THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997

INTRODUCTION

The Food and Drug Administration Modernization Act of 1997 (Modernization Act) is the culmination of a comprehensive legislative reform effort designed to streamline regulatory procedures within the Food and Drug Administration (FDA) and to improve the regulation of drugs, medical devices, and food. Passed by the 105th Congress on November 9, 1997, with wide bipartisan support, the legislation is principally designed to ensure the timely availability of safe and effective drugs, biologics, and medical devices by expediting the premarket review process for new products, while maintaining FDA's "gold standard" for product approval. The majority of the provisions of the Modernization Act take effect 90 days after the date of enactment.

Since passage of the Federal Food and Drugs Act in 1906, and the Federal Food, Drug, and Cosmetic Act (FDC Act) in 1938, FDA's regulatory role has expanded considerably from that of removing unsafe or misbranded products from the marketplace, to determining whether drugs and medical devices are safe and effective for their intended use. FDA's ability to accomplish the duties embodied in this expanded role, however, has not kept pace with the agency's statutory responsibilities, resulting in an overly burdensome regulatory system. The requirements for the clinical testing and premarket review of new products have become increasingly complex, time-consuming, and costly. As a result, patients have been denied timely access to safe and useful drugs and medical devices. In short, during the past twenty years, every administration has recognized the need for reforming FDA and modernizing the agency's product approval system to achieve an appropriate balance between safeguarding the public from risk and facilitating the development, testing, and timely approval of safe and effective products that benefit the public health.

This important legislation improves FDA's public accountability and establishes, for the first time, an FDA mission statement that helps define the scope of the agency's regulatory responsibilities. The legislation amends the FDC Act to require the Secretary of Health and Human

Services (hereinafter FDA) to prepare a plan for implementing FDA's statutory compliance in consultation with appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and the regulated industry. FDA's compliance plan must be published in the Federal Register and reviewed biannually by the agency. This is intended to eliminate backlogs in the drug and medical device approval process and ensure the timely review of applications. As part of the agency's new mission statement, FDA must promptly and efficiently review clinical research and take appropriate action on the marketing of regulated products so that innovation and product availability are not impeded or discouraged.

A key provision of the legislation is the re-authorization of the Prescription Drug User Fee Act of 1992 (PDUFA I), which permits the continued collection of user fees from prescription drug manufacturers to augment FDA resources earmarked for the review of human drug applications. This is essential to provide the resources necessary to ensure the prompt approval of safe and effective new drugs and other therapies. Other important provisions of the legislation include the creation of a statutory fast track approval process for drugs for serious or life-threatening diseases and conditions, the establishment of a data bank of information on clinical trials for such conditions (in collaboration with the appropriate agencies within the National Institutes of Health), the authorization of the use of expert scientific panels in the review of clinical investigations of drugs, and the expansion of the rights of drug and device manufacturers to disseminate treatment information.

The legislation improves the regulation of medical devices through reforms that relate to the review of applications, standards, and data requirements. For example, the legislation includes a provision that mandates priority review for breakthrough technologies in medical devices and grants FDA the authority to contract with outside scientific experts for the review of medical device applications. The legislation also provides for national uniformity in the labeling of over-the-counter drugs (OTC) and cosmetics.

Regarding the regulation of food products, a significant provision of the legislation provides for streamlined procedures and greater flexibility in FDA regulations regarding nutrient content and health claims. The legislation amends the FDC Act to permit health and nutrient content claims on food labels, provided that a scientific body of the U.S. Government has published an authoritative

statement endorsing the claim. Another significant provision of the legislation establishes a "notification" procedure for the marketing of indirect food additives.

The Modernization Act provides a legislative framework that embodies many of the bipartisan conclusions and recommendations made during the past 20 years by expert administrative advisory panels and congressional committees concerned with FDA reform. The legislation reflects congressional concern that FDA's past regulatory practices have hindered the dynamic and innovative growth of America's pharmaceutical, biotech, medical device, and food industries and that the agency has been out of step with recent scientific and technological advances in the development and testing of new products.

During the past few years, these concerns have become more pressing both for Congress and the President, particularly in light of U.S. efforts to harmonize regulatory requirements with other national regulatory authorities, and the European Union's move to adopt a uniform approval system for drugs and medical devices. By streamlining functions at FDA and eliminating outdated regulatory requirements, the legislation addresses an overly complex, burdensome, and expensive regulatory system to make it ready for the 21st century.

Provided below are summaries of the main sections of the Modernization Act in the order that they appear in the law. Title I addresses changes to the law affecting drugs; Title II, devices; Title III, food; and Title IV, the general provisions applicable to all or most product categories.

TITLE I: IMPROVING REGULATION OF DRUGS

Secs. 101 - 107. User fees.

The PDUFA I has been reauthorized for an additional five years. Fiscal Year (FY) 1997 funding levels for FDA must be maintained ("the trigger") before the agency may collect user fees. FDC Act § 736(f)(1).

