDCA Act or the Fair Packaging and Labeling Act (FLPA) and the administrative implementation thereunder. This provision covers any requirement relating to the subject matter in any provision of the two statutes involved and any requirement relating to the dissemination of information in any manner about nonprescription drugs, other than a State or local requirement switching a nonprescription drug to prescription status.

Section 523(b) provides that a State may petition the FDA for an exemption from this authority. After providing notice and an opportunity for written and oral presentations, the FDA may by regulation grant an exemption from the general rule of national uniform-

ity if the State requirement is justified by compelling local conditions or protects an important public interest, would not cause any nonprescription drug to be in violation of any applicable requirement or prohibition under Federal law, and would not unduly burden interstate commerce.

Sec. 509. Requirements of radiopharmaceuticals

Section 509(a) provides, that, not later than 180 days after enactment, after consultation with individuals and organizations, the FDA must establish proposed regulations governing the premarket approval of radiopharmaceutical articles, taking into account their appropriate use, pharmacological and toxicological activity, and estimated absorbed radiation dose. Not later than 1 year after the date of enactment, the FDA must issue final regulations.

Section 509(b) provides that, with regard to diagnostic radiopharmaceuticals, the approved indications may refer to specified manifestations of disease or may refer to a diagnostic procedure. All product premarket approval applications for radiopharmaceutical articles, and all other matters relating to radiopharmaceuticals, are required to be reviewed and acted upon by a single office in the FDA center responsible for drugs and that office shall report directly to the center director. A single advisory committee may provide conclusions and recommendations regarding any radiopharmaceutical matter.

Section 509(c) defines the term “radiopharmaceutical.”

Section 509(d) provides that the FDA is required to establish quantifiable performance standards to measure the performance of the agency in approving radiopharmaceutical articles as part of its performance standards for all agency activities.

TITLE VI—DEVICE REGULATORY REFORM

Sec. 601. Short title

Section 601 provides that this title be cited as the “Medical Device Reform Act of 1996.”

Sec. 602. Premarket notification

Section 602(a) amends section 510 of the FFDCFA to exempt from premarket notification all class I devices (except those identified by the FDA under subsection (n) as requiring premarket notification to protect the public health) and those class II devices that FDA determines do not need such notification. Within 30 days of enactment, the FDA is required to publish in the Federal Register a list of each type of class II device that does not require premarket notification under section 510(k). Any person may petition the FDA to exempt other types of class II devices, and the FDA must respond within 180 days of receipt of the petition. The FDA is also required to review and respond and respond to all premarket notifications within 90 days of receipt. The FDA may not withhold a determination regarding these matters because of a failure to comply with any provision of the FFDCFA unrelated to a substantial equivalent decision.

Section 602(b) amends section 513 of the FFDCFA to allow a person who submits a premarket notification under section 510(k) of

the FFDCA to obtain advisory committee review with respect to the classification of a device into class III. The FDA has 10 days after receiving the conclusions and recommendations of the advisory committee to determine the final classification of the device.

Section 602(c) amends section 513 of the FFDCA to provide that, for the purpose of determining the intended use of a predicate device for a substantial equivalent determination, each use reasonably included, as determined by the FDA, within a general use for the predicate device shall be deemed a legally marketed use.

Section 602(d) amends section 513 of the FFDCA to provide that any change or modification to a device, other than a major change or modification in the intended use, or a significant change or modification in design that has a significant effect on safety or effectiveness, shall not require an additional premarket notification under section 510(k) if, prior to commercial distribution, the change is supported by appropriate data or information, including data or information demonstrating compliance with good manufacturing practice regulations promulgated under section 520(f), and is shown by such data or information not to adversely affect safety or effectiveness. All data to support such a change to the device shall be made available to the FDA upon request and shall be maintained for at least a period of time equal to the commercial life of the device.

Sec. 603. Medical device approval standards

Section 603(a) amends section 513(a)(3) of the FFDCA to clarify that the FDA may determine the effectiveness of a device on the basis of one or more well-controlled investigations, including one or more clinical investigations.

Section 603(b) amends section 513(a)(3) of the FFDCA to provide that the FDA shall accept retrospective or historical clinical data as a control in a study for use in determining the effectiveness of a device if sufficient valid data are available and the effects of the device are clearly defined and well understood. The FDA may not require clinical studies using prospective concurrent controls to support the effectiveness of a device unless the effects of the device are not clearly defined and well understood as determined by the FDA or retrospective or historical data are not available that meet the standards of the FDA for quality and completeness or there is a compelling public health reason not to rely on retrospective or historical data as a control.

Sec. 604. Tracking

Section 604 amends section 519(e) of the FFDCA to authorize device tracking for a class II or class III device the failure of which would be life-threatening or have permanently debilitating effects and which is permanently implanted or life-sustaining or life-supporting and used outside a device user facility. Any patient receiving a device subject to tracking under this section may refuse to release or refuse permission to release identifying information for the purpose of tracking.

Sec. 605. Postmarket surveillance

Section 605 revises section 522 of the FFDCa relating to postmarket surveillance of devices.

Amended section 522(a) provides that the FDA may require a manufacturer to conduct postmarket surveillance for any device of the manufacturer that is a permanent implant the failure of which may cause serious, adverse health consequences or death, or that is intended for use in supporting or sustaining human life or that potentially presents a serious risk to human health.

Amended section 552(b) provides that each manufacturer required to conduct surveillance of a device shall, within 30 days of receiving notice from the FDA, submit to the FDA for approval a protocol for the required surveillance. Within 60 days of receiving the protocol, the FDA shall determine if the principal investigator has sufficient qualifications and if the protocol will result in collection of useful data necessary to protect the public health and to provide safety and effectiveness information for the device. The FDA may not approve the protocol until it has been reviewed by a qualified FDA advisory committee.

Sec. 606. Device distributor reporting

Section 519 of the FFDCa is amended to eliminate reporting requirements for device distributors.

Sec. 607. Premarket approval

Section 607(a) amends section 515(d) of the FFDCa to establish new requirements and procedures with respect to premarket approval of class III devices. The FDA is required to accept data relating to safety and effectiveness from investigations if the data relate to an earlier version of the device which has been modified and the modification does not constitute a significant change that would invalidate the data, or the data are available for use under the FFDCa and are relevant to the design and intended use of the device. Each premarket application is required to be reviewed according to an established schedule. The FDA shall meet with an applicant within 90 days of the receipt of the premarket approval application. If the application does not appear in a form which would require approval under the FFDCa, the FDA must, in writing prior to the meeting, present to the applicant a description of the deficiencies and the information required to bring the application into such form. The FDA shall refer an application to an advisory committee for review unless this is not required. The FDA must meet with the applicant within 15 days of the date of the advisory committee review to discuss the status of the application, including a discussion on what action is necessary to bring the application into a form that would require approval. Prior to that meeting, the FDA shall in writing set forth an agenda for the meeting and a full description of the additional information necessary for approval of the application. The applicant may decline any such meeting.

Not later than 135 days after receipt of a premarket approval application, if an advisory committee is not required, the FDA shall inform the applicant whether the application is in a form that would require approval under this subsection. If the application is in a form which would require approval, the FDA shall present in

writing to the applicant a description of all additional information necessary to receive approval. If the application is not in a form which would require approval, the FDA shall deny approval and, prior to the meeting, present in writing each basis for denying approval and the additional information required for approval. FDA must approve or deny an application within 180 days of receipt, or within 180 days of receipt for an application subject to expedited review. Review of a premarket approval application by the FDA shall not take more than the statutory time period, which may not be extended if the application is amended.

Section 607(b) requires the FDA to amend its regulations governing premarket approval to conform to the new statutory requirements, including the provisions relating to changes relating to the product and its manufacturer that do not require a supplemental premarket approval application. The FDA shall require device manufacturers to maintain the information relied upon to support a change that is not subject to premarket approval of a supplement, which shall become part of the device master file, and give notice to the FDA of the change. The information shall be maintained for the expected life of the device but not less than 2 years after commercial distribution.

Sec. 608. Device performance standards

Section 608(a) amends section 514 of the FFDCa to facilitate review of a device by recognition of appropriate medical device performance standards developed by organizations accredited by the American National Standards Institute (ANSI), the International Standards Organization (ISO), the International Electrotechnical Commission (IEC), and any other organization certified by the FDA for this purpose. For organizations other than ANSI, ISO, and IEC, the FDA is required to establish a procedure governing certification of the competence of any national or international standards-setting organization to develop standards for medical devices. Certification must be based on formal written criteria that include specified elements. The FDA may impose a reasonable fee for certifying these organizations. The FDA is required to recognize standards adopted by ANSI, ISO, or IEC and must review and may recognize standards adopted by other organizations it has accredited. When the FDA recognizes a standard, it must publish a notice in the Federal Register listing the name of the standard and shall provide any person who so requests a copy of the standard. The FDA is required to promulgate regulations under which it may withdraw the certification it has granted to a standard-setting organization or may withdraw recognition of a standard adopted by ANSI, ISO, or IEC upon a determination that it no longer meets appropriate requirements. The FDA may also promulgate performance standards that differ from or are not established by certified organizations. The FDA may not require, as a condition for approving a medical device, conformity with a standard recognized under this section if the applicant demonstrates a reasonable assurance that the device is substantially equivalent to a legally marketed predicate device or provides reasonable assurance and that the device is safe and effective.

The FDA may revoke recognition of performance standards previously recognized under this section upon a determination that the standard is insufficient to provide reasonable assurance of safety and effectiveness. The FDA must notify the standard-setting organization and specify the basis for the revocation.

A performance standard recognized under this section is required to provide reasonable assurance of safety and effectiveness. Such a performance standard shall, where necessary, include provisions with respect to the construction, components, ingredients, and properties of the device and the compatibility of the device with power systems and connections to the systems, provisions for testing, provisions for measurement of performance, and provisions requiring that the results of the tests demonstrate conformity with the standard. A performance standard shall, where appropriate, require the use and prescribe the form and content for adequate labeling.

In lieu of requiring data demonstrating conformity of a device with a standard under this section, the FDA shall accept a certification that the device conforms with each identified standard. Where appropriate, the FDA may require data demonstrating such conformity. The FDA shall require an applicant who certifies that a device conforms to an applicable standard to maintain data demonstrating such conformance for the life of the device and to make the data available to the FDA upon request.

Section 608(b) amends section 501(e) of the FFDCA to provide that a device that is represented as certified to be in compliance with a standard recognized under section 514(c) is adulterated unless the device is in all respects in conformity with the standard.

Sec. 609. Accredited-party participation

Section 609 amends subchapter A of chapter V of FFDCA to add a new section 523A to establish a 3-year pilot program on the use of accredited third parties to review and approve section 510(k) premarket notifications and section 515 premarket approval applications.

Section 523A(a) provides that, within 1 year after enactment, the FDA shall accredit individuals and organizations outside the Department of HHS to review and recommend to FDA approval or denial of premarket notifications under section 510(k) and premarket approval applications under section 515.

Section 523A(b) establishes procedures for accreditation of individuals and organizations qualified to conduct such reviews. The criteria for accreditation shall include criteria to avoid conflicts of interest and to assure confidentiality of submissions.

Section 523A(c) authorizes the FDA to suspend or withdraw accreditation for failure to meet the criteria for accreditation

Section 523A(d) provides that a person who submits to the FDA a premarket submission for a device for review and classification or for approval of the device must be given the option to select an accredited party to review such submissions. For persons electing to use this option, the FDA is required to identify no less than 2 accredited persons from whom the selection may be made. Compensation for accredited party review is to be determined by agree-

ment between the accredited party and the person who engages the services of the accredited party.

Section 523A(e) provides that, when a person submitting a premarket notification of premarket approval application exercises the option to obtain third party review, the person shall first submit the notification or application to the FDA for review to determine completeness for filing. No later than 15 days after receipt of a premarket notification or 30 days after receipt of a premarket approval application, the FDA shall forward the submission to the accredited individual or organization. Upon receiving the conclusions and recommendations of the accredited individual or organization, the FDA shall have 15 days to act upon a premarket notification and 45 days to act upon a premarket approval application. If the FDA takes action different from that recommended by the accredited individual or organization, the agency must provide detailed reasons.

Section 523A(f) provides that this program shall remain in force for 3 years from the date of the first FDA accreditation of an individual or organization.

Section 523A(g) provides for reports to the committees of Congress with respect to FDA implementation of this program. After 2 years of operation, the FDA must contract with an independent research organization to examine the program and prepare a full evaluation.

TITLE VII—ANIMAL DRUG REGULATORY REFORM

Sec. 701. Short title

Section 701 provides that the title be cited as the “Animal Drug Regulatory Reform Act of 1996.”

Sec. 702. Evidence of effectiveness

Section 702(a) amends section 512(d) of the FFDCA to provide that substantial evidence of effectiveness for an animal drug means evidence from one or more scientifically sound studies, that taken together provide reasonable assurance that the drug will have the claimed or intended effect. A study shall be considered to be scientifically sound if it is designed and conducted in a manner that is consistent with generally recognized scientific procedures and principles.

Section 702(b) amends section 512(d) of the FFDCA to provide that, where a new animal drug contains more than one already approved active ingredient or the labeling suggests use of the drug in combination with another already approved animal drug, the FDA may only consider with respect to the combination whether any of the active ingredients at the longest withdrawal time is above its safe concentration or interferes with the method of analysis for another active ingredient.

Section 702(c) amends section 512(c)(2)(F)(iii) of the FFDCA by providing market exclusivity based upon substantial evidence of effectiveness rather than upon new clinical or field investigations and by providing that such studies must be required for approval rather than essential to approval.

Section 702(d) amends section 512(d)(1) of the FFDCA to provide that the requirement of substantial evidence of effectiveness shall not apply to a claim for use of an animal drug in a minor species or for a minor use if there is an approved new animal drug application for the drug.

Section 702(e) amends section 512(d)(1)(C) of the FFDCA to conform it to the new definition of substantial evidence of effectiveness.

Section 702(f) provides that, not later than 6 months after enactment, the FDA shall issue proposed rules implementing the amendments made by this section. Not later than 18 months after the date of enactment, the FDA shall issue final regulations. In issuing regulations and reviewing new animal drug applications, the FDA is required to define “substantial evidence” of effectiveness in a manner that encourages the submission of applications for production drugs that conserve food resources, for veterinary prescription drugs whose use is designed to rely on the experience and training of practitioners, and of supplemental applications for uses in minor species, for minor uses, and for permitted unlabeled uses. The regulations must also take into account the citizen petition submitted by the American Veterinary Medical Association and the Animal Health Institute on October 21, 1991, relating to labeling a veterinary prescription drug with a dosage rather than a single dosage level. Finally, the regulations must provide for the opportunity for a conference prior to the submission of a new animal drug application on investigational new animal drug application, and prior to the submission of a request for an investigational exemption, to make a decision establishing a submission or an investigational requirement. That decision shall bind the FDA and the applicant unless new scientific information requires a change. Not later than 10 days after each such conference, the FDA shall provide by written order a scientific justification specific to the animal drug and the intended uses under consideration for requiring studies of types other than the types of studies specified in section 512(d)(4) as being essential to provide substantial evidence of effectiveness for the intended uses of the animal drug.