Under the reauthorization provisions of the Modernization Act (PDUFA II), the entire fee for a human drug (or biologic) application or supplement is due in full on submission of the application (under PDUFA I, only 50 percent of the filing fee was required on submission). § 736(a)(1)(B). The applicant forfeits 25 percent of the total filing fee if the application or supplement is refused for filing. § 736(a)(1)(D). A new provision in PDUFA II provides that if an application or supplement is withdrawn after review begins, a refund or partial refund may be made solely at the discretion of FDA. FDA's determination in such a case is not reviewable. § 736(a)(1)(G).

Certain Applications Are Now Exempt From User Fees

Marketing applications for supplemental applications for pediatric use are exempt from user fees. § 736(a)(1)(F). Designated orphan drugs are also exempt, unless the application "includes an indication for other than a rare disease or condition." § 736(a)(1)(E).

Clarification of Products Subject to User Fees

A biological product that is "licensed for further manufacturing use only," is not subject to the user fee under PDUFA II. However, "a large volume biological product intended for single dose injection for intravenous use or infusion" will be assessed a fee. § 735(1). Applications submitted by State or Federal governmental entities for products that are not distributed commercially are also exempt from user fees. Id.

Clarification of Establishment and Product Fees

Minor clarifications were made to the definitions of "final dosage form" and "prescription drug establishment" for purposes of determining which prescription drug establishments are subject to the fee. Under the new definition, a prescription drug establishment that manufactures a drug product in final dosage form is subject to the fee if the prescription drug product does not require "substantial" further manufacturing. § 735(4) and (5).

PDUFA II also changes the procedures by which prescription drug establishment fees are assessed. Previously, the person that owned a prescription drug establishment was assessed the fee.

PDUFA II will assess the fee against the person that "is named as the applicant in a human drug application" for each establishment that is listed in the application as a manufacturer of that drug, and that actually manufactured the drug during the fiscal year. If "an establishment is listed in a human drug application by more than one applicant," then the establishment fee is divided equally and assessed among the applicants. § 736(a)(2)(A). An establishment that manufactures a drug product during a fiscal year for which the full establishment fee has been assessed before the establishment manufactured the drug, will not be assessed any share of the establishment fee until the next fiscal year. § 736(a)(2)(B).

To correct an unintended result of PDUFA I, manufacturers of antibiotics will not be subject to the product fee once a generic competitor is approved. § 736(a)(3).

New Fee Amounts

Fee amounts have been established as follows: Full application fees are $250,704 in FY 1998, $256,338 in FYs 1999 and 2000, $267,606 in FY 2001, and $258,451 in FY 2002. Fees for other applications are: $125,352 in FY 1998, $128,169 in FYs 1999 and 2000, $133,803 in FY 2001, and $129,226 in FY 2002. § 736(b)(1). Fees will be adjusted for inflation each fiscal year. § 736(c)(1). Also, FDA will adjust the fees each fiscal year according to FDA's annual workload. § 736(c)(2). PDUFA II does not set specific establishment or product fees, but establishes the total revenues from these fees to be collected by FDA per fiscal year. § 736(b)(2) and (3).

Fee Waivers, Reductions, and Refunds

The fee waiver and reduction provisions from PDUFA I have been retained. In addition, small business entities are eligible for a waiver on the first application submitted. Subsequent applications, including supplemental applications, are assessed the full fee. § 736(d)(3)(B). This marks a change from PDUFA I. Small business entities had been assessed one-half the application fee for the first application submitted and were permitted to defer payment of the fee for one year.

PDUFA II adds the requirement that fee waivers, reductions, and refunds must be requested in writing within 180 days after the fee is due. § 736(i). Under PDUFA I, there was no deadline for requesting a waiver, reduction, or refund. Under a special rule, requests for waivers, reductions, and

refunds for fees assessed prior to October 1, 1997 must be submitted within one year of the date of enactment of the Modernization Act. If the request relates to an application that was submitted before October 1, 1997, the request will be evaluated according to PDUFA I.

PDUFA II Performance Goals

Performance goals will be set forth in letters from the Department of Health and Human Services to Congress. Modernization Act § 101(4).

Sec. 111. Pediatric studies of drugs.

Earlier this year, FDA proposed regulations requiring manufacturers to assess the safety and effectiveness for pediatric use of many new drugs. 62 Fed. Reg. 43900 (Aug. 15, 1997). Congress agreed with the purpose behind these proposed regulations, and commended FDA for its efforts, but chose a somewhat different approach.

The Modernization Act adds new section 505A to the FDC Act and extends market exclusivity by six months for clinical studies conducted in pediatric populations. "Pediatric studies" is defined to mean "at least one clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies)" in the intended pediatric age groups. § 505A(g).

Market Exclusivity

If, prior to the approval of a 505(b)(1) application, FDA determines that information about a drug may produce health benefits in a pediatric population, and requests such studies in writing (including a timeframe for completion of the studies), and the studies are completed within the timeframe and accepted by FDA, then the sponsor or manufacturer will qualify for six months of extra market exclusivity. § 505A(a).

Six months may be added to Waxman-Hatch exclusivity and Orphan Drug exclusivity. § 505A(a)(1)(A) and (B). Six months may also be added to market exclusivity if a pioneer drug is the subject of a listed patent and: the patent is certified to be expired; the patent is certified to expire on a certain date and the studies are completed before expiration of the patent (including any patent

extensions); or if the patent is certified to be invalid or not infringed, but a court determines the patient is valid and would be infringed. § 505A(a)(2)(A) and (B).

Market Exclusivity for Already Marketed Drugs

Within 180 days of enactment, FDA must develop, prioritize, and publish a list of approved drugs for which additional pediatric studies may produce health benefits in the pediatric population. The list must be updated annually. § 505A(b). FDA may make a request for pediatric studies for drugs on the list. If FDA makes a written request to the holder of a 505(b)(1) application for pediatric studies (including a timeframe), the holder agrees to the request, completes the studies within the timeframe, and the reports are accepted, then six months may be added to market exclusivity. § 505A(c).

Conduct of Pediatric Studies

There are two ways for conducting requested pediatric studies. First, FDA and the sponsor (or holder) of a 505(b)(1) application can agree on the conduct and timeframe of the pediatric studies. If FDA and the sponsor (or holder) agree on written protocols for the studies, when the studies are completed and the reports are submitted, FDA has 60 days to notify the sponsor (or holder) whether the studies were conducted in accordance with the written request and agreement and were reported in accordance with FDA's filing requirements. § 505A(d)(1) and (2).

Second, in the absence of a written protocol agreement, FDA has 90 days to accept or reject the submitted reports and so notify the sponsor (or holder). FDA's responsibility is to determine "whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols," and have been reported in accordance with FDA's filing requirements. § 505A(d)(3). In either case, FDA must publish a notice of any determination that the requirements for conduct of pediatric studies have been met, and that submissions and approvals under 505(b)(2) and 505(j) will be subject to the additional period of exclusivity. § 505A(f).

Delay of Effective Date for Certain Applications

If pediatric studies are submitted prior to expiration of a patent or Waxman-Hatch exclusivity, but have not been accepted or rejected by FDA at the time of the expiration, then approval of 505(b)(2) and 505(j) applications may be delayed up to 90 days while FDA reviews the pediatric studies. The six months of exclusivity runs during this period of delay. § 505A(e).

Limitations

Additional exclusivity is limited to one award per product, with one exception. If a drug is awarded six months of exclusivity that is added to three years of Waxman-Hatch exclusivity, the applicant can obtain an additional six months of exclusivity by obtaining approval of a supplemental new drug application (NDA) for a new pediatric indication. However, this second six-month period may not be added to FDC Act patent protections or orphan drug exclusivity. § 505A(h).

Sunset

No additional exclusivity is available unless the 505(b)(1) application is submitted on or before January 1, 2002, with one exception. Six months of exclusivity is available if a drug is in commercial distribution as of the date of enactment of the Modernization Act, the drug is included in FDA's list as of January 1, 2002, and FDA determines there is a continuing need for pediatric information about the drug. § 505A(j).

Sec. 112. Expediting study and approval of fast track drugs.

This provision replaces section 506 of the FDC Act in its entirety. New section 506 essentially codifies FDA's accelerated approval regulations for drugs and biologics. See 21 C.F.R. Part 314, Subpart H, and 21 C.F.R. Part 601, Subpart E.

FDA shall, at the request of a sponsor, "facilitate the development and expedite the review" of a drug "if it is intended for treatment of a serious or life-threatening condition and it demonstrates

the potential to address unmet medical needs for such a condition." § 506(a)(1). Congress defined "serious and life-threatening" using FDA's definition published in the preamble to the proposed accelerated approval regulations. House Report 105-310 at 55-56 (1997) (see also 57 Fed. Reg. 13234 (April 15, 1992)).

The Modernization Act refers to such a drug as a "fast track product." The sponsor of a new drug may request FDA to designate the drug a fast track product with, or at any time after, the submission of an investigational new drug application (IND). § 506(a)(2). FDA must decide whether the drug is a fast track product within 60 days of the request for designation. § 506(a)(3).

Approval of an application for a fast track product can be based on an effect on a clinical endpoint, or on a surrogate endpoint that is reasonably likely to predict clinical benefit. § 506(b)(1). As with FDA's accelerated approval regulations, approval of a fast track product may be subject to post-approval studies to validate the surrogate endpoint or confirm the effect on the clinical endpoint, and prior review of promotional materials. § 506(b)(2). Approval of a fast track product may be withdrawn under expedited procedures (which must include an informal hearing) if the sponsor fails to conduct a required post-approval study with due diligence, a post-approval study fails to verify clinical benefit, other evidence indicates the fast track product is not safe or effective under the conditions of use, or the sponsor disseminates false or misleading promotional materials. § 506(b)(3).

The Modernization Act directs FDA to initiate review of an application for a fast track product before the application is complete. If a preliminary review of the clinical data suggests efficacy, FDA must evaluate for filing, and may review, portions of the application. This "rolling review" is available if the applicant provides a schedule for submission of remaining information and pays any user fee. § 506(c)(1). However, the PDUFA review clock does not begin to run until the application is complete. § 506(c)(2).