Sec. 703. Limitation of residues

Section 703 amends section 512(d)(1)(F) of the FFDCA to state that a new animal drug application may be disapproved on the basis of information that the labeled use will result in a residue in excess of a tolerance found by the FDA to be safe.

Sec. 704. Adulterated drugs

Section 704 amends section 501(a)(2) of the FFDCA to specify separate GMP requirements for animal drugs that are appropriate for such drugs and that will ensure that the drug meets the requirements of the FFDCA for use in animals other than man.

Sec. 705. Veterinary feed directives

Section 705(a) amends section 503(f)(1)(A) of the FFDCA to exclude veterinary feed directive drugs and animal food containing such drugs from the requirement for a veterinary prescription.

Section 705(b) amends chapter V to add a new section 504 governing veterinary feed directive drugs.

Section 504(a) provides that a drug intended for use in or on animal feed which is limited to use under the professional supervision of a licensed veterinarian is a veterinary feed directive drug. Any animal feed containing such a drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice. A veterinary feed directive drug is exempt from the requirement of a prescription. A veterinary feed directive is lawful if it contains the information required by the FDA and complies with the conditions and indications for use established for the drug. Appropriate records must be maintained relating to veterinary feed directive drugs and must be made available to the FDA upon request. A person who distributes animal feed containing a veterinary feed directive drug must notify the FDA.

Section 504(b) provides that a veterinary feed directive drug and any feed bearing or containing such a drug shall be deemed to be misbranded if the drug and feed labeling fail to bear such cautionary statement and other information as the FDA may require or if the advertising fails to conform to the requirements of section 512(i) or other FDA requirements.

Section 504(c) provides that a veterinary feed directive drug and an animal feed bearing or containing such a drug shall not be deemed to be a prescription article under any Federal or State law.

Section 705(c) contains conforming amendments.

Section 705(d) amends section 301(e) of the FFDCA to make a violation of section 504 of the FFDCA a prohibited act.

Sec. 706. Times frames for approval

Section 706 amends section 512(c)(1) of the FFDCA to require action on a new animal drug application within 90 days rather than the present 180 days.

TITLE VIII—FOOD REGULATORY REFORM

Sec. 801. Short title

Section 801 provides that the title be cited as the "Food Regulatory Reform Act of 1996."

Sec. 802. Indirect food additives

Section 802(a) amends section 409 of the FFDCA to add an alternative approval procedure for indirect food additives. Any person may submit a notification for an indirect food additive at least 90 days prior to the introduction or delivery for introduction of the additive in interstate commerce, demonstrating that the labeled use of the product is safe. Within 90 days after receipt of the notification, the FDA shall either approve or disapprove the notification and publish a notice of this determination in the Federal Register. If the notification is approved, the FDA shall promulgate an appropriate food additive regulation.

Section 802(b) amends section 201 of the FFDCA, as amended by section 408, by adding a new definition of the term "indirect food

additive,” which means a food additive intended to contact food but that is not intended for consumption as a food ingredient.

Sec. 803. Health claims of food products

Section 803 amends section 403(r)(3) of the FFDCA to authorize the use in food labeling of health claims consisting of information published by authoritative government scientific bodies. Any claim that is subject to the requirements for health claims established under the Nutrition Labeling and Education Act of 1990 and which would otherwise require specific authorization by the FDA prior to use may be used in food labeling without FDA authorization if it consists of or otherwise summarizes or reflects information contained in a publication by a Federal Government scientific organization or by the National Academy of Sciences or one of its component organizations. If any such claim is used a copy must be provided to the FDA, along with the published information on which it is based, at least 90 days prior to its first use. This provision applies to all food products, including dietary supplements.

TITLE IX—ESTABLISHMENT OF CENTERS FOR EDUCATION AND RESEARCH ON DRUGS, DEVICES, AND BIOLOGICAL PRODUCTS

Sec. 901. Centers for education and research on drugs, devices, and biological products

Section 901 amends chapter IX of the FFDCA to add a new section 908 to establish centers for education and research on drugs, devices, and biological products.

Section 908(a) requires the FDA to establish a consortium of three or more centers for research and education on drugs, devices, and biological products.

Section 908(b) provides that the entities shall be selected by a peer review selection procedure.

Section 908(c) provides for two types of grant activities. Required activities shall include state-of-the-art clinical and laboratory research that increases awareness of new uses of products and the unforeseen risks of new uses of products, provides objective clinical information, and improves the quality of health care while reducing the cost of health care through the prevention of adverse effects of these products and the consequences of such effects. Research on the comparative effectiveness and safety of these products is also a required activity. Discretionary activities includes surveillance of adverse effects, a study of new or unapproved uses for marketed products, and a study of the therapeutic characteristics of clinically special populations. No money awarded under this provision may be used to assist the FDA in the review of new drugs.

Section 908(d) provides for grant applications to the FDA.

Section 908(e) establishes an oversight committee within the FDA.

Section 908(f) requires a report to Congress on the activities undertaken pursuant to this provision.

Section 908(g) authorizes appropriations.

TITLE X—PROGRAM IN CLINICAL PHARMACOLOGY

This title extends the authority for 2 fiscal years for a clinical pharmacology education program initially authorized under section 2(b) of public law 102-222.

VIII. ADDITIONAL VIEWS

ADDITIONAL VIEWS OF SENATORS KENNEDY, PELL, AND SIMON

The stated goal of S. 1477 is to better balance FDA's twin goals of protecting the American consumer from unsafe or ineffective drugs, devices, and foods and ensuring timely review and availability of new or improved medical products and better food technology. No one disputes that this balance is important. At the outset, we emphasize that certain provisions in S. 1477 are constructive. Among other useful provisions, the bill codifies regulatory reforms that FDA has already adopted, modernizes the legislative authority governing regulation of biologics, gives FDA flexibility to adopt other reforms, and creates new procedures to encourage collaboration, predictability, and efficiency in the testing and review of new products and new uses of approved products.

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

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

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

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

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

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

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

Weakening FDA's authority to require appropriate consumer labelling for drugs, thus denying consumers the reliable information they need to protect themselves against adverse drug reactions.

S. 1477 unacceptably weakens essential FDA oversight of drug and biologic manufacturing. Section 604 eliminates FDA's ability to require pre-approval of any manufacturing changes for drugs and biologics, including blood and vaccines, even if the change has a substantial potential to harm public health. Instead, section 604 would require certain kinds of validation or testing and reporting to FDA, depending on the kind of product involved. However, history teaches that manufacturing changes can make a product unsafe or less effective and that validation or testing against finished product specifications may not detect problems and protect the public. For example, changing the solvent used to kill viruses like HIV or hepatitis in blood products can result in products that transmit life-threatening diseases. A change in the filters or virus lines used to produce vaccines can turn a protective vaccine into a deadly one. A change in the filters used to produce the Cutter polio vaccine resulted in 200 cases of polio in the 1950's, before FDA required more rigorous standards. Even with the tight controls now in place, there have been 26 cases in just the last two years—including cases involving vaccines—where only FDA intervention prevented thousands of patients from being exposed to dangerous products.

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

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

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

reviewers would be so extensive, that it is hard to see how FDA's review would be much more than a rubber stamp.

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

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

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

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

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

Without additional resources, FDA will be unable to meet these targets. In addition, as it strives to come closer to these goals without enough funds or personnel it may be forced to perform a less than thorough review. Further, as noted above, if FDA does not

meet the timeframes, FDA must, at the request of the applicant, pay a third party to review a product—further bleeding the agency of the resources it needs to meet the deadlines. It is hard to see how this catch-22 benefits the American consumer.

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

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

Turning over important FDA functions to the private sector and bleeding the agency of resources threatens public health in other ways. At the same time as FDA is forced to comply with numerous new bureaucratic requirements, it will lose the independent, committed, expert, public servants on whose work public safety depends. FDA will no longer have expertise (now developed through the review of product applications and conducting facility inspections) to be an effective post-approval guardian. Yet post-market surveillance has repeatedly protected Americans from harm. Among the problem drugs that FDA post-market surveillance efforts identifies are Orflex, Selacryn, Zomax, Merital, and Omniflox. Device surveillance has resulted in critical corrections to such devices as pacemakers, infant ventilators, and patient restraints and the withdrawal from the market of Orcolon, an eye gel that caused causes of blindness. Surveillance was responsible for identifying potentially fatal allergic reactions to sulfites, which are a common preservative in food, and putting in place a warning. FDA surveillance picked up counterfeit infant formula that would have injured infants if consumed.

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

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

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

The primary justification for radical reforms included in S. 1477 is that FDA is too slow to approve products, thereby denying patients needed treatment already available in foreign countries. Although there may have been some basis for this concern a decade ago, it is not valid today. FDA cut average time to approval by 40% between 1987 and 1992. According to the General Accounting Office, in 1994, the U.S. was reviewing drugs as fast as, or faster than Great Britain and other foreign countries. Since the Prescription Drug User Fee Act (PDUFA) was negotiated by FDA, Congress, and industry and passed in 1992, review times have dropped even farther. In fact, drug user fees have proved an overwhelming success. According to FDA, median time to approval dropped farther in 1995. Moreover, under PDUFA, by FY 97, FDA was to be

conducting a complete review 90% of applications for priority drugs within six months and other drugs within twelve months. By FY 95, FDA had already surpassed the 1997 goal—by conducting a complete review of 96% of applications within these time limits.

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

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

Nevertheless, even without the additional resources that user fees would have provided, FDA has successfully decreased median review times for premarket notifications, the premarket submission used for 98% of all devices, to 91 days, only one day shy of the 90 days in regulation, while the average review time is 138 days. At the end of FY 95 only 9 premarket notifications were active and overdue (past 90 days), as compared with 460 at the end of FY 94 and 1,894 at the end of FY 93.

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

this, FDA states it held more than 200 pre-submission meetings with companies and reviewed more than 100 pre-IDE submissions.

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

We are prepared to work with Senator Kassebaum and others to modify S. 1477 so that it is truly a responsible, moderate reform program that will improve the public health. While we respect the good-faith efforts that have been made to date, we must oppose passage of S. 1477 in its current form.

EDWARD KENNEDY.
PAUL SIMON.
CLAIBORNE PELL.

ADDITIONAL VIEWS OF SENATORS DODD, MIKULSKI, AND
HARKIN

Legislation, in our view, is needed to improve the efficiency and effectiveness of the U.S. Food and Drug Administration. Recognizing that regulatory delays put lives at risk just as surely as undue haste, we believe there is much that can be done to speed the FDA approval process without harm to public health and safety. S. 1477 is a strong step in that direction.

We also recognize that further improvements to this legislation can and should be made before it is approved by the Senate and enacted into law. If FDA reform is to succeed and truly help patients, the legislation must be bi-partisan and moderate. We are encouraged by the spirit of bi-partisanship so far in the process and hope it continues as the bill is taken up on the Senate floor.

The Chairman has indicated her willingness to work with us on a number of key areas. These include, but are not limited to:

1. Time Frames and Enforcement of Time Frames (Hammers). S. 1477 sets strict timelines for the agency that they must meet by 1998. If the time frames are not met, FDA must contract out all products at the request of the manufacturer. It is our view that the goal of the legislation is to make the agency work more efficiently and meet timelines. We do not believe that mandatory contracting out will necessarily achieve this end. We are concerned that the legislation is setting up the agency to fail in certain product areas and could undermine the very successful Prescription Drug User Fee Act. We believe in a strong role for FDA and do not want to see all its work farmed out to private parties whose track record on timeliness, efficiency, and cost effectiveness is yet untested. We therefore hope to work on better measures to ensure that the agency improves its record.

2. Manufacturing Changes. We understand that S. 1477 was intended to allow pharmaceutical and biological product manufacturers to make minor manufacturing changes without waiting for agency approval as long as the changes would not affect safety and effectiveness. The Committee acknowledged during mark up that the language in the bill did not adequately reflect the Committee's intent and we hope to work in a bi-partisan manner to revise the language.

3. Access to Unapproved Therapies. While we strongly support expanding the ability of patients to have access to unapproved therapies that are being tested, we want to ensure that the study of these therapies continues with due diligence.

4. Off Label Dissemination of Information. The issue of dissemination of information on off label uses was taken out of the bill with the expectation that a compromise could be reached. While we see the value in greater flow of information to patients and doctors, we have serious concerns about the original language of the provi-

sion. These include the need to ensure that the information that is provided is balanced and that some incentive exists for manufacturers to continue to conduct research on off label uses to determine whether or not they are safe and effective. Although negotiations had been proceeding well on this issue, agreement was not reached.

It is our hope to work with the Chairman and members of the Committee to work out these and other controversial provisions in the bill. It is our view that those who want a bill this year should be able to work out these issues and pass bi-partisan legislation that truly helps patients.

CHRISTOPHER J. DODD.
TOM HARKIN.
BARBARA A. MIKULSKI.

ADDITIONAL VIEWS OF SENATOR HARKIN

In addition to the views I share with Senators Dodd and Mikulski I believe that improvements should be made to the provisions in S. 1477 regarding third party review of medical devices. The third party review provisions were added during Committee consideration of the bill and described by proponents as a “pilot” to test whether the use of third party reviewers would reduce delays in medical device approvals. But, these provisions are very broad in scope and it is my hope that the “pilot” can be narrowed to address the concerns outlined below.

The “pilot” in S. 1477 does not limit in any way the number of third parties to be accredited nor the number and types of products to be reviewed outside the agency. I believe that a test of third party review should be limited to less complex devices that pose a smaller potential risk to patients should they malfunction. This simply makes common sense—test an unproven process in a manner that, regardless of outcome, poses the least possible risk to public health and safety.

Provisions in S. 1477 do give FDA final product review decisions. However, I am concerned that given the time-frames for FDA action, substantive and meaningful review by FDA will be extremely difficult, if not impossible.

In addition, under S. 1477 the manufacturer of the device selects the reviewer and also directly pays the reviewer. Direct payment by the manufacturer to the reviewer, without approval or even review by FDA, creates obvious conflicts of interests. In S. 1477 the FDA is charged with promulgating rules to prevent conflicts of interest but such conflicts are inherent in a system that allows the manufacturer to both select and directly pay the reviewer. I believe the Secretary should approve payment agreements.

I am not opposed to a pilot project to determine the effectiveness of third party review of devices but such a pilot should be limited and should not include high risk or life-sustaining devices. Only after third party review has proven to be effective in the review of low risk devices should it be expanded to include all medical devices.

TOM HARKIN.

ADDITIONAL VIEWS OF SENATOR PAUL WELLSTONE

While I strongly support responsible reform of the U.S. Food and Drug Administration, I voted against S. 1477 because it included some provisions which I believe would undermine the ability of the FDA to protect the public health. Senator Kassebaum has indicated a serious willingness to work on these provisions before the bill reaches the Senate floor. I look forward to ultimately supporting S. 1477 as I believe the legislation includes a number of very important and constructive reforms. It is my hope that responsible FDA reform that would improve the effectiveness and the timeliness of the regulatory process while maintaining the safety standards that Americans count on everyday will be signed into law this year.