FDA is required to increase the awareness of this provision by disseminating a description to physicians, patient organizations, and pharmaceutical and biotechnology companies. § 506(d)(1). FDA must also establish a program to encourage development of surrogate endpoints for fast track products. § 506(d)(2). Finally, FDA must provide policy and procedure guidance within one year of enactment of the statute. Modernization Act § 112(b).

Sec. 113. Information program on clinical trials for serious or life-threatening diseases.

Physicians treating patients with cancer and AIDS currently have access to information on clinical trials for these diseases through two government supported databases, PDQ® (Physician's Data Query) for cancer and ACTIS (AIDS Clinical Trial Information Service) for HIV and AIDS. The PDQ system was established by the National Cancer Institute (NCI) and the ACTIS system was developed as a result of the Health Omnibus Programs Extensions Act of 1988. Public interest in the information contained in both databases is high and now Congress seeks to expand the availability of clinical trial information to other patients with serious or life-threatening illnesses. Specifically, the Modernization Act amends section 402 of the Public Health Service Act (PHS Act) (42 U.S.C. § 282) to require the Director of the National Institutes of Health (NIH) to establish, maintain and operate a databank on clinical trials for drugs for serious or life-threatening diseases and conditions. Notably, information on devices is not included, but the statute provides that a report on the feasibility of including information on device investigations must be submitted to Congress within two years.

The databank is to include information describing the purpose of each experimental drug as well as eligibility criteria, a description of the location of trial sites and a point of contact for those wanting to enroll. Information on treatments available under treatment INDs and Group C cancer drugs (as defined by the NCI) will also be included. With the consent of the sponsor, other information such as the results of the trials, including information on potential toxicities or side effects of the treatments may be included in the databank.

Like the ACTIS database (and unlike PDQ), inclusion of industry trials in this new databank will be mandatory. Although submission of the data may initially be made by sponsors on a voluntary basis, it must be forwarded no later than 21 days following approval of the trial by FDA. A sponsor can request that information on a specific investigation not be disclosed in the databank, provided that the sponsor has submitted a detailed certification to FDA that disclosure of the information would substantially interfere with the timely enrollment of subjects in trial. However, the final determination of whether to include the information will rest with FDA.

Sec. 114. Health care economic information.

FDA policy currently requires pharmacoeconomic claims made in labeling or advertising to be supported by two well-controlled clinical studies. FDA Division of Drug Marketing, Advertising, and Communications (DDMAC), Principles for the Review of Pharmacoeconomic Promotion (Draft), Mar. 20, 1995. The Modernization Act amends section 502(a) of the FDC Act to establish more flexible standards for the dissemination of cost-effectiveness and other pharmacoeconomic information by manufacturers of drugs and biologics to certain categories of customers and potential customers.

The new standards apply to "health care economic information," which is defined as any analysis that identifies, measures, or compares the economic consequences, including costs of health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention. Such information will not be considered false or misleading, nor to violate new drug application (NDA) or biologic licensing restrictions, if: it is provided to a "formulary committee or similar entity" that selects drugs for managed care or similar organizations; it "directly relates" to an approved indication; and it is based on "competent and reliable scientific evidence."

The provision requires that a manufacturer's data substantiating health care economic information be made available to FDA on request.

Sec. 115. Clinical investigations.

The Modernization Act amends section 505(d) of the FDC Act to provide that, when appropriate, based on relevant science, the “substantial evidence” of efficacy required for approval of a new drug application may consist of data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation). The provision simply provides FDA the explicit statutory authority to approve a new drug based on data from a single trial (and confirmatory evidence), which the agency has already acknowledged it has the discretion to do.

The Modernization Act also amends section 505(b)(1) of the FDC Act to require FDA to develop guidance on the inclusion of women and minorities in the trials relied upon to establish effectiveness. In developing the guidance, FDA is to consult with both NIH and representatives of the drug manufacturing industry.

Sec. 116. Manufacturing changes for drugs.

The Modernization Act adds a new section 506A to the FDC Act, which establishes requirements relating to manufacturing changes for new drugs and biologics.

Specifically, the provision requires that, whenever a change is made in the manufacture of a new drug or biologic, the manufacturer must validate the effect of that change on the identity, strength, quality, purity, and potency of the drug as those characteristics relate to the safety or effectiveness of the drug, before the product is distributed. However, the requirements for reporting the manufacturing change to FDA vary depending on the nature of the change.

For major changes, manufacturers must submit a supplemental application, and the drug cannot be distributed until the supplemental application has been approved. Major changes are defined as those determined to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as those characteristics relate to the safety or effectiveness of the drug. Such a change includes a change that: is made in the qualitative or quantitative formulation of the drug involved or in the specifications in the approved application or license; is determined in an FDA regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug as manufactured without the change; or is another type or change determined in an FDA regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug.

Other changes, as determined by FDA, will fall into two categories: changes that may be made and implemented immediately and reported to FDA; or those changes that will require a supplemental application but which may be implemented if FDA has not notified the company within 30 days after submission of the supplemental application that a prior approval is required.

FDA also has the authority to identify changes that may be implemented at the time a supplemental application is submitted.