FDA approval is recognized around the world as “the gold standard”. This standard has opened markets, increased demand for U.S. products, and protected consumers. But beyond looking to the FDA to protect us from unsafe products, American patients need the FDA to do its job in a timely manner. The technologies that the FDA regulates are changing rapidly and dramatically. Americans cannot afford a regulatory system ill-equipped to speed those advances.

While the FDA has made great strides in implementing the Re-inventing Government initiatives and expediting review for certain breakthrough drugs, these efforts must be consistent across other new products and for patients suffering from all types of debilitating and life-threatening illnesses.

Many of the provisions in S. 1477 would take a serious step toward addressing Americans’ concerns with the FDA. The legislation would improve the predictability, timeliness and focus of the regulatory process for medical products. The legislation would also improve communication and collaboration between the FDA and the regulated industries. I strongly endorse the view that these objectives can be met and unnecessary regulatory burdens can be minimized without compromising the quality of the review.

COLLABORATIVE PROCESS REFORMS

Because of my interest in achieving a more collaborative process, I strongly support provisions in the legislation to encourage collaboration at the early stages of product development. The bill requires the FDA to provide applicants the opportunity to meet with FDA officials to develop and agree in writing on a protocol for clinical studies. In addition, to facilitate collaboration and communication throughout the review process, the bill requires the FDA to provide for periodic meetings to ensure the applicants would be promptly informed of any deficiencies in their application and that questions could be addressed right away.

Importantly, the committee imposed a structured PMA review cycle on the FDA to ensure that benchmarks define the timeliness

of the agency's review effort for breakthrough medical devices. I believe that improved communication and collaboration during the review process will significantly improve timeliness and benefit both patients and the regulated industries.

In addition, these important provisions would go a long way towards answering concerns about the predictability of the approval process for medical products. An inability to predict processes, costs, and outcomes is about the worst thing that government can impose on business. Companies—especially small companies—must be able to budget for the review process, predict the process, and know that they are being treated fairly. Currently, manufacturers say that decisions and requests for data and additional information are made in an arbitrary manner. I am convinced that both the FDA and the industry would like to make their working relationship less adversarial and more collaborative; these proposals would facilitate that goal. Improving predictability, collaboration and timeliness would lower medical product development costs and enable patients to access new technologies faster.

EFFECTIVENESS STANDARD

I strongly endorse the committee's view that the standard proof of effectiveness for medical devices must be viewed as separate and distinct from that for new drugs. Unlike drugs, medical devices tend to evolve incrementally with new device generations often adding new therapeutic and diagnostic features. In determining the effectiveness of a device, the FDA should accept retrospective data and historical data as a control if data are available that meet the FDA's standards for quality and completeness and the effect of the device on disease progression is well understood. This would leave the FDA the discretion it needs to conduct randomized trials when necessary while at the same time reducing costly and time-consuming requirements on applicants and enabling new and innovative technologies to reach patients in a more timely manner.

RECOGNITION OF PERFORMANCE STANDARDS TO FACILITATE MEDICAL DEVICE REVIEWS

I strongly endorse the requirement that the FDA recognize nationally and internationally recognized consensus performance standards and accept certification by a manufacturer that a device conforms to such standards for the purpose of facilitating medical device review. Currently, the lack of clear performance standards for the review of Class II and III devices is a barrier to the improvement of the quality, timeliness, and predictability of the review process. In addition, the harmonization of performance standards for devices would promote international trade. The FDA would retain full authority to withdraw recognition of a performance standard and to approve or disapprove a premarket application or notification.

OUTSTANDING CONCERNS

Provisions of the legislation that I believe would undermine the ability of the FDA to protect the public and that must be addressed include first and foremost a requirement that the Agency contract

out applications in a particular product category if the Agency has failed to meet the statutory deadline for action on at least 95% of the applications in the product category. While I absolutely agree that the Agency should be held accountable for consistently meeting statutory deadlines, I believe that this provision is unnecessarily harsh and could actually aggravate the ability of the Agency to meet its goals and seriously jeopardize the public health. Under this provision, contracting out would be required even if doing so would increase review costs or if the quality of product reviews by the private contractors could not be assured.

I am also concerned about the elimination of the FDA's ability to require pre-approval for critical manufacturing changes to drugs and biologics under S. 1477. While I understand the benefit of allowing and encouraging companies to make improvements in their manufacturing processes without having to wait for FDA approval, the current language in the bill unacceptably weakens essential oversight of drug and biologic manufacturing.

Because I believe it is essential that we explore new approaches to improving our medical device review process. I voted in favor of Senator Coats' amendment to require the FDA to establish a three year pilot for third party review of Class II and III medical devices. Clearly conflict of interest concerns about arise in a situation where manufacturers are directly paying a private organization for the review of their device. However, this amendment requires that the program be eliminated to a three year pilot, that the FDA accredit the pool of qualified third parties to conduct the reviews, that the manufacturer only be able to choose an accredited reviewer from a list pre-selected by the FDA, and that the FDA retain full authority to make final product review decisions, regardless of the third party decision. It should also be noted that the FDA has already initiated a third party review pilot for medical devices and has taken precautions to mitigate against conflict of interest concerns.

While changes may need to be made to the Coats amendment to clarify the scope of the pilot and ensure that "every device at CDRH" is not eligible for third party review, the intent of this amendment was that the FDA gather meaningful data through the pilot and thus include more types of devices than the current pilot—as long as suitable third parties are available that meet the FDA's accreditation standards. At the end of the three year pilot the FDA and Congress should have the data they will need to be able to evaluate in a meaningful way the quality, timeliness, cost, and potential conflict of interest concerns of third party review.

I am committed to working with Senator Kassebaum and other members of the Committee to address these concerns and to improving some of the other provisions of the bill that may still need work. I have a strong desire to see FDA reform legislation that has the confidence and support of the American people signed into law this year.

PAUL D. WELLSTONE.

IX. CHANGES IN EXISTING LAW

In compliance with rule XXVI paragraph 12 of the Standing Rules of the Senate, the following provides a print of the statute or the part or section thereof to be amended or replaced (existing law proposed to be omitted is enclosed in black brackets, new matter is printed in italic, existing law in which no change is proposed is shown in roman):

FEDERAL FOOD, DRUG, AND COSMETIC ACT

CHAPTER II—DEFINITIONS

SEC. 201. [321] For the purposes of this Act—

(a)(1) * * *

* * * * *

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

(hh) The term “indirect food additive” means a food additive that is intended to contact food but that is not intended for consumption as a food ingredient.

* * * * *

CHAPTER III—PROHIBITED ACTS AND PENALTIES

PROHIBITED ACTS

SEC. 301. [331] The following acts and the causing thereof are hereby prohibited:

(a) * * *

* * * * *

(e) The refusal to permit access to or copying of any record as required by [section 412] *section 412, 504, or 703*; or the failure to establish or maintain any record, or make any report, required [under section 412,] *under section 412, 504, 505 (i) or (k), 507(d) or (g), 512(a)(4)(C), 512 (j), (l) or (m), 515(f), or 519* or the refusal

to permit access to or verification or copying of any such required record.

* * * * *

MISBRANDED FOOD

SEC. 403. [343] A food shall be deemed to be misbranded—

(a) * * *

* * * * *

(C) *Notwithstanding the provisions of subparagraphs (A)(i) and (B), a claim of the type described in paragraph (1)(B) which is not authorized by the Secretary in a regulation promulgated in accordance with subparagraph (B) shall be authorized and may be made if—*

(i) an authoritative scientific body of the United States Government with official responsibility for public health protection or research directly relating to human nutrition (such as the National Institutes of Health or the Centers for Disease Control and Prevention), the National Academy of Sciences, or subdivisions of the scientific body or the National Academy of Sciences, has published statements, conclusions, or recommendations in effect recognizing that the relationship between the nutrient and disease or health-related condition to which the claim refers is supported by pertinent scientific evidence; and

(ii) the manufacturer or distributor of the food for which such claim is made has submitted to the Secretary at least 90 days before the first introduction of such food into interstate commerce a notice of claim, including a concise description of the basis upon which such manufacturer or distributor relied for determining that the requirements of clause (i) have been satisfied.

* * * * *

FOOD ADDITIVES

Unsafe Food Additives

SEC. 409. [348] (a) * * *

* * * * *

Alternative Approval Procedure

(j)(1) As an alternative to the approval procedure established under subsection (b), any person may submit a notification for an indirect food additive under this subsection.

(2) Any person who proposes to begin the introduction or delivery for introduction into interstate commerce of an article intended for use as an indirect food additive may submit to the Secretary, at least 90 days prior to making such introduction or delivery, a notification containing information demonstrating that the labeled use of the article is safe.

(3) Within 90 days after the receipt of the notification by the Secretary, the Secretary shall—

(A) either—

(i)(I) approve the notification if the article is safe for its intended use; or

(II) disapprove the notification if the article has not been shown to be safe for its intended use; and

(B) publish a notice of this determination in the Federal Register and, if the notification is approved, promulgate an appropriate regulation pursuant to subsection (c).

* * * * *

CHAPTER V—DRUGS AND DEVICES

SUBCHAPTER A—DRUGS AND DEVICES

ADULTERATED DRUGS AND DEVICES

SEC. 501. [351] A drug or device shall be deemed to be adulterated—

(a)(1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or (2)(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to [health; or] *health*; (B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identify and strength, and meets the quality and purity characteristics, which it purports or is represented to [possess;] *possess*; or (C) *if it is a drug intended for use by animals other than man and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice requirements (appropriate for animal drugs) adopted pursuant to regulations issued by the Secretary to ensure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to posses for use in animals other than man*; or (3) if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health; or (4) it bears or contains, for purposes of coloring only, a color additive which is unsafe within the meaning of section 721(a), or (B) it is a color additive the intended use of which in or on drugs or devices is for purposes of coloring only and is unsafe within the meaning of section 721(a); or (5) if it is a new animal drug which is unsafe within the meaning of section 512; or (6) if it is an animal feed bearing or containing a new animal drug, and such animal feed is unsafe within the meaning of section 512.

* * * * *

[(e)] (e)(1) If it is, or purports to be or is represented as, a device which is subject to a performance standard established under [section 514] *section 514(b)*, unless such device is in all respects in conformity with such standard.

(2) If it is, or purports to be or is represented as, a device which is certified to be in compliance with any voluntary standard recognized under section 514(c), unless such a device is in all respects in conformity with such a standard.

* * * * *

EXEMPTIONS AND CONSIDERATION FOR CERTAIN DRUGS, DEVICES, AND BIOLOGICAL PRODUCTS

SEC. 503. [353] (a) * * *

* * * * *

(f)(1)(A) A drug intended for use by animals [other than man] other than man, other than a veterinary feed directive drug intended for use in animal feed or an animal feed bearing or containing a veterinary feed directive drug,

* * * * *

VETERINARY FEED DIRECTIVES DRUGS

SEC. 504. (a)(1) A drug intended for use in or on animal feed that is limited by an approved application filed pursuant to section 512(b) to use under the professional supervision of a licensed veterinarian is a veterinary feed directive drug. Any animal feed bearing or containing a veterinary feed directive drug shall be fed to animals only by or upon the lawful veterinary feed directive issued by a licensed veterinarian in the course of the professional practice of the veterinarian. When labeled, distributed, held, and used in accordance with this section, a veterinary feed directive drug and any animal feed bearing or containing a veterinary feed directive drug shall be exempt from section 502(f).

(2) A veterinary feed directive is lawful if it—

(A) contains such information as the Secretary may, by general regulation or by order, require; and

(B) is in compliance with the conditions and indications for use of the drug set forth in the notice published pursuant to section 512(i).

(3)(A) Any persons involved in the distribution or use of animal feed bearing or containing a veterinary feed directive drug, and the licensed veterinarian issuing the veterinary feed directive, shall maintain a copy of the veterinary feed directive applicable to each such feed, except in the case of a person distributing such feed to another person for further distribution, such person distributing the feed shall maintain a written acknowledgment from the person to whom the feed is shipped stating that that person shall not ship or move such feed to an animal production facility without a veterinary feed directive or ship such feed to another person for further distribution unless that person has provided the same written acknowledgment to the immediate supplier of that person.

(B) Every person required under the subparagraph (A) to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(C) Any person who distributes animal feed bearing or containing a veterinary feed directive drug shall upon first engaging in such distribution notify the Secretary of the name and place of business of that person. The failure to provide such notification shall be deemed to be an act which results in the drug being misbranded.

(b) A veterinary feed directive drug and any feed bearing or containing a veterinary feed directive drug shall be deemed to be misbranded if the drug and feed labeling fails to bear such cautionary statement and such other information as the Secretary may, by general regulation or by order, prescribe, or the drug and feed advertising fails to conform to the conditions and indications for use published pursuant to section 512(i) or fails to contain the general cautionary statement prescribed by the Secretary.

(c) Neither a drug subject to this section, nor animal feed bearing or containing such a drug, shall be deemed to be a prescription article under any Federal or State law.

NEW DRUGS

SEC. 505. [355] (a) * * *

* * * * *

(c)(1) * * *

* * * * *

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

* * * * *

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

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and pu-

rity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b); or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is presented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. *Substantial evidence may consist of data from 1 well-controlled clinical investigation and confirmatory evidence obtained prior to, or after, such investigation.*

* * * * *

[(i) The] *(i)(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—*

[(1)] *(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, or preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;*

[(2)] *(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and*

[(3)] *(C) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of*

such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b).

* * * * *

(2)(A) *A clinical investigation of a new drug (including a biological product) may begin 30 days after the date on which the Secretary receives from the sponsor of the investigation a notification containing information about the drug and the clinical investigation unless, prior to the 30-day period, the Secretary informs the sponsor in writing that the investigation may not begin, and specifies the basis for the decision and the information needed in order for the clinical investigation to commence.*

(B) *Not later than 1 year after the date of enactment of the Food and Drug Administration Performance and Accountability Act of 1996, the Secretary, after consultation with experts in the development, clinical investigation, and regulation of drugs, physicians and other health care practitioners, and representatives of patient and consumer advocacy groups and the regulated industries, shall publish in the Federal Register criteria for the type and amount of information relating to the safety of an investigational drug to be included in a notification described in subparagraph (A). In the establishment of the criteria, the Secretary shall take into account the recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The Secretary shall periodically review, and may revise, the criteria.*

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

(3)(A) *The Secretary may place a clinical hold on any ongoing clinical investigation if the Secretary determines that such action is necessary for the protection of human subjects.*

(B) *If the Secretary places a clinical hold on a clinical investigation, the Secretary shall immediately advise the sponsor for the investigation in writing of such action, and provide the sponsor an opportunity to meet with the Secretary not later than 10 business days after the receipt of such a communication to discuss the clinical hold. Not later than 10 days after such a meeting, the Secretary shall provide to the sponsor in writing the conditions for the withdrawal of the clinical hold. Any written request received by the Secretary from the sponsor requesting that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, not later than 20 days after the receipt of the request.*

* * * * *

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

(a) **MARKET EXCLUSIVITY FOR APPROVED APPLICATIONS WITH PEDIATRIC STUDIES SUBMITTED BY AN APPLICANT.**—*If an application submitted under section 505(b)(1) is approved on or after the date of enactment of this section, and such application includes reports of pediatric studies described and requested in subsection (c), and such studies are completed and the reports thereof submitted in accordance with subsection (c)(2) or completed and the reports thereof accepted in accordance with subsection (c)(3), the Secretary may not*

make the approval of an application submitted under section 505(b)(2) or 505(j) that refers to the drug for which the section 505(b)(1) approval is granted effective prior to the expiration of 6 months from the earliest date on which the approval of such application for the drug under section 505(b)(2) or 505(j), respectively, could otherwise be made effective under the applicable provisions of this chapter.