New section 506A of the FDC Act will take effect when implementing regulations are promulgated, or 24 months after the date of enactment of the Modernization Act.

Sec. 117. Streamlining clinical research on drugs.

The Modernization Act amends section 505(i) of the FDC Act. The provision codifies FDA's IND regulations in several respects. This section provides that a clinical investigation of a new drug may begin 30 days after the sponsor or manufacturer submits certain information, including information on the design of the investigation, certified reports of basic information necessary to assess safety, chemistry and manufacturing information, controls available for the drug, and tabular data from animal or human studies. § 505(i)(2).

FDA may impose a clinical hold based on a determination, confirmed in writing, that the drug represents an unreasonable risk to the safety of the subjects (considering the qualifications of the investigators, information about the drug, the design of the study, the condition for which the drug is to be investigated, and the health of the subjects). FDA may also impose a clinical hold for any other reasons established by regulation (including reasons established by regulation prior to the date of enactment of the Modernization Act). § 505(i)(3)(A) and (B).

In a provision that has no counterpart in FDA's regulations, a sponsor may request, in writing, that a clinical hold be removed. The request must include "sufficient information to support the removal" of the clinical hold. The Modernization Act requires FDA to respond within 30 days and to specify the reasons a clinical hold was not removed. § 505(i)(3)(C).

Sec. 118. Data requirements for drugs and biologics.

In a provision not intended to be codified in the FDC Act, the Modernization Act requires FDA to publish guidance describing when abbreviated study reports may be submitted in lieu of full reports in NDAs and biologics license applications (BLAs). FDA must identify the types of studies

for which abbreviated reports may be submitted and must develop appropriate abbreviated report formats.

Sec. 119. Content and review of applications.

The Modernization Act amends sections 505(b) and 505(j) of the FDC Act to bring more certainty to the recommendations provided by FDA staff in the review of plans for the development of trials to support both NDAs and ANDAs.

First, FDA is required, upon a reasonable written request, to meet with sponsors of INDs or applicants for NDAs or ANDAs to agree on the design of clinical trials intended to form the basis of effectiveness claims, or, in the case of ANDAs, to agree on the design of bioavailability and bioequivalence studies. Minutes of the meeting will be kept by FDA and are available to sponsors upon request. Moreover, any agreement reached between the sponsor and FDA on the design of a clinical trial must be documented and made part of the administrative record.

These agreements may not be changed after testing begins, except upon written agreement of the sponsor or upon a written decision by the director of the reviewing division that a "substantial scientific issue essential to determining the safety or effectiveness of the drug" was identified after testing began. The sponsor must be given an opportunity for a meeting on the issue. Any such decision by a director is binding and cannot be changed by the field or compliance personnel, unless that staff person can demonstrate to the director why the change is needed. Decisions by the director or the reviewing division will be in writing and sponsors will have the opportunity for a meeting at which the director will document the scientific issues involved.

The Modernization Act also requires FDA to issue guidance to agency reviewers. The guidance documents are to address the objectivity, promptness, technical excellence, and knowledge of regulatory and scientific standards required for conducting reviews. The standards established in these documents are to apply to all reviewers.

Sec. 120. Scientific advisory panels.

New section 505(n) of the FDC Act requires FDA to establish advisory committees, or rely on existing advisory committees, to provide expert advice and recommendations to FDA on clinical investigations of drugs or biologics and agency approval of these products. In general, these provisions codify the policies and procedures expressed in FDA's Handbook for FDA Advisory Committees (1994).

Each panel must consist of members qualified by training and experience to evaluate the safety and effectiveness of drugs referred to the panel. The members, "to the extent feasible," will be experienced "in the development, manufacture, or utilization of such drugs." § 505(n)(3)(A). The Modernization Act requires committees to include "members with diverse expertise" and specifically mentions the fields of "clinical and administrative medicine" and "pharmacoeconomics." § 505(n)(3)(B). A consumer representative, "a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel," and "two or more members" who have particular expertise in the disease or condition for which the drug is being reviewed must be on each committee. § 505(n)(3)(C) and (D).

The Modernization Act also provides for the disclosure of possible conflicts of interest of the committee members, orders FDA to educate and train advisory committee members, and provides for the compensation of advisory committee members. § 505(n)(4)-(6). FDA may not grant a conflict of interest waiver when the committee member's own scientific work is involved.

Advisory committee matters must be "presented to the panel not more than 60 days after the matter is ready for such review" and electronic communication may be used to convene the meeting. § 505(n)(7). Within 90 days of a recommendation by the scientific panel, FDA must review the recommendations, "and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached." Final decisions, including a rationale for the decision, must be documented. § 505(n)(8).

Sec. 121. Positron emission tomography.

The Modernization Act adds a new section 201(ii) to the FDC Act to define "compounded positron emission tomography drug."

Mostly in provisions not intended to be codified in the FDC Act, the new law imposes a moratorium on the application to positron emission tomography (PET) drugs of section 505 of the FDC Act, which requires the premarket approval of new drugs. The moratorium extends also to the application of current good manufacturing practice requirements (GMP). During the moratorium, the preparation of PET drugs would be required to conform only to PET compounding standards and applicable monographs of the United States Pharmacopeia (USP). The moratorium in both cases ends after the later of (1) four years, or (2) two years following the issuance by FDA of new GMP requirements and procedures for section 505 approval of PET drugs.