(b) *MARKET EXCLUSIVITY FOR APPROVED APPLICATIONS WITH PEDIATRIC STUDIES REQUESTED BY THE SECRETARY.*—If the Secretary makes a written request for pediatric studies described in subsection (c) to the holder of an approval under section 505(b)(1) for a drug, and such studies are completed and the reports thereof submitted in accordance with subsection (c)(2) or completed and the reports thereof accepted in accordance with subsection (c)(3), the Secretary may not make the approval of an application submitted under section 505(b)(2) or 505(j) that refers to the drug subject to the section 505(b)(1) approval effective prior to the expiration of 6 months from the earliest date on which an approval of such application under section 505(b)(2) or 505(j), respectively, could otherwise be made effective under the applicable provisions of this chapter. Nothing in this subsection shall affect the ability of the Secretary to make effective a section 505(b)(2) or 505(j) approval for a subject drug if such approval is proper under such section and is made effective prior to the submission of the reports of pediatric studies described in subsection (c).

(c) *CONDUCT OF PEDIATRIC STUDIES.*—

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

(2) *WRITTEN PROTOCOLS TO MEET THE STUDIES REQUIREMENT.*—If the sponsor or holder and the Secretary agree upon written protocols for such studies, the studies requirement of subsection (a) or (b) is satisfied upon the completion of the studies in accordance with the protocols and the submission of the reports thereof to the Secretary. Not later than 60 days after the submission of the report of the studies, the Secretary shall determine if such studies were or were not conducted in accordance with the written protocols and reported in accordance with the requirements of the Secretary for filing and so notify the sponsor or holder.

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

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

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

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

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

[CERTIFICATION OF DRUGS CONTAINING INSULIN

[SEC. 506. [356] (a) The Secretary, pursuant to regulations promulgated by him, shall provide for the certification of batches of drugs composed wholly or partly of insulin. A batch of any such drug shall be certified if such drug has such characteristics of identity and such batch has such characteristics of strength, quality, and purity, as the Secretary prescribes in such regulations as necessary to adequately insure safety and efficacy of use, but shall not otherwise be certified. Prior to the effective date of such regulations the Secretary, in lieu of certification, shall issue a release for any batch which, in his judgment, may be released without risk as to the safety and efficacy of its use. Such release shall prescribe the date of its expiration and other conditions under which it shall cease to be effective as to such batch and as to portions thereof.

[(b) Regulations providing for such certification shall contain such provisions as are necessary to carry out the purposes of this section, including provisions prescribing (1) standards of identity and of strength, quality, and purity; (2) tests and methods of assay to determine compliance with such standards; (3) effective periods for certificates, and other conditions under which they shall cease to be effective as to certified batches and as to portions thereof; (4) administration and procedure; and (5) such fees, specified in such regulations, as are necessary to provide, equip, and maintain an adequate certification service. Such regulations shall prescribe no standard of identity or of strength, quality, or purity for any drug different from the standard of identity, strength, quality, or purity set forth for such drug in official compendium.

[(c) Such regulations, insofar as they prescribe tests or methods of assay to determine strength, quality, or purity of any drug, different from the tests or methods of assay set forth for such drug in an official compendium, shall be prescribed, after notice and opportunity for revision of such compendium, in the manner provided in the second sentence of section 501(b). The provisions of subsections (e), (f), and (g) of section 701 shall be applicable to such portion of any regulation as prescribes any such different test or methods, but shall not be applicable to any other portion of any such regulation.

[CERTIFICATION OF ANTIBIOTICS

[SEC. 507. [537] (a) The Secretary, pursuant to regulations promulgated by him, shall provide for the certification of batches of drugs (except drugs for use in animals other than man) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof. A batch of any such drug shall be certified if such drug has such characteristics of identity and such batch has such characteristics of strength, quality, and purity, as the Secretary prescribes in such regulations as necessary to adequately insure safety and efficacy of use, but shall not otherwise be certified. Prior to the effective date of such regulations the Secretary, in lieu of certification, shall issue a release for any batch which, in his judgment, may be released without risk as to the safety and efficacy of its use. Such release shall prescribe the date of its expiration and other conditions under which it shall cease to be effective as to such batch and as to portions thereof. For purposes of this section and of section 502(l), the term "antibiotic drug" means and drug intended for use by man containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including the chemically synthesized equivalent of any such substance).

[(b) Regulations providing for such certifications shall contain such provisions as are necessary to carry out the purposes of this section, including provisions prescribing (1) standards of identity and of strength, quality, and purity; (2) tests and methods of assay to determine compliance with such standards; (3) effective periods for certificates, and other conditions under which they shall cease to be effective as to certified batches and as to portions thereof; (4) administration and procedure; and (5) such fees, specified in such regulations, as are necessary to provide, equip, and maintain an adequate certification service. Such regulations shall prescribe only such tests and methods of assay as will provide for certification or rejection within the shortest time consistent with the purposes of this section.

[(c) Whenever in the judgment of the Administrator, the requirements of this section and of section 502(l) with respect to any drug or class of drugs are not necessary to insure safety and efficacy of use, the Administrator¹ shall promulgate regulations exempting such drug or class of drugs from such requirements. In deciding whether an antibiotic drug, or class of antibiotic drugs, is to be ex-

empted from the requirement of certification the Secretary shall give consideration, among other relevant factors, to—

【(1) whether such drug or class of drugs is manufactured by a person who has, or hereafter shall have, produced fifty consecutive batches of such drug or class of drugs in compliance with the regulations for the certification therefore within a period of not more than eighteen calendar months, upon the application by such person to the Secretary; or

【(2) whether such drug or class of drugs is manufactured by any person who has otherwise demonstrated such consistency in the production of such drug or class of drugs, in compliance with the regulations for the certification thereof, as in the judgment of the Secretary is adequate to endure the safety and efficacy of use thereof.

When an antibiotic drug or a drug manufacturer has been exempted from the requirement of certification, the manufacturer may still obtain certification of a batch or batches of that drug if he applies for an meets the requirements for certification. Nothing in this Act shall be deemed to prevent a manufacturer or distributor of an antibiotic drug from making a truthful statement in labeling or advertising of the product as to whether it has been certified or exempted from the requirement of certification.

【(d) The Administrator shall promulgate regulations exempting from any requirement of this section and of section 502(1), (1) drugs which are to be stored, processed, labeled, or repacked at establishments other than those where manufactured, on condition that such drugs comply with all such requirements upon removal from such establishments; (2) drugs which conform to applicable standards of identity, strength, quality, and purity prescribed by these regulations and are intended for use in manufacturing other drugs; and (3) drugs which are intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and efficacy of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning the exemption under clause (3) upon—

【(1) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of pre-clinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

【(2) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and

【(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such

drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application for certification or release pursuant to subsection (a).

Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

[(e) No drug which is subject to this section shall be deemed to be subject to any provision of section 505 except a new drug exempted from the requirements of this section and of section 502(l) pursuant to regulations promulgated by the Secretary. For purposes of section 505, the initial request for certification, as thereafter duly amended, pursuant to this section, of a new drug so exempted shall be considered a part of the application filed pursuant to section 505(b) with respect to the person filing such request and to such drug as of the date of the exemption. Compliance of any drug subject to section 502(l) or this section with section 501(b) and 502(g) shall be determined by the application of the standards of strength, quality, and purity, the tests and methods of assay, and the requirements of packaging, and labeling, respectively, prescribed by regulations promulgated under this section.

[(f) Any interested person may file with the Administrator a petition proposing the issuance, amendment, or repeal of any regulation contemplated by this section. The petition shall set forth the proposal in general terms and shall state reasonable grounds therefor. The Administrator shall give public notice of the proposal and an opportunity for all interested persons to present their views thereon, orally or in writing, and as soon as practicable thereafter shall make public his action upon such proposal. At any time prior to the thirtieth day after such action is made public any interested person may file objections to such action, specifying with particularity the changes desired, stating reasonable grounds therefor, and requesting a public hearing upon such objections. The Administrator shall thereupon, after due notice, hold such public hearing. As soon as practicable after completion of the hearing, the Administrator shall by order make public his action on such objections. The Administrator shall base his order only on substantial evidence of record at the hearing and shall set forth as part of the order detailed findings of fact on which the order is based. The order shall be subject to the provision of section 701 (f) and (g).

[(g)(1) Every person engaged in manufacturing, compounding, or processing any drug within the purview of this section with respect to which a certificate or release has been issued pursuant to this section shall establish and maintain such records, and make such

reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such person with respect to such drug, as the Secretary may by general regulation, or by order with respect to such certification or release, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to make, or to facilitate, a determination as to whether such certification or release should be rescinded or whether any regulation issued under this section should be amended or repealed. Regulations and orders issued under this subsection and under clause (3) of subsection (d) shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

[(2) Every person required under this section to maintain records, and every person having charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

[(h) In the case of a drug for which, on the day immediately preceding the effective date of this subsection, a prior approval of an application under section 505 had not been withdrawn under section 505(e), the initial issuance of regulations providing for certification or exemption of such drug under this section shall, with respect to the conditions of use prescribed, recommended, or suggested in the labeling covered by such application, not be conditioned upon an affirmative finding of the efficacy of such drug. Any subsequent amendment or repeal of such regulations so as no longer to provide for such certification or exemption on the ground of a lack of efficacy of such drug for use under such conditions of use may be effected only on or after that effective date of clause (3) of the first sentence of section 505(e) which would be applicable to such drug under such conditions of use if such drug were subject to section 505(e), and then only if (1) such amendment or repeal is made in accordance with the procedure specified in subsection (f) of this section (except that such amendment or repeal may be initiated either by a proposal of the Secretary or by a petition of any interested person) and (2) the Secretary finds, on the basis of new information with respect to such drug evaluated together with the information before him when the application under section 505 became effective or was approved, that there is a lack of substantial evidence (as defined in section 505(d)) that the drug has the effect it purports or is represented to have under such conditions of use.]

REGISTRATION OF PRODUCERS OF DRUGS AND DEVICES

SEC. 510. [360] (a) As used in this section—

* * * * *

(k) Each person who is required to register under this section and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device [intended for human use] *intended for human use (except a device*

that is classified inot class I under section 513 or 520 and is not identified in a list under subsection (n), or a device that is classified into class II under section 513 or 520 and is except from the requirements of this subsection under subsection (l)) shall, at least ninety days before making such introduction or delivery, [report to] shall notify the Secretary to report to the Secretary (in such form and manner as the Secretary shall by regulation prescribe)—

* * * * *

The Secretary shall review the notification required by this subsection and make a determination under section 513(f)(1)(A) within 90 days of receiving the notification.

(l) Not later than 30 days after the date of enactment of this subsection, the Secretary shall publish in the Federal Register a list of each type of class II device that does not require a notification under subsection (k) to provide reasonable assurance of safety and effectiveness. Each type of class II device so identified by the Secretary not to require the notification shall be exempt from the requirement to provide notification under subsection (k) as of the date of the publication of the list in the Federal Register. Beginning on the date that is 1 day after the date of the publication of a list under this subsection, any person may petition the Secretary to exempt a type of class II device from the notification requirement of subsection (k). The Secretary shall respond to the petition within 120 days of the receipt of the petition and determine whether or not to grant the petition in whole or in part.

(m) The Secretary may not withhold a determination of the initial classification of a device under section 513(f)(1) because of a failure to comply with any provision of this Act unrelated to a substantial equivalent decision, including a failure to comply with good manufacturing practices under section 520(f).

(n) Not later than 15 days after the date of enactment of this subsection, the Secretary shall publish in the Federal Register a list of each type of class I device that shall not be considered exempt from the notification requirement of section 510(k) because such notification is necessary to protect the public health. If the Secretary fails to publish the list within 15 days after the date of enactment of this subsection, all types of class I devices shall be exempt from the requirement to provide notification under subsection 510(k).

* * * * *

NEW ANIMAL DRUGS

SEC. 512. [306b] (a)(1) * * *

* * * * *

(C) such animal feed, [its labeling] its labeling, its distribution, its holding, and such use conform to the conditions and indications of use published pursuant to subsection (i) of this section and to the application with respect thereto approved under subsection (m) of this section.

* * * * *

(c)(1) Within [one hundred and eighty] 90 days after the filing of an application pursuant to subsection (b), or such additional period as may be agreed upon by the Secretary and the applicant, the

Secretary shall either (A) issue an order approving the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or (B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicants elects to accept the opportunity for a hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

* * * * *

(iii) If a supplement to an application approved under subsection (b)(1) is approved after the date of enactment of this paragraph and the supplement contains **【reports of new clinical or field investigations (other than bioequivalence or residue studies) and】** *substnatial evidence of effectiveness as defined in subsection (d)(4), any study of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) 【essential to】 required* for the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b)(2) for a change approved in the supplement effective before the expiration of 3 years from the date of the approval of the supplement.

* * * * *

(d)(1) * * *

* * * * *

【(F) upon the basis of the information submitted to him as part of the application or any other information before him with respect to such drug, the tolerance limitation proposed, if any, exceeds that reasonably required to accomplish the physical or other technical effect for which the drug is intended;】

(F) on the basis of information submitted to the Secretary as part of the application or any other information before the Secretary with respect to such drug, any use prescribed, recommended, or suggested in labeling proposed for such drug will result in a residue of such drug in excess of a tolerance found by the Secretary to be safe for such drug;

* * * * *

he shall issue an order refusing to approve the application, If, after such notice and opportunity for hearing, the Secretary finds that subparagraphs (A) through (I) do not apply, he shall issue an order approving the application. *Subparagraph (E) shall not apply to a claim for use of the drug described in subparagraph (E) in a minor species, or for a minor use of the drug, as the terms "minor species" and "minor use" are defined in regulations issued by the Secretary,*

if there is an application filed under subsection (b) for the drug, and the application is approved, prior to the submission of the claim.

* * * * *

[(3) As used in this subsection and subsection (e), the term “substantial evidence” means evidence consisting of adequate and well-controlled investigations, including field investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(3) *In a case in which a new animal drug contains more than 1 active ingredient, or the labeling of the drug prescribes, recommends, or suggests use of the drug in combination with another animal drug, and the active ingredients or drugs in the combination have been separately approved for particular uses and species prior to the approval of the application for the same uses and species in combination (or, in the absence of such approvals, after evaluating the safety and efficacy of the combination itself), the Secretary may only consider with respect to the combination whether any of the active ingredients or any of the drugs in the combination, respectively, at the longest withdrawal time of any of the active ingredients or drugs in the combination, respectively—*

(A) *is above its safe concentration (such as exceeding its established tolerance, as measured by its marker residue); or*

(B) *interferes with the methods of analysis for another of the active ingredients or drugs in the combination, respectively.*

(4)(A) *As used in this subsection and subsections (c)(2)(F)(iii) and (e)(1)(C), the term “substantial evidence” means evidence from 1 or more scientifically sound studies, including as appropriate in vitro studies, studies in laboratory animals (including a target species), bioequivalence studies, and any studies voluntarily undertaken by or for the applicant, that taken together provide reasonable assurance that the drug will have the claimed or intended effect of the drug.*

(B) *For purposes of subparagraph (A), a study shall be considered to be scientifically sound if the study is designed and conducted in a manner that is consistent with generally recognized scientific procedures and principles.*

(e)(1) * * *

* * * * *

(C) *on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence (as defined in subsection (d)(4)) that such drug will have the effect if purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof;*

* * * * *

(i) *When a new animal drug application filed pursuant to subsection (b) is approved, the Secretary shall by notice, which upon*

publication shall be effective as a regulation, publish in the Federal Register the name and address of the applicant and the conditions and indications of use of the new animal drug covered by such application, including any tolerance and withdrawal period or other use restrictions and, if such new animal drug is intended for use in animal feed, appropriate purposes and conditions of use (including special labeling **requirements**) *requirements and any requirement that an animal feed bearing or containing the new animal drug be limited to use under the professional supervision of a licensed veterinarian* applicable to any animal feed for use in which such drug is approved, and such other information, upon the basis of which such application was approved, as the Secretary deems necessary to assure the safe and effective use of such drug. Upon withdrawal of approval of such new animal drug application or upon its suspension, the Secretary shall forthwith revoke or suspend, as the case may be, the regulation published pursuant to this subsection (i) insofar as it is based on the approval of such application.

* * * * *

(m)(1) * * *

* * * * *

(i) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports in accordance with a regulation or order under **paragraph (5)(A) of this subsection** *paragraph (5)(A) or under section 504(a)(3)(A)*, or the applicant has refused to permit access to, or copying or verification of, such records as required by **subparagraph (B) of such paragraph** *paragraph (5)(B) or section 504(a)(3)(B)*;

* * * * *

CLASSIFICATION OF DEVICES INTENDED FOR HUMAN USE

Device Classes

SEC. 513. **[360c]** (a)(1) * * *

* * * * *

(3)(A) Except as authorized by subparagraph (B), the effectiveness of devices is, for purposes of this section and sections 514 and 515, to be determined, in accordance with regulations promulgated by the Secretary, on the basis of **well-controlled** *one or more well-controlled investigations*, including **clinical investigations** *one or more clinical investigations* where appropriate, by experts qualified by training and experience to evaluate the effectiveness of the device, from which investigations it can fairly and responsibly be concluded by qualified experts that the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device.

* * * * *

(C) *The Secretary shall accept, for the purpose of facilitating a review of a premarket application, a supplement to a premarket appli-*

cation, or a premarket notification of a device, 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.

(D) The Secretary may not require a person intending to conduct clinical trials to conduct clinical trials using prospective concurrent controls in determining whether there is a reasonable assurance of effectiveness for a device or whether a device is substantially equivalent to a predicate device unless—

- (i) the effects of the device on the cure, mitigation, treatment, or prevention of a disease or condition are not clearly defined and well understood as determined by the Secretary; or
- (ii) retrospective or historical data are not available that meet the standards of the Secretary for quality and completeness; or
- (iii) there is a compelling public health reason to not rely on retrospective or historical data as a control.

* * * * *

Initial Classification and Reclassification of Certain Devices

(f)(1) * * *

* * * * *

A device classified in class III under this paragraph shall be classified in that class until the effective date of an order of the Secretary under paragraph (2) classifying the device in class I or II.], unless within 30 days of receiving an order classifying the device into class III, the individual who submits a notification under section 510(k) requests an advisory committee review and recommendation with respect to the classification of the device and a final order of classification from the Secretary. After the request, a device classified into class III under this paragraph shall not be deemed to be finally classified until an advisory committee established under subsection (b) reviews the request with respect to the classification of the device and, within 60 days of the date of receiving the request, recommends to the Secretary a classification for the device based on the classification criteria set forth in subparagraphs (A) through (C) of subsection(a)(1). Thereafter, the Secretary shall have 10 days after the date of receiving the recommendation of the advisory committee to determine by order the final classification of the device by applying the classification criteria set forth in subparagraphs (A) through (C) of subsection(a)(1).

* * * * *

Substantial Equivalence

(i)(1)(A) For purposes of determinations of substantial equivalence under subsection (f) and section 520(l), the term “substantially equivalent” or “substantial equivalence” means, with respect to a device being compared to a predicate device, that the device has the same intended use, which, as determined by the Secretary, shall include each use reasonably included within a general use, as

the predicate device and that the Secretary by order has found that the device—

* * * * *

(4)(A) Any change or modification to a device initially classified under section 513(f), other than a major change (including any major modification) in the intended use or a change or modification in design that is significant and significantly affects safety or effectiveness, shall not require an additional notification under section 510(k) if, prior to the commercial distribution of the device—

(i) the change or modification is supported by appropriate data or information, (including data or information demonstrating compliance with good manufacturing practice regulations promulgated under section 520(f)); and

(ii) the change or modification is shown by such data or information to not adversely affect the safety or effectiveness of the device.

(B) All data or information relied upon to document that a change to (including any modification of) the device does not require an additional notification under section 510(k) shall be made available to the Secretary upon request and shall be maintained, at least for a period of time equal to the expected life of the device or 2 years after the date of commercial distribution of the device by the manufacturer, whichever is greater.

* * * * *

PERFORMANCE STANDARDS

Provisions of Standards

SEC. 514. [360d] (a)(1) * * *

* * * * *

Performance Standards of Standard-Setting Organizations

(c)(1) For the purpose of facilitating a review of a device under sections 510(k), 513(f), 515, or 520, the Secretary shall recognize appropriate device performance standards developed by any standard setting organization accredited by the American National Standards Institute (ANSI), the International Standards Organization (ISO), or the International Electrotechnical Commission (IEC).

(2)(A) For any standard-setting organization not identified in paragraph (1), and for the purpose of facilitating a review of devices under sections 510(k), 513(f), 515, or 520, the Secretary shall establish a procedure governing the certification by the Food and Drug Administration of the competence of such an organization to develop standards for devices.

(B) A certification of a standard-setting organization not identified in paragraph (1) shall be based on formal, written criteria that include requirements with respect to the role of the organization in the scientific community, scientific or medical expertise, standard writing experience, conflict of interest considerations, and the openness of the standard setting process of the organization.

(C) *The Secretary may impose a reasonable one-time fee on the standard-setting organization for certification pursuant to this paragraph.*

(3)(A) *Upon being notified by a standard-setting organization described in paragraph (1) that a standard has been adopted by the organization, the Secretary shall recognize the standard by publishing a notice in the Federal Register listing the name of the standard.*

(B) *Upon being notified by a standard-setting organization certified under paragraph (2) that a standard has been adopted by the organization, the Secretary shall review and may recognize the standard by publishing a notice in the Federal Register listing the name of the standard.*

(4) *The Secretary may withdraw recognition of a performance standard adopted by a standard-setting organization described in paragraph (1) or a standard-setting organization certified under paragraph (2) if the Secretary determines that the standard is insufficient to facilitate a review of a device. The Secretary shall notify the standard-setting organization and specify the basis for the withdrawal.*

(5) *The Secretary shall promulgate regulations under which the Secretary may withdraw the certification of a standard-setting organization described in paragraph (2), or may no longer rely upon standards adopted by a standard-setting organization described in paragraph (1), if the Secretary determines that such organization no longer possesses the appropriate scientific or medical expertise, conflict of interest practices, standard-writing experience, or any other qualification necessary to the development of device standards.*

(6) *As provided for in this section, the Secretary may promulgate performance standards for a device that differs from or is not established by, an organization described in paragraph (1) or an organization certified under paragraph (2).*

(7) *The Secretary shall not require, as a condition for approving an application under section 515 or 520 or classifying a device under sections 510(k) and 513(f), conformity with a device standard recognized under this subsection if the person requesting such approval or classification submits evidence to demonstrate a reasonable assurance that the device is substantially equivalent to a legally marketed predicate device or provides reasonable assurance that the device is safe and effective.*

(8) *A performance standard recognized pursuant to this subsection for a device—*

(A) shall include provisions to provide reasonable assurance of the safe and effective performance of the device;

(B) shall, where necessary to provide reasonable assurance of the safe and effective performance of the device, include—

(i) provisions with respect to the construction, components, ingredients, and properties of the device and the compatibility of the device with power systems and connections to the systems;

(ii) provisions for the testing (on a sample basis or, if necessary, on an individual basis) of the device or, if it is determined that no other more practicable means are available to the Secretary to assure the conformity of a device to

the standard, provisions for the testing (on a sample basis or, if necessary, on an individual basis) of the device by the Secretary or by another person at the direction of the Secretary;

(iii) provisions for the measurement of the performance characteristics of the device; and

(iv) provisions requiring that the results of each or certain of the tests of the device required to be made under clause (ii) demonstrate that the device is in conformity with those portions of the standard for which the test or tests were required; and

(C) shall, where appropriate, require the procedures, for the proper installation, maintenance, operation, and use of the device.

(9) The Secretary shall accept a certification by a person who has made a submission pursuant to section 510(k), 515, or 520 that the device conforms with each standard identified in the certification. The Secretary may, where appropriate, require data demonstrating conformity with a standard recognized under this subsection.

(10) The Secretary shall require a person who makes a certification under paragraph (9) that a device conforms to an applicable performance standard recognized under this subsection or who makes a certification that a device conforms to a standard established under subsection (a) or (b) to maintain data demonstrating conformity of the device to the standard for a period of time equal to the period of time for the design and expected life of the device. Such data shall be made available to the Secretary upon request.

PREMARKET APPROVAL

General Requirement

SEC. 515. [360e] (a) A class III device—

* * * * *

Action on an Application for Premarket Approval

(d)(1)(A) As promptly as possible, but in no event later than one hundred and eighty days after the receipt of an application under subsection (c) (except as provided in section 520(l)(3)(D)(ii) or unless, in accordance with subparagraph (B)(i), an additional period as agreed upon by the Secretary and the applicant), the Secretary, after considering the report and recommendation submitted under [paragraph (2) of such subsection] *paragraph (4)*, shall—

(i) issue an order approving the application if he finds that none of the grounds for denying approval specified in [paragraph (2) of this subsection] *paragraph (4)* applies; or

(ii) deny approval of the application if he finds (and sets forth the basis for such finding as part of or accompanying such denial) that one or more grounds for denial specified in [paragraph (2) of this subsection] *paragraph (4)* apply. *With respect to an application submitted under this subsection for a device for a life-threatening disease or condition, a seriously debilitating disease or condition, or for any other serious disease or condition that provides therapy or diagnosis not available*

from another approved device or offers a significant improvement over another approved device, the Secretary shall approve or deny the approval of the application within 180 days after the receipt of the application.

(iii) The Secretary shall accept and review data and any other information from investigations conducted under the authority of regulations required by section 520(g) to make a determination of whether there is a reasonable assurance of safety and effectiveness of a device subject to a pending application under this section if—

(I) the data or information is derived from investigations of an earlier version of the device, the device has been modified during or after the investigations, and the modification of the device does not constitute a significant change in the design or in the basic principles of operation of the device that would invalidate the data or information;

or

(II) the data or information on a device approved under this section is available for use under this Act and is relevant to the design and intended use of the device subject to the pending application.

(2) Each application received under section 515(c) shall be reviewed in the following manner to achieve final action on the application within 180 days of the receipt of the application:

(A) The Secretary shall meet with an applicant within 90 days of the receipt of the application to discuss the review status of the application. If the application does not appear in a form that would require an approval under this subsection, the Secretary shall in writing, and prior to the meeting, present to the applicant a description of any deficiencies in the application and what information is required to bring the application into a form that would require an approval.

(B) The Secretary shall refer an application to a panel established under section 513 for review and an approval recommendation, (unless a panel is not required under subsection (c)(2)) within 30 days of the date of the meeting referred to in subparagraph (A) or at the next scheduled panel meeting following the meeting referred to in subparagraph (A), whichever occurs first.

(C) The Secretary shall meet with the applicant within 15 days of the date of the panel review to discuss the status of the application, including a discussion on what action is necessary to bring the application into a form that would require approval under this subsection. Prior to the meeting, the Secretary shall in writing, set forth an agenda for the meeting (including a complete description of the subject matter to be discussed at the meeting), and a full description of the additional information necessary to bring the application into a form that would require an approval under this subsection. Participation of the applicant at such a meeting shall be at the discretion of the applicant.

(D) The Secretary shall meet with the applicant not later than 135 days after the receipt of an application under subsection (c), if an advisory panel is not required under subsection

(c)(2), and inform the applicant whether or not the application is in a form that would require approval under this subsection. If the application is in such form, the Secretary shall, at or prior to the meeting, present in writing to the applicant a description of all additional information necessary to require an approval of the application under this subsection. If the application is not in such form, the Secretary shall deny approval of the application and prior to the meeting, present in writing to the applicant each basis for denying approval of the application and the additional information required to bring the application into a form that would require approval.

(E) The Secretary shall issue an order approving or denying an application within 180 days of the receipt of the application under subsection (c).

(3) The time for the review of an application by the Secretary under this subsection shall not take more than 180 days and such time may not be extended if the application is amended.

[(2)] (4) The Secretary shall deny approval of an application for a device if, upon the basis of the information submitted to the Secretary as part of the application and any other information before him with respect to such device, the Secretary finds that—

* * * * *

[(3)] (5) An applicant whose application has been denied approval may, by petition filed on or before the thirtieth day after the date upon which he receives notice of such denial, obtain review thereof in accordance with either paragraph (1) or (2) of subsection (g), and any interested person may obtain review, in accordance with paragraph (1) or (2) of subsection (g), of an order of the Secretary approving an application.

* * * * *

RECORDS AND REPORTS ON DEVICES

General Rule

SEC. 519. [360i] (a) Every person who is a manufacturer[, importer, or distributor] or importer of a device intended for human use shall establish and maintain such records, make such reports, and provide such information, as the Secretary may by regulation reasonably require to assure that such device is not adulterated or misbranded and to otherwise assure its safety and effectiveness. Regulations prescribed under the preceding sentence—

* * * * *

(4) shall not impose requirements unduly burdensome to a device manufacturer[, importer, or distributor] or importer taking into account his cost of complying with such requirements and the need for the protection of the public health and the implementation of this Act;

* * * * *

(7) may not require that the identity of any patient be disclosed in records, reports, or information required under this subsection unless required for the medical welfare of an individual, to determine the safety or effectiveness of a device, or

to verify a record, report, or information submitted under this Act[;]; *and*

(8) may not require a manufacturer[, importer, or distributor] *or importer* of a class I device to—

(A) maintain for such a device records respecting information not in the possession of the manufacturer[, importer, or distributor], *or importer*, or

(B) to submit for such a device to the Secretary any report or information—

(i) not in the possession of the manufacturer[, importer, or distributor], *or importer*, or

(ii) on a periodic basis,

unless such report or information is necessary to determine if the device should be reclassified or if the device is adulterated or misbranded[; and].