Within two years after enactment, FDA is required to issue appropriate procedures for the approval of PET drugs. Appropriate GMP requirements must also be developed. In developing the GMP requirements and approval procedures, FDA is to take into account any relevant differences between not-for-profit institutions that compound the drugs for their patients, and commercial manufacturers. FDA is also required to consult with patient advocacy groups, professional associations, manufacturers, physicians, and scientists prior to establishing the approval procedures and GMP requirements.

FDA is directed to revoke inconsistent, previously issued agency documents relating to premarket approval and GMP requirements for PET drugs. During the moratorium, the IND requirements will continue to apply to PET drugs.

Sec. 122. Requirements for radiopharmaceuticals.

A provision not intended to be codified in the FDC Act acknowledges the special characteristics of radiopharmaceuticals used for diagnostic and monitoring purposes that should be taken into account in evaluating their safety and efficacy. "Radiopharmaceutical" is defined, for purposes of this section only, as: (1) an article (A) that is intended for use in the diagnosis or monitoring of a disease or a manifestation of a disease in humans; and (B) which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons; or (2) any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such article. This provision does not apply to therapeutic radiopharmaceuticals.

Not later than 180 days after enactment, FDA must issue regulations governing the approval of radiopharmaceuticals. The regulations must provide that the determination of safety and effectiveness should include consideration of (1) the proposed use of the radiopharmaceutical in the practice of medicine, (2) the pharmacological and toxicological activity of the radio-pharmaceutical (including any carrier or ligand component), and (3) the estimated absorbed radiation dose of the radiopharmaceutical.

In addition, the provision acknowledges that the indications for which radiopharmaceuticals are used may, in appropriate cases, refer to manifestations of disease (such as biochemical, physiological, anatomic, or pathological processes) common to or present in one or more disease states. This provision addresses diagnostic radiopharmaceuticals that are used to provide images of processes in the body that may be caused by a number of different disorders. Consistent with this manner of use, the provision permits the indications for such a radiopharmaceutical, in clinically appropriate cases, to refer to such processes rather than referring to the specific underlying disorders.

Sec. 123. Modernization of regulation.

Biological Products

The Modernization Act revises section 351 of the PHS Act to make the approval and review process for biologics more similar to the one for other drugs. The most important change is that the new law requires only one license to market a biological product, a biological license application (BLA), eliminating the need for a separate license for the facility, i.e., the establishment license application (ELA).

A definition of "biological product" has been added as new section 351(i) of the PHS Act. Revised section 351(a) of the PHS Act states that a biological product may not be introduced into interstate commerce unless the product has a biologics license, and the package is marked with the product's name, the manufacturer's name, address, and license number, and the product's expiration date. By regulation, FDA must establish requirements.

The Modernization Act directs FDA to take measures to minimize the differences in the review and approval of biological products and other drugs. FDA is required to establish, by regulation, the requirements for the approval, suspension, and revocation of a biologics license. Biologics must be demonstrated to be "safe, pure, and potent." The applicant must demonstrate that its facility is in compliance with GMPs, and agree to a preapproval inspection of the facility for compliance with GMPs.

Clinical Laboratories Improvement Act (CLIA)

The Modernization Act amends section 353 of the PHS Act to provide that approval of a test for home use by FDA results in waived status under the CLIA. This provision clarifies that when FDA already has determined that a diagnostic product, available either by prescription or OTC, can be used safely and effectively by a layperson at home, such a product should not require additional review or action to determine whether CLIA requirements can be waived for this product. Congress included this provision because the Centers for Disease Control and Prevention (CDC) has denied waived status for at least one test approved for home use.

Sec. 124. Pilot and small scale manufacture.

The Modernization Act amends sections 505(c) and 512(c) of the FDC Act to provide that a new drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval prior to manufacture of the drug in a larger facility. FDA retains the authority to require full-scale production prior to approval.

Sec. 125. Insulin and antibiotics.

The Modernization Act repeals sections 506 and 507 of the FDC Act. This has the effect of eliminating the requirements for batch certification of insulin and certain antibiotic products. Moreover, the repeal of section 507 also results in applications for new antibiotics being submitted to the FDA under section 505, which provides these products the benefits of the Waxman-Hatch exclusivity provisions.

Sec. 126. Elimination of certain labeling requirements.

The Modernization Act amends section 503(b)(4) of the FDC Act to eliminate the requirement for inclusion of the label statement "Caution: Federal law prohibits dispensing without a prescription." The new requirement is the inclusion of the symbol "Rx only," at a minimum.

The labeling requirement of section 502(d) for "habit forming" drugs has been eliminated.

Sec. 127. Application of Federal law to practice of pharmacy compounding.

The Modernization Act adds a new section 503A to the FDC Act to exclude compounded drugs from the FDC Act's provisions for new drugs and GMPs, provided that the drugs are compounded according to specific requirements. New section 503A, which does not apply to radiopharmaceuticals or compounded PET drugs, takes effect one year after enactment.