[(9) shall require distributors who submit such reports to submit copies of the reports to the manufacturer of the device for which the report was made.]

* * * * *

Certification

(d) Each manufacturer[, importer, or distributor] *and importer* required to make reports under subsection (a) shall submit to the Secretary annually a statement certifying that—

(1) the manufacturer[, importer, or distributor] *or importer* did file a certain number of such reports, or

(2) the manufacturer[, importer, or distributor] *or importer* did not file any report under subsection (a).

[Device Tracking

[(e) Every person who registers under section 510 and is engaged in the manufacture of—

[(1) a device the failure of which would be reasonably likely to have serious adverse health consequences and which is (A) a permanently implantable device, or (B) a life sustaining or life supporting device used outside a device user facility, or

[(2) any other device which the Secretary may designate, shall adopt a method of device tracking.]

Device Tracking

(e) The Secretary may by regulation require a manufacturer to adopt a method of tracking a class II or class III device—

(1) the failure of which would be reasonably likely to be life-threatening or have serious adverse health consequences; and

(2) which is—

(A) permanently implantable; or

(B) life sustaining or life supporting and used outside a device user facility.

Any patient receiving a device subject to tracking under this section may refuse to release, or refuse permission to release, the patient's name, address, social security number, or other identifying information for the purpose of tracking.

Reports of Removals and Corrections

(f)(1) Except as provided in paragraph (2), the Secretary shall by regulation require a manufacturer~~], importer, or distributor]~~ or importer of a device to report promptly to the Secretary any correction or removal of a device undertaken by such manufacturer, importer, or distributor if the removal or correction was undertaken—

(A) to reduce a risk to health posed by the device, or

(B) to remedy a violation of this Act caused by the device which may present a risk to health.

A manufacturer~~], importer, or distributor]~~ or importer of a device who undertakes a correction or removal of a device which is not required to be reported under this paragraph shall keep a record of such correction or removal.

* * * * *

GENERAL PROVISIONS RESPECTING CONTROL OF DEVICES INTENDED FOR HUMAN USE

General Rule

SEC. 520. ~~360j]~~ (a) * * *

* * * * *

(m)(1) * * *

* * * * *

The request shall be in the form of an application submitted to the Secretary. Not later than 30 days after the date of the receipt of the application, the Secretary shall issue an order approving or denying the application.

* * * * *

[(5) An exemption under paragraph (2) shall be for a term of 18 months and may only be initially granted in the 5-year period beginning on the date regulations under paragraph (6) take effect. The Secretary may extend such an exemption for a period of 18 months if the Secretary is able to make the findings set forth in paragraph (2) and if the applicant supplies information demonstrating compliance with paragraph (3). An exemption may be extended more than once and may be extended after the expiration of such 5-year period.

[(6) Within one year of the date of the enactment of this subsection, the Secretary shall issue regulations to implement this subsection.]

* * * * *

(6) The procedures and conditions prescribed pursuant to paragraph (2)(A) shall be subject to subparagraphs (B) and (C) of section 505(i)(2), except that the provision of subparagraph (B) of such section relating to the consideration of the recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use shall not apply to this paragraph.

(7) The Secretary shall, not later than 120 days after the date of enactment of this paragraph, by regulation amend the content of parts 812 and 813 of title 21 of the Code of Federal Regulations to

update the procedures and conditions under which devices intended for human use may upon application be granted an exemption from certain requirements under this Act. The regulation shall—

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

(B) permit, without approval of a supplement to an application for an investigational device exemption, changes or modifications to clinical protocols that do not affect the validity of data or information resulting from the completion of an approved protocol so long as such changes do not affect any patient protection provisions of the protocol.

* * * * *

【POSTMARKET SURVEILLANCE

【SEC. 522. 【3601】 (a) In General.—

【(1) REQUESTED SURVEILLANCE.—The Secretary shall require a manufacturer to conduct postmarket surveillance for any device of the manufacturer first introduced or delivered for introduction into interstate commerce after January 1, 1991, that—

【(A) is a permanent implant the failure of which may cause serious, adverse health consequences or death,

【(B) is intended for a use in supporting or sustaining human life, or

【(C) potentially presents a serious risk to human health.

【(2) DISCRETIONARY SURVEILLANCE.—The Secretary may require a manufacturer to conduct postmarket surveillance for a device of the manufacturer if the Secretary determines that postmarket surveillance of the device is necessary to protect the public health or to provide safety or effectiveness data for the device.

【(b) SURVEILLANCE APPROVAL.—Each manufacturer required to conduct a surveillance of a device under subsection (a)(1) shall, within 30 days of the first introduction or delivery for introduction of such device into interstate commerce, submit, for the approval of the Secretary, a protocol for the required surveillance. Each manufacturer required to conduct a surveillance of a device under subsection (a)(2) shall, within 30 days after receiving notice that the manufacturer is required to conduct such surveillance, submit, for the approval of the Secretary, a protocol for the required surveillance. The Secretary, within 60 days of the receipt of such protocol, shall determine if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct such surveillance and if such protocol will result in collection of useful data or other information necessary to protect the public health and to provide safety and effectiveness information for the device. The Secretary may not approve such a protocol until

it has been reviewed by an appropriately qualified scientific and technical review committee established by the Secretary.】

SEC. 522. POSTMARKET SURVEILLANCE.

(a) *IN GENERAL.*—The Secretary may require a manufacturer to conduct postmarket surveillance for any device of the manufacturer that—

- (1) is a permanent implant the failure of which may cause serious, adverse health consequences or death;
- (2) is intended for a use in supporting or sustaining human life; or
- (3) potentially presents a serious risk to human health or creates public health concerns that justify surveillance under this section.

(b) *SURVEILLANCE APPROVAL.*—Each manufacturer required to conduct a surveillance of a device under subsection (a) shall, within 30 days of receiving notice from the Secretary that the manufacturer is required under this section to conduct the surveillance, submit for the approval of the Secretary, a protocol for the required surveillance. The Secretary, within 60 days of the date of the receipt of the protocol, shall determine if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct the surveillance and if the protocol will result in collection of useful data or other information necessary to protect the public health and to provide safety and effectiveness information for the device. The Secretary may not approve the protocol until the protocol has been reviewed by a qualified scientific and technical review committee established by the Secretary.

SEC. 523. STATE AND LOCAL REQUIREMENTS RESPECTING NON-PRESCRIPTION DRUGS INTENDED FOR HUMAN USE.

(a) *LIMITATION.*—

(1) *IN GENERAL.*—Except as provided in subsection (b), no State or political subdivision thereof may establish or continue in effect any requirement—

(A) that relates to the regulation of a drug intended for human use that is not subject to the requirements of section 503(b)(1); and

(B) that is different from or in addition to, or that is otherwise not identical with, a requirement of this Act or the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.), and the administrative implementation of such Act.

(2) *SPECIAL RULE.*—For purposes of this section, a requirement relating to the regulation of a drug described in paragraph (1) shall be deemed to include any requirement relating to the subject matter in any provision of this Act, the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.), and any requirement relating to the dissemination of information in any manner about such drug, but shall not include any requirement relating to the dispensing of a drug only upon prescription of a practitioner licensed by law to administer such drug.

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

proposed requirement relating to the regulation of a drug intended for human use—

(1) that is justified by compelling local conditions or protects an important public interest that would otherwise be unprotected;

(2) that would not cause any drug intended for human use that is not subject to the requirements of section 503(b)(1) to be in violation of any applicable requirement or prohibition under Federal law; and

(3) that would not unduly burden interstate commerce.

SEC. 523A. ACCREDITED-PARTY PARTICIPATION.

(a) *IN GENERAL.*—Not later than 1 year after the date of enactment of this section, the Secretary shall accredit persons, including any entity or any individual who is not an employee of the Department to review and initially classify devices under section 513(f)(1) that are subject to a report under section 510(k) and to review and recommend to the Secretary approval or denial of applications submitted under section 515(c)(1).

(b) *ACCREDITATION.*—Not later than 6 months after the date of enactment of this section, the Secretary shall establish and publish in the Federal Register requirements to accredit or deny accreditation to a person who makes a request for accreditation to carry out the activities described in subsection (a). The requirements shall, at a minimum, advise such person how to become accredited, and set forth criteria for accreditation including criteria to avoid conflicts of interest and to ensure that persons to be accredited are capable of maintaining the confidentiality of submissions consistent with section 552 of title 5, United States Code, and the regulations of the Food and Drug Administration. The Secretary shall respond to a request for accreditation not later than 60 days after the receipt of the request. The accreditation of a person shall specify the activities under subsection (a) which such person is authorized to carry out in the place of the Secretary.

(c) *WITHDRAWAL OF ACCREDITATION.*—The Secretary may suspend or withdraw accreditation of any person accredited under this section, after providing notice and an opportunity for an informal hearing, if such person acts or fails to act in a manner that is substantially inconsistent with the purposes of this section, including the failure to avoid conflicts of interest, the failure to protect confidentiality of information, or the failure to competently review premarket submissions for devices.

(d) *SELECTION AND COMPENSATION.*—A person who submits a premarket submission for a device to the Secretary for review and classification, or approval of a device, shall have the option to select an accredited person to review such submission. The Secretary shall identify for the person no less than 2 accredited persons from whom the selection may be made. Compensation for an accredited person shall be determined by agreement between the accredited person and the person who engages the services of the accredited person.

(e) *REVIEW BY SECRETARY.*—

(1) *IN GENERAL.*—If a person exercises the option to obtain review of a premarket submission that is an application or a notification by an accredited person, the Secretary shall complete a filing review for a premarket approval application under section

515(c)(1) not later than 30 days after receipt of such application, or shall ensure the completeness of a premarket notification submission under section 510(k) not later than 15 days after receipt of such submission, prior to referring the premarket submission for review by the accredited person selected by the person submitting the premarket submission.

(2) *REPORT ON CLASSIFICATION, APPROVAL, OR DENIAL.*—The Secretary shall require an accredited person, upon recommending a classification of a device or approval or denial of an application for a device, to report to the Secretary the reasons of the accredited person for such classification or approval or denial. For devices reviewed and initially classified under section 513(f)(1) and subject to a report under section 510(k), the Secretary shall have not more than 15 days to review the submission. For applications submitted under section 515(c)(1), the Secretary shall have not more than 45 days to review the application. The Secretary may change the classification under section 513(f)(1), or the approval or disapproval of the application under section 515(d), that is recommended by the accredited person, and in such case shall notify the person making the submission of the detailed reasons for the change.

(f) *DURATION.*—This section shall remain in force for a period of 3 years from the date on which the Secretary accredits the first person to conduct initial classifications under section 513(f)(1) and to conduct premarket approval reviews under section 515.

(g) *REPORTS.*—

(1) *IMPLEMENTATION OF ACCREDITATION PROCESS.*—Not later than 1 year after the date of enactment of this section, the Secretary shall prepare and submit to the committees of Congress with oversight authority over the Food and Drug Administration a report concerning each action the Secretary has taken to implement the accreditation of persons to undertake the activities described in subsection (a).

(2) *EXAMINATION OF THE USE OF ACCREDITED PERSONS.*—

(A) *IN GENERAL.*—Not later than 2 years after the date on which the Secretary accredits the first person to conduct initial classifications under section 513(f)(1) and to conduct premarket approval reviews under section 515, the Secretary shall contract with an independent research organization to prepare and submit to the Secretary a written report examining the use of accredited persons under this section. The Secretary shall submit the report to the committees described in paragraph (1) not later than 30 months after the date on which the Secretary accredits the first person to conduct initial classifications under section 513(f)(1) and to conduct premarket approval reviews under section 515.

(B) *CONTENTS.*—The report by the independent research organization described in subparagraph (A) shall identify the benefits or detriments to public and patient health of using accredited persons to conduct such reviews, and shall summarize all relevant data, including data on the review of accredited persons (including review times, recommendations, and compensation), and data on the review of the

Secretary (including review times, changes, and reasons for changes).

* * * * *

Subchapter D—Unapproved Therapies and Diagnostics and Collaborative Research

SEC. 551. EXPANDED ACCESS TO UNAPPROVED THERAPIES AND DIAGNOSTICS.

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

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

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

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

(b) *PROTOCOLS.*—A manufacturer or distributor may submit to the Secretary 1 or more expanded access protocols covering expanded access use of a drug or device described in subsection (a). The protocols shall be subject to the provisions of section 505(i) for a drug and section 520(g) for a device and may include any form of use of the drug or device outside a clinical investigation, prior to approval of the drug or device for marketing, including protocols for treatment, use, parallel track, emergency use, uncontrolled trials, and single patient protocols.

(c) *FEES.*—A manufacturer or distributor may assess a fee for an investigational drug or device under an expanded access protocol so long as the fee is not more than that necessary to recover the costs of the manufacture and handling of the drug or device. The Secretary shall be notified in advance of the assessing of any such charges.

(d) *NOTIFICATION OF AVAILABILITY.*—The Commissioner shall inform national, State, and local medical associations and societies, voluntary health associations, and other appropriate persons about the availability of an investigational drug or device under expanded access protocols under this section. Such notification shall identify—

(1) *the investigational drug or device;*

(2) *the expanded access use of the investigational drug or device; and*

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

SEC. 552. COLLABORATIVE RESEARCH DESIGN.

(a) *REVIEW OF DESIGN.*—

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

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

(3) *WRITTEN REVIEW.*—*The Secretary shall meet with the person within 30 days after the request and shall provide to the person a written review of the protocol, including any deficiencies in the protocol. A written summary shall be made of the meeting. The summary shall include the written review of the protocol and, after agreement by the person and the Secretary, shall be made part of the product review file maintained by the Food and Drug Administration.*

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

(1) *An agreement may be modified at any time by mutual consent of the sponsor of a preclinical or clinical investigation and the Secretary.*

(2) *An agreement may be modified by the sponsor unilaterally, if the change is to a protocol and the change is one that would not require the approval of the Secretary under the applicable regulations.*

(3) *An agreement may be modified by the Secretary unilaterally, if the change to the agreement is—*

(A) *made by the director of the office of the Food and Drug Administration responsible for regulating the drug or device that is the subject of the agreement; and*

(B) *set forth in writing, including an explanation of the scientific or clinical need for the change.*

The director described in paragraph (3)(A) may not delegate the regulatory responsibility described in such paragraph.

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

(d) *GUIDELINES AND LIMITATION.*—*The Secretary shall issue guidelines to implement this section. Such guidelines shall address the responsibilities of the person requesting the meeting, as well as the responsibilities of the Secretary. Repeated failure to follow the*

guidelines may be grounds for a refusal by the Secretary to meet with a person requesting a meeting under this section.