Under new section 503A, a licensed pharmacist or licensed physician may compound drugs for an identified individual patient based on a valid prescription. In certain situations, a drug may be compounded before receiving a prescription. New section 503A(b) imposes several restrictions on compounding, one of which limits the bulk drug substances that may be used in compounding. Another restriction prevents the compounding of drugs that were withdrawn or removed from the market because they are unsafe or not effective; these drugs will appear on a list published by FDA. New section 503A(b) prohibits routine compounding or compounding in "inordinate" amounts of drugs which are copies of commercially available drugs. This section also prohibits compounding of drugs that FDA will identify in regulations as presenting demonstrable difficulties in compounding which adversely affect the drug's safety and effectiveness.

A state and FDA may enter into a memorandum of understanding (MOU) to address the distribution of "inordinate" amounts of compounded drugs interstate and to provide for appropriate state investigation of complaints on compounded drugs that are distributed outside that state. If a state does not enter into an MOU, a pharmacy or physician may distribute compounded drugs outside that state, but may not distribute an amount that exceeds five percent of the total prescriptions distributed or dispensed by the pharmacy or physician. The advertising and promotion of the

compounding of a specific drug, class of drug, or type of drug is prohibited, but advertising and promotion of compounding services is permitted.

Sec. 128. Reauthorization of clinical pharmacology program.

This provision reauthorizes grants for a pilot program for training individuals in clinical pharmacology at medical schools. Under The Health Education Assistance Loan Legislation of 1991, the Commissioner of FDA was authorized to award a grant for a pilot program for the training of individuals in clinical pharmacology at an appropriate medical school without such a program.

Sec. 129. Regulations for sunscreen products.

In a provision not intended to be codified in the FDC Act, the Modernization Act provides that not later than 18 months after the date of enactment, FDA must publish regulations for OTC "sunscreen products for the prevention or treatment of sunburn." This refers to the publication of FDA's final monograph for sunscreens in the agency's OTC Drug Review, which has been pending for almost 20 years.

Sec. 130. Reports of postmarketing approval studies.

The Modernization Act adds a new section 506B to the FDC Act to require sponsors who have agreed to conduct a postmarketing study to submit a report on the status of that study within one year after approval of the drug, and annually thereafter until the study is completed or terminated. The report is to describe the progress on the study or the reasons for failure to undertake the study.

New section 506B applies to all agreements to undertake postmarketing studies entered into prior to the date of enactment. Sponsors who have entered into those agreements have six months from the date that FDA issues regulations on the report format to submit an update. Any information provided to FDA in the reports will be considered public to the extent that the information is necessary to identify the sponsor and to establish the status of a study and the reasons, if any, for

failure to carry out the study. This information will then be published annually by FDA in the Federal Register.

By October 1, 2001, FDA must submit a report to Congress summarizing the reports received and evaluating the performance of sponsors in fulfilling the agreements with respect to postmarketing studies. The report will also include an evaluation of the timeliness of FDA's review of the postmarketing studies and any recommendations concerning the postmarketing studies.

Sec. 131. Notification of discontinuance of a life saving product.

The Modernization Act adds a new section 506C to the FDC Act to require a sole manufacturer of a drug that is life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition, to give FDA at least six-months' notice of plans to discontinue manufacture of the product. This requirement does not apply when a product originally derived from human tissue is replaced by a recombinant product.

The notice period may be reduced if the manufacturer certifies that good cause exists for the reduction. Examples of "good cause" include: a public health problem that may result from continued manufacture; the lack of adequate biomaterial for manufacture; economic hardship or increased product liability for the manufacturer from continued manufacture; availability of a six-month supply for distribution during the six-month period; or the manufacturer has filed for bankruptcy.

TITLE II: IMPROVING REGULATION OF DEVICES

Sec. 201. Investigational device exemptions.

The Modernization Act amends section 520(g) of the FDC Act to require FDA to promulgate within one year of enactment new regulations pertaining to devices under investigational device exemptions (IDEs). These regulations are to establish the procedures and conditions under which an IDE sponsor may make developmental changes to its device, including manufacturing changes, or changes in the clinical protocol, without submitting an additional IDE application or supplement.

Developmental changes to a device under investigation are permitted so long as they do not constitute a significant change in design or in basic operational principles. Further, any changes in the clinical protocol must not: affect the validity of data resulting from completion of an approved protocol; change the likely patient risk-benefit ratio on which the original protocol was based; affect the scientific soundness of the investigational plan; or affect the rights, safety, or welfare of the human subjects involved in the investigation. For either a developmental change to a device or a change in clinical protocol, a sponsor must determine on the basis of credible evidence that the applicable conditions are true, and submit to FDA notice of the change within five days of making such change.