* * * * *

CHAPTER VII—GENERAL AUTHORITY

SUBCHAPTER A—GENERAL ADMINISTRATIVE PROVISIONS

REGULATIONS AND HEARINGS

SEC. 701. [371] [(a) The] (a)(1) *The authority to promulgate regulations for the efficient enforcement of this Act, except as otherwise provided in this section, is hereby vested in the Secretary.*

(2)(A) *Not later than 180 days after the date of enactment of the Food and Drug Administration Performance and Accountability Act of 1996, the Secretary shall establish a procedure governing the development and use of all policy statements of general applicability that provide guidance relating to the conduct of preclinical or clinical investigations or other testing to support an application or submission (including a petition, notification, or any other similar form of request) under section 409, 505, 510(k), 512, 515, or 721 or that provide guidance on the submission of an application or submission (including a petition, notification, or any other similar form of request) under section 409, 505, 510(k), 512, 515, or 721 (including any guidance, guideline, points-to-consider, protocol, recommendation, or similar document regardless of the form or designation). The procedure shall provide an opportunity for affected persons to participate in the development and continued use of a policy statement by sharing expertise or experience, or providing comment, before the policy statement is adopted and after the policy statement is implemented, except that if the Secretary determines that there is a public health need to issue the policy statement immediately, the Secretary shall provide an opportunity for affected persons to provide comment promptly after the policy statement is issued.*

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

* * * * *

Subchapter D—Review of Applications, Inspections, Environmental Impact Reviews, and Manufacturing Changes

SEC. 741. CONTENT AND REVIEW OF AN APPLICATION.

(a) **IN GENERAL.**—*This section applies to an application or submission (including a petition, notification, or any other similar form of request) submitted for approval or clearance of a new drug, device, biological product, new animal drug, animal feed bearing or containing a new animal drug, color additive, or food additive.*

(b) **FILING REQUIREMENTS.**—*Not later than 60 days after the date of enactment of this section, the Commissioner shall establish and publish in the Federal Register a mechanism to ensure the fair and consistent application of filing requirements.*

(c) *CLASSIFICATION OF A PRODUCT.*—Not later than 60 days after the receipt of a written request of a person who submits an application or submission (including a petition, notification, or any other similar form of request) for information respecting the classification of an article as a drug, biological product, or device or the component of the Food and Drug Administration that will regulate the article (including a request respecting a combination product subject to section 503(g)), the Secretary shall provide the person a written statement that identifies the classification of the article or the component of the Food and Drug Administration that will regulate the article. The Secretary's statement shall be binding and may not be modified by the Secretary except with the written agreement of the person who submitted the request. If the Secretary does not provide the statement within the 60-day period, the classification and component designated by the person submitting the request shall be final and binding and may not be modified by the Secretary except with the written agreement of the person.

(d) *REASONABLE DATA REQUIREMENTS.*—Not later than 1 year after the date of enactment of the Food and Drug Administration Performance and Accountability Act of 1996, the Secretary, after consultation with experts in the development and testing of articles that are new drugs, biological products, devices, food additives, new animal drugs, animal feed bearing or containing a new animal drug, color additives, or food additives, experts in the regulation of such articles, consumer and patient advocacy groups, and the regulated industries, shall publish in the Federal Register criteria for the type and amount of information relating to safety or effectiveness to be included in an application for the approval of an article that is a new drug, biological product, device, food additive, new animal drug, animal feed bearing or containing a new animal drug, color additive, or food additive, or a new use of an approved article that is a new drug, biological product, device, food additive, new animal drug, animal feed bearing or containing a new animal drug, color additive, or food additive. In establishing the criteria for drugs, the Secretary shall consider any recommendations of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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

- (1) any potential use not included in the labeling;
- (2) the cost-effectiveness of an article described in this subsection, unless the proposed labeling explicitly includes a representation about cost-effectiveness; and
- (3) the clinical outcome resulting from the use of a diagnostic device, unless the labeling explicitly includes a representation regarding clinical outcome.

SEC. 742. CONTRACTS FOR EXPERT REVIEW.

(a) *IN GENERAL.*—

- (1) *AUTHORITY.*—The Secretary may contract with outside organizations and individuals, with expertise in relevant disciplines, to review, evaluate, and make conclusions and rec-

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

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

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

(B) whenever contracts will improve the efficiency, timeliness, and quality of the review of applications or submissions (including petitions, notifications, or any other similar form of requests) for the approval or clearance of new drugs, new animal drugs, biological products, devices, and food additives; and

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

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

(b) *ELIGIBILITY REQUIREMENTS.*—Not later than 90 days after the date of enactment of this section, the Secretary shall by regulation establish the requirements that an organization or individual shall meet to be eligible to conduct reviews under subsection (a). Such regulations shall provide for the protection of confidential or proprietary information and shall provide for protection against conflicts of interest.

(c) *REVIEW OF EXPERT'S EVALUATION.*—

(1) *IN GENERAL.*—Subject to paragraph (2), the official of the Food and Drug Administration responsible for any matter for which expert review is used pursuant to this section shall personally review the conclusions and recommendations of the expert review organization or individual and shall make a final decision regarding the matter under review within 60 days after receiving the conclusions and recommendation.

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

(d) *REPORT TO CONGRESS.*—Not later than 2 years after the date of enactment of this section, the Secretary shall prepare and submit to Congress a report on the use of the authority to contract with outside organizations and individuals for expert reviews. Such report shall include an evaluation of the extent to which such contracting improves the efficiency of review and the expertise available to the Food and Drug Administration.

SEC. 743. PROMPT AND EFFICIENT REVIEW.

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

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

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

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

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

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

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

(b) *REVIEW PROCEDURES AND POLICIES.*—The Secretary shall establish procedures and policies to facilitate a collaborative review process between the Food and Drug Administration and the applicant, petitioner, or person who submits a notification with respect to an application, petition, or notification described in subsection (a).

(a). As part of this collaborative process—

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

(2) meetings (except that meetings shall not be required with respect to matters relating to a notification submitted under section 510(k)) shall be held before the expiration of one-half of the statutory time period for review of the application or petition and before the expiration of three-quarters of such period, or within 15 days after a scientific review group has convened and made recommendations on an application or petition, unless the Commissioner and the applicant or petitioner determine that a meeting is unnecessary;

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

(4) the Secretary shall, prior to the meetings described in paragraph (2), present to the applicant or petitioner in writing a description of any deficiencies of the application or petition and the information necessary to bring the application or petition into a form that would require approval.

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

(c) *APPROVAL, DISAPPROVAL, AND CLASSIFICATION.*—

(1) *CONSIDERATION OF INTERNATIONAL APPROVALS.*—Beginning July 1, 1998, if the Secretary fails to meet a time period for action on an application or notification for the approval or clearance of an article that is a new drug, device, biological product, or new animal drug that offers a significant improvement over an existing approved article or a petition for the approval of a direct food additive that has the potential to make

foods more wholesome and contribute to a healthier diet, , and such an article has been approved for marketing in the European Union or the United Kingdom, the Secretary shall, within 30 days after a request of a person who submits an application, notification, or petition described in this paragraph, either approve or disapprove the application, notification, or petition and notify the person in writing of that decision. In the case of a disapproval, or a determination that a device is not substantially equivalent, such notification shall set forth the reasons for the disapproval or the determination.

(2) APPEAL.—A person whose application, notification, or petition has been disapproved (including a determination that a device does not meet the requirements relating to substantial equivalence) under paragraph (1) may obtain judicial review under—

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

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

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

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

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

(d) CONTRACTS FOR EXPERT REVIEW.—

(1) IN GENERAL.—Beginning July 1, 1998, if the Secretary in any fiscal year fails to meet the statutory time period for action on an application, notification, or petition for at least 95 percent of the applications, notifications, and petitions submitted in a particular product category, the Secretary shall—

(A) in the following fiscal year contract with expert organizations and individuals under section 742, to review applications, notifications, and petitions of persons who submit the applications, notifications, and petitions in that following fiscal year and who consent to the review; and

(B) in the following fiscal year and with the consent of the persons described in this subparagraph, contract with expert organizations and individuals under section 742, to review applications, notifications, and petitions that were submitted by persons in any preceding fiscal year and that the Secretary has failed to review within the statutory time period of action on the applications, notifications, and petitions with respect to the particular product category.

(2) APPROVAL.—If an organization or individual selected to conduct a review under paragraph (1) recommends the approval or clearance of an application, notification, or petition described in paragraph (1), the Secretary shall, within 60 days after receiving the determination of the organization or individual (but not later than the time period for review set forth in this Act), either approve or disapprove the application, notification, or petition, and, in the case of a disapproval, notify the

person who submitted the application, notification, or petition in writing of the basis for the disapproval. The person may appeal an adverse decision under subsection (c)(2).

SEC. 744. GOOD MANUFACTURING PRACTICE INSPECTION.

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

(b) *ELIGIBILITY REQUIREMENTS.*—If the Secretary elects to accredit organizations to conduct inspections under section 704, the Secretary shall by regulation, within 90 days after the date of enactment of this section, establish the requirements that an organization shall meet to be eligible to be accredited to participate as a qualified organization to conduct inspections under subsection (a). Such regulation shall provide for the protection of confidential or proprietary information and shall provide for protection against conflicts of interest.

(c) *ACCREDITATION.*—Not later than 90 days after the date on which the Secretary receives an application for accreditation under this section, the Secretary shall review the application and determine whether an applicant is in compliance with the requirements established under this section. Within the 90-day period, the Secretary shall grant accreditation or shall deny accreditation and specify in writing the reasons for the denial and the requirements that shall be met to obtain accreditation.

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

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

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

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

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

SEC. 745. ENVIRONMENTAL IMPACT REVIEW.

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

(1) that there is a reasonable probability that the environmental impact of the action is sufficiently substantial and with-

in the factors that the Secretary is authorized to consider under this Act; and

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

SEC. 746. MANUFACTURING CHANGES.

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

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

(1) shall require validation; and

(2)(A) if there is no change in the approved qualitative and quantitative formulation relating to the new drug, biological product, or new animal drug or in the approved release specifications relating to the new drug, biological product, or new animal drug, or if there is a change in the approved qualitative or quantitative formula or in the approved release specifications of a type permitted by the Secretary by regulation, may be made at any time so long as the change is reported annually to the Secretary; or

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

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

(1) shall require validation; and

(2)(A) if the change relates solely to a modification of the manufacturing facility or change in personnel, with no change in the approved manufacturing process or release specifications, may be made at any time so long as the change is reported annually to the Secretary; and

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

(d) SPECIAL DETERMINATION FOR A BIOLOGICAL PRODUCT.—A determination shall be made, prior to approval of a biological product under section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)), whether the product can be adequately characterized for purposes of this subsection. With respect to biological products approved prior to the date of enactment of the Food and Drug Admin-

istration Performance and Accountability Act of 1996, the determination shall be made not later than 90 days after the date of enactment of such Act. Any determination made under this subsection is subject to change based upon new scientific information.

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EXPORTS OF CERTAIN UNAPPROVED PRODUCTS

SEC. 802. [382] (a) * * *

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(h) EXPORTATION OF UNAPPROVED PRODUCTS.—Insulin and antibiotics may be exported without regard to the requirements in this section if the insulin and antibiotics meet the requirements of section 801(e)(1).

[(h)] (i) For purposes of this section—

“(1) a reference to the Secretary shall in the case of a biological product which is required to be licensed under the Act of March 4, 1913 (37 Stat. 832–833) (commonly known as the Virus-Serum Toxin Act) be considered to be a reference to the Secretary of Agriculture, and

(2) the term “drug” includes drugs for human use as well as biologicals under section 351 of the Public Health Service Act or the Act of March 4, 1913 (37 Stat. 832–833) (commonly known as the Virus-Serum Toxin Act).

* * * * *

SEC. 903. [393] FOOD AND DRUG ADMINISTRATION.

(a) IN GENERAL.—There is established in the Department of Health and Human Services the Food and Drug Administration (hereinafter in this section referred to as the “Administration”). *The mission of the Administration is to promote and protect the public health by—*

(1) *facilitating the rapid and efficient development and availability of articles subject to the regulation of the Administration;*

(2) *protecting the public from unsafe or ineffective articles subject to the regulation of the Administration; and*

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

(b) COMMISSIONER.—

(1) APPOINTMENT.—There shall be in the Administration a Commissioner of Food and Drugs (hereinafter in this section referred to as the “Commissioner”) who shall be appointed by the President by and with the advice and consent of [the Senate.] *the Senate for a term of 5 years. The Commissioner shall be appointed to serve 1 term. An individual serving in the office of Commissioner may be removed from office only pursuant to a finding by the President of neglect of duty or malfeasance in office.*

* * * * *

(3) PERFORMANCE STANDARDS AND REVIEW.—

(A) IN GENERAL.—*Not later than 180 days after the date of enactment of this paragraph, the Secretary, after con-*

sultation with experts in the development, clinical investigation, and regulation of drugs, biological products, new animal drugs, devices, food additives, and color additives and representatives of patient and consumer advocacy groups, health and technology professionals, and the regulated industries, shall develop and publish in the Federal Register quantifiable performance standards for action by the Administration on—

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

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

(B) REVIEW OF PERFORMANCE STANDARDS.—The performance standards required by subparagraph (A) shall be reviewed annually by the Secretary, and after consultation with experts in the development, clinical investigation, and regulation of drugs, biological products, new animal drugs, devices, food additives, and color additives, and representatives of patient and consumer advocacy groups, health and technology professionals, and the regulated industries, may be revised, annually by the Secretary.

(C) AGENCY OBJECTIVES.—The performance standards required by subparagraph (A) shall establish objectives for the Administration that—

(i) expedite the clinical investigation of an article that is a new drug, device, or biological product through closer collaboration between the Administration and the sponsor of the investigation;

(ii) expedite the review of an application for a new drug, device, or biological product—

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

(II) for any other serious condition if the new drug, device, or biological product provides therapy that is not available from other approved therapy or offers significant improvement over other approved therapy or diagnostic or monitoring agents;

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

(iv) establish a schedule to bring the Administration into full compliance by July 1, 1998, with the time pe-

riods specified in this Act for the review of all applications; and

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

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

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

(i) provides detailed data on the actual performance of the Administration relating to the action taken by the Administration with respect to the applications and submissions described in subparagraph (A)(i) and the activities relating to advisory committees described in subparagraph (A)(ii);

(ii) compares the performance of the Administration with each applicable performance standard developed and published under subparagraph (A);

(iii) describes—

(I) any priorities established with respect to action to be taken by the Administration on matters relating to the applications and submissions described in subparagraph (A)(i) and the activities relating to advisory committees described in subparagraph (A)(ii);

(II) how such priorities are implemented, and

(III) the data on each priority category;

(iv) analyzes any failure to achieve any of the performance standards;

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

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

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

(i) the submission of any investigational application;

(ii) the application of any clinical hold;

(iii) the submission of any application, petition, or notification for approval or clearance;

(iv) the acceptance for filing of any application, petition, or notification for approval or clearance;

(v) the occurrence of any unapprovable action;

(vi) the occurrence of any approvable action; and

(vii) the approval or clearance of any application, petition, or notification.

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

* * * * *

SEC. 904. [394] SCIENTIFIC REVIEW GROUPS.

[Without] (a) *IN GENERAL.*—Without regard to the provisions of title 5, United States Code, governing appointments in the competitive service and without regard to the provisions of chapter 51 and subchapter III of chapter 53 of such title relating to classification and General Schedule pay rates, the Commissioner of Food and Drugs may—

* * * * *

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

(c) *MEMBERSHIP AND MEETING REQUIREMENTS.*—

(1) *SCOPE.*—The Commissioner shall consult with a scientific review group in determining the matters that the group will consider at the meetings of the scientific review group.

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

(3) *TERMS.*—A member of a scientific review group shall serve for a term of 3 years, and may have such membership renewed for not more than 1 additional term. An individual may serve on more than one scientific review group. The chairperson of a scientific review group shall be a member who has served on the scientific group for at least 3 years. The term of the chairperson may be renewed for not more than 3 terms.

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

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

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

(1) *IN GENERAL.*—When a scientific review group reviews an application or submission (including a petition, notification, or any other similar form of request) for approval or clearance, or some part thereof, submitted for an article under section 409, 505, 510(k), 513(f), 512, 515, or 721, the Secretary shall provide the person who submitted the application or submission with copies of all documents provided to the members of the scientific

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

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

(e) *FDA ACTIONS.*—Not later than 60 days after the date a scientific review group makes its conclusions and recommendations on any matter under review of the group, the official of the Food and Drug Administration responsible for the matter shall review the conclusions and recommendations of the group, make a final determination on the matter, and notify the affected persons of the determination in writing and, if the determination differs from the conclusions and recommendations of the group, include the reasons for the difference.

* * * * *

SEC. 906. INFORMATION SYSTEM.

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

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

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

(b) *REVIEW BY SCIENTIFIC REVIEW GROUP.*—

(1) *IN GENERAL.*—The sponsor of a preclinical or clinical investigation, or the applicant for the approval or clearance of an application or submission (including a petition, notification, or

any other similar form of request), shall have the right to request an evaluation by an appropriate scientific review group established under section 904 of any significant scientific issue pending before, or any significant scientific decision made by, the Secretary under this Act. An appropriate scientific review group shall review the request and determine whether to conduct an evaluation within 30 days after the date the request is received by the Secretary.

(2) *SCOPE.*—The significant scientific issues that a scientific review group may evaluate include matters involving a decision by the Secretary not to permit a clinical investigation to begin or to continue, a refusal by the Secretary to file an application, a protocol design, and decisions relating to a pending application or submission (including a petition, notification, or any other similar form of request). The significant scientific issues shall not have been previously reviewed by a scientific review group.

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

(c) *ADDITIONAL INFORMAL AND FORMAL PROCEDURES.*—

(1) *IN GENERAL.*—For purposes of obtaining conclusions and recommendations regarding the resolution of any significant scientific dispute, the Secretary is authorized to use such additional informal and formal procedures as may be considered useful. The procedures may include the use of—

(A) panels of qualified Food and Drug Administration officials to make conclusions and recommendations regarding the resolution of any significant scientific dispute;

(B) panels of qualified Federal Government employees who are not employees of the Food and Drug Administration to make conclusions and recommendations regarding the resolution of any significant scientific dispute; and

(C) outside mediators and arbitrators who are not Federal Government employees to make conclusions and recommendations regarding the resolution of any significant scientific dispute.

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

(d) *REVIEW OF RECOMMENDATIONS.*—Not later than 60 days after the date on which a matter that is presented for resolution under this section has been the subject of conclusions and recommendations, the official of the Food and Drug Administration responsible for the matter shall review the conclusions and recommendations, make a final determination on the matter, and notify the parties of the determination in writing and if the determination differs from the conclusions and recommendations, the reasons for the difference.

SEC. 908. EFFECTIVE MEDICATION GUIDES.

(a) *IN GENERAL.*—Not later than 30 days after the date of enactment of this section, the Secretary shall request that national organizations representing health care professionals, consumer organizations, voluntary health agencies, the pharmaceutical industry, drug wholesalers, patient drug information database companies, and

other relevant parties collaborate to develop a long-range comprehensive action plan to achieve goals consistent with the goals of the proposed rule of the Food and Drug Administration on "Prescription Drug Product Labeling: Medication Guide Requirements" (60 Fed. Reg. 44182; relating to the provision of oral and written prescription information to consumers).

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

- (1) identify the plan goals;
- (2) assess the effectiveness of the current private-sector approaches used to provide oral and written prescription information to consumers;
- (3) develop guidelines for providing effective oral and written prescription information consistent with the findings of any such assessment;
- (4) develop a mechanism to assess periodically the quality of the oral and written prescription information and the frequency with which the information is provided to consumers; and
- (5) provide for compliance with relevant State board regulations.

(c) *LIMITATION ON THE AUTHORITY OF THE SECRETARY.*—The Secretary shall have no authority to implement the proposed rule described in subsection (a), or to develop any similar regulation, policy statement, or other guideline specifying a uniform content or format for written information voluntarily provided to consumers about prescription drugs if, not later than 120 days after the date of enactment of this section, the national organizations described in subsection (a) develop and begin to implement a comprehensive, long-range action plan (as described in subsection (a)) regarding the provision of oral and written prescription information.

(d) *SECRETARY REVIEW.*—Not later than January 1, 2001, the Secretary shall review the status of private-sector initiatives designed to achieve the goals of the plan described in subsection (a), and if such goals are not achieved, the limitation in subsection (c) shall not apply, and the Secretary shall seek public comment on other initiatives that may be carried out to meet such goals. The Secretary shall not delegate such review authority to the Commissioner.

SEC. 909. CENTERS FOR EDUCATION AND RESEARCH ON DRUGS, DEVICES, AND BIOLOGICAL PRODUCTS.

(a) *IN GENERAL.*—The Secretary, acting through the Commissioner, shall establish a consortium of 3 or more centers for research and education on drugs, devices, and biological products in accordance with subsection (b).

(b) *GRANT AUTHORITY.*—The Secretary, acting through the Commissioner, shall make grants to 3 or more private entities to assist each of the entities in the establishment and operation of a center for research and education on drugs, devices, and biological products. In awarding a grant under this subsection, the Secretary shall use a peer-review selection procedure.

(c) *AUTHORIZED GRANT ACTIVITIES.*—

- (1) *REQUIRED ACTIVITIES.*—A grant awarded under subsection (b) shall be used to—
 - (A) conduct state-of-the-art clinical and laboratory research that—

(i) increases awareness of new uses of drugs, devices, or biological products and the unforeseen risks of new uses of drugs, devices, or biological products;

(ii) provides objective clinical information to—

(I) health care practitioners or other providers of health care goods or services;

(II) pharmacy benefit managers;

(III) health maintenance organizations or other managed health care organizations; and

(IV) health care insurers or governmental agencies; and

(iii) improves the quality of health care while reducing the cost of health care through the prevention of adverse effects of drugs, devices, or biological products and the consequences of such effects, such as unnecessary hospitalizations; and

(B) conduct research on the comparative effectiveness and safety of drugs, devices, or biological products.

(2) *DISCRETIONARY ACTIVITIES.*—A grant awarded under subsection (b) may be used to conduct—

(A) surveillance of the adverse effects of drugs, devices, or biological products;

(B) a study of new or unapproved uses for marketed drugs, devices, or biological products; or

(C) a study of the therapeutic characteristics of clinically special populations, such as children, women, and elderly individuals.

(3) *LIMITATION.*—A grant awarded under subsection (b) may not be used to assist the Secretary in the review of new drugs.

(d) *APPLICATION.*—An entity that desires to receive a grant under this section shall submit to the Secretary an application at such time, in such manner, and accompanied by such information as the Secretary may require.

(e) *ESTABLISHMENT OF AN OVERSIGHT COMMITTEE.*—The Secretary shall establish within the Food and Drug Administration a committee to provide oversight of the research and educational activities of the consortium of centers described in subsection (a). The committee shall be composed of—

(1) a representative from each of the centers;

(2) a representative from the Food and Drug Administration;

(3) a representative from consumer advocacy groups; and

(4) a representative from the pharmaceutical, device, or biological products industry.

(f) *REPORT.*—Not later than September 30, 1999, the Secretary shall prepare and submit to the Chairmen and Ranking Members of the Committee on Labor and Human Resources of the Senate and the Committee on Commerce of the House of Representatives a report on the activities of the consortium of centers established pursuant to this section. The report shall include an analysis on the impact of the centers on the safe use of drugs, devices, and biological products and recommendations on whether the funding for the centers should be extended and increased.

(g) *AUTHORIZATION OF APPROPRIATIONS.*—There are authorized to be appropriated to carry out this section \$9,000,000 for fiscal year

1997, \$12,000,000 for fiscal year 1998, \$15,000,000 for fiscal year 1999, and \$15,000,000 for fiscal year 2000.

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PUBLIC HEALTH SERVICE ACT

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PART F—LICENSING—BIOLOGICAL PRODUCTS AND CLINICAL LABORATORIES

SUBPART 1—BIOLOGICAL PRODUCTS

REGULATION OF BIOLOGICAL PRODUCTS

[SEC. 351. [262] (a) No person shall sell, barter, or exchange, or offer for sale, barter, or exchange in the District of Columbia, or send, carry, or bring for sale, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession, any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, of arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man, unless (1) such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product has been propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license, issued by the Secretary as hereinafter authorized, to propagate or manufacture, and prepare such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product for sale in the District of Columbia, or for sending, bringing, or carrying from place to place aforesaid; and (2) each package of such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product is plainly marked with the proper name of the article contained therein, the name, address, and license number of the manufacturer, and the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific results. The suspension or revocation of any license shall not prevent the sale, barter, or exchange of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid which has been sold and delivered by the licensee prior to such suspension or revocation, unless the owner or custodian of such virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid has been notified by the Secretary not to sell, barter, or exchange the same.]

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

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

(B) each package of the biological product is plainly marked with the proper name of the biological product contained therein, the name, address, and applicable license number of the

manufacturer of the biological product, and the expiration date of the biological product.

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

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

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

(i) the product that is the subject of the application is safe and effective in accordance with sections 505(c) and 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355 (c) and (d)), or meets standards designed to ensure that the product is safe, pure, and where appropriate, potent; and

(ii) the methods used in, and the facilities and control used for, the manufacture, processing, packing, and holding of such product meet standards designed to ensure that the product continues to meet the requirements of clause (i).

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

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

(4)(A) Requirements prescribed under paragraph (3) shall include a requirement for preapproval inspection under subsection (c).

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

(5)(A) Except as provided in subparagraph (C), an approved license for a biological product may be revoked if the Secretary determines, on the record after providing opportunity for a hearing in accordance with section 554 of title 5, United States Code, that the requirements for approval specified in paragraph (3) are no longer met with respect to such product, or that other public health reasons, prescribed by regulation, exist. No action to revoke a license based on findings of an inspection shall be initiated prior to the submission and review by the Secretary of a written response submitted by the licensee to a notice of inspectional findings so long as such written response is received within 30 days after the date of receipt by the licensee of the findings. The revocation of any product license shall not prevent the continued use of any licensed biological product that has been sold and delivered by the licensee unless the biological product is subject to recall under subsection (d).

(B) If at any time before the Secretary has taken final action to revoke a license, the licensee requests an inspection by the Secretary to determine whether the licensee is in compliance with applicable standards, the Secretary shall conduct an inspection within 30 days after the date of the request. If the requested inspection confirms

that the licensee is not in compliance with applicable standards, the 30-day requirement for inspection shall not apply to any subsequent request by the licensee under this subparagraph for inspection. If the inspection confirms that the licensee is in compliance with all applicable requirements, the Secretary shall withdraw any proposed action within 30 days after the inspection.

(C) If the Secretary determines that conditions exist that constitute a danger to health, the Secretary shall suspend the license, notify the licensee that the licensee's license is suspended, and require notification of the suspension to any consignee. Within 30 days thereafter, the Secretary shall initiate the hearing process under subparagraph (A).

(6) The requirements of paragraph (1) do not apply to a biological product for which there is in effect an investigational new drug application under section 505(i) of the Federal Food, Drug, and Cosmetic Act.

[(b) No person shall falsely label or mark any package or container or any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid; nor alter any label or mark on any package or container of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid so as to falsify such label or mark.]

(b) No person shall falsely label or mark any package or container of any biological product or alter any label or mark on the package so as to falsify the label or mark.

(c) Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacturer and preparation of any [virus, serum, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid] biological product for sale, barter, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession.

[(d)(1) Licenses for the maintenance of establishments for the propagation or manufacture and preparation of products described in subsection (a) of this section may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations, and they meet such standards. All such licenses shall be issued, suspended, and revoked as prescribed by regulations and all licenses issued for the maintenance of establishment for the propagation or manufacture and preparation, in any foreign country, of any such products for sale, barter, or exchange in any State or possession shall be issued upon condition that the licenses will permit the inspection of their establishments in accordance with subsection (c) of this section.]

[(2)(A)] (d)(1) Upon a determination that a batch, lot, or other quantity of a product licensed under this section presents an imminent or substantial hazard to the public health, the Secretary shall issue an order immediately ordering the recall of such batch, lot, or other quantity of such product. An order under this paragraph

shall be issued in accordance with section 554 of title 5, United States Code.

[(B)] (2) Any violation of [subparagraph (A)] paragraph (1) shall subject the violator to a civil penalty of up to \$100,000 per day of violation. The amount of a civil penalty under this subparagraph shall, effective December 1 of each year beginning 1 year after the effective date of this subparagraph, be increased by the percent change in the Consumer Price Index for the base quarter of such year over the Consumer Price Index for the base quarter of the preceding year, adjusted to the nearest $\frac{1}{10}$ of 1 percent. For purposes of this subparagraph, the term “base quarter”, as used with respect to a year, means the calendar quarter ending on September 30 of such year and the price index for a base quarter is the arithmetical mean of such index for the 3 months comprising such quarter.

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(i) For purposes of this section, the term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic biologic product, or arsphenamine or its derivative (or any other analogous biological product) applicable to the prevention, treatment, or cure of diseases or conditions of human beings.

(j)(1) Sections 505(i), 903, and 904 of the Federal Food, Drug, and Cosmetic Act shall apply to all biological products, and references in such sections to new drug applications shall be deemed to include product license applications for biological products.

(2) Requirements involving labeling or advertising for biological products shall be established in accordance with sections 201(m) and 502(n) of the Federal Food, Drug, and Cosmetic Act.

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PUBLIC LAW 102-222

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SECTION 1. HEALTH EDUCATION ASSISTANCE LOANS.

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SEC. 2. PILOT PROGRAM IN CLINICAL PHARMACOLOGY.

(a) ESTABLISHMENT.—* * *

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(b) AUTHORIZATION OF APPROPRIATIONS.—There is authorized to be appropriated for fiscal years 1992 through 1996 \$750,000 for each fiscal year [to carry out this section], and fiscal years 1997 and 1998 \$1,900,000 for each fiscal year, to carry out this section.

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