With respect to the submission of an IDE for a class III or implantable device, FDA must allow the sponsor opportunity to submit an investigational plan (including a clinical protocol) before the sponsor submits a formal application to either the agency or an institutional review committee. If the sponsor submits a written request for a meeting with FDA to discuss the investigational plan, FDA must meet with the sponsor within 30 days of such request. Any agreement reached between FDA and a sponsor with respect to the parameters of an investigational plan shall be documented and made part of the administrative record, and may only be changed with the sponsor's written agreement or pursuant to the identification by the agency of a substantial scientific issue affecting the safety or effectiveness of the device. In the latter case, the director of the office in which the device is reviewed shall document the scientific issue and provide an opportunity for a meeting with the sponsor to discuss it.

A new section 515(d)(1)(B)(iii) provides that FDA will accept and review "statistically valid and reliable data," as well as other information obtained from IDE investigations, to determine whether a device subject to a pending premarket approval application (PMA) is safe and effective, if (1) the data or information is derived from investigations on an earlier version of the device, the device was modified during or after the investigations but before the submission of the PMA, and the change is not a "significant change" in the design or basic operating principles of the device; or (2) the data or information relates to a device with an approved PMA, and is relevant to the design and intended use of the device at issue.

Sec. 202. Special review for certain devices.

Section 515(d) of the FDC Act has been amended to provide for priority review of devices that represent breakthrough technologies, devices for which no approved alternatives exist, devices offering significant advantages over existing approved alternatives, or devices the availability of which is in the best interest of patients.

Sec. 203. Expanding humanitarian use of devices.

The existing humanitarian use exemption in section 520(m) of the FDC Act permits FDA to waive the requirement for a demonstration of the effectiveness of a device necessary for premarket approval when: (1) the device at issue is intended to address a disease or condition affecting fewer than 4,000 persons in the United States, (2) the device would not be available unless FDA grants such an exemption, and (3) the device does not pose an unreasonable or significant risk of illness or injury to patients and the probable health benefit of the device outweighs the risk of illness or injury from its use. Devices granted a humanitarian use exemption may be used only in facilities that have an established institutional review board (IRB) to supervise the clinical testing of devices, and only if the IRB approves the use of the exempted device.

The Modernization Act modifies section 520(m) in several respects. First, it establishes a 75-day time limit for FDA review of a humanitarian use exemption application. Second, new language added to section 520(m)(4) allows a physician to administer a humanitarian use device without IRB approval (provided the IRB is later notified of the use) if waiting would cause the patient serious harm or death. Third, section 520(m)(5), which established an 18-month, renewable exemption term, has been replaced with a provision stating that FDA may require a person who receives a humanitarian use exemption to demonstrate continued compliance with the requirements for exemption, if FDA believes such demonstration is necessary to protect public health or if the agency has reason to believe the criteria are no longer being met. FDA may suspend or withdraw a humanitarian use exemption after notice and opportunity for an informal hearing.

Sec. 204. Device standards.

The existing statutory provision authorizing FDA to establish device performance standards through notice and comment rulemaking, section 514 of the FDC Act, was enacted in 1976 and amended in 1990. However, FDA has not adopted a single performance standard under this provision. The Modernization Act amends section 514 of the FDC Act and provides an alternative to the existing procedures for adoption of performance standards which allows FDA to "recognize," by publication in the Federal Register, standards or parts of standards developed by nationally or internationally recognized standard development organizations. Recognition of a standard may be withdrawn by FDA through publication of a notice in the Federal Register if the agency decides that such standard is no longer appropriate for meeting an FDC Act requirement for devices.

A manufacturer who chooses to use a recognized standard must provide to FDA a declaration of conformity certifying that the device complies with the standard. FDA may reject such certification, however, if the agency determines that the data and information on which a manufacturer relies to make a declaration of conformity does not demonstrate compliance with the performance standard or that the recognized standard relied upon is inapplicable to the device. A manufacturer is required to keep the data and information relied upon for a declaration of conformity for two years after the date of the classification or approval of the device, or for the expected design life of the device, whichever is longer, and to provide such information to the agency upon request.

Significantly, a new "prohibited act" has been added to the list in section 301 of the FDC Act: falsification of declaration of conformity to a "recognized" standard, and the failure to provide supporting data or information demonstrating conforming to a "recognized" standard when requested by the agency. The Modernization Act also amends section 501(e) of the FDC Act to specify that a device purported or represented to be in conformance with a "recognized" standard is adulterated unless the device conforms in all respects to the applicable standard.

Sec. 205. Scope of review; collaborative determinations of device data requirements.

The Modernization Act amends section 513(a)(3) of the FDC Act in several respects. First, it requires FDA, in determining the effectiveness of a device for which a PMA application has been submitted under section 515, to consider the extent to which reliance on postmarket controls can reduce the amount of data that would otherwise be required for approval of the application.

Second, FDA must meet with device manufacturers prior to the commencement of clinical trials, within 30 days of a manufacturer's request, to discuss the type of scientific evidence the manufacturer must submit to establish effectiveness. The request must include a full description of the device, its proposed conditions of use, a proposed plan for determining whether there is a reasonable assurance of effectiveness, and information (if available) regarding the expected performance of the device. FDA has 30 days after the meeting to confirm in writing the type of scientific evidence that must be submitted. In making its determination, FDA must consider the "least burdensome appropriate means of evaluating device effectiveness" that is reasonably likely to result in approval. The written confirmation is binding upon the agency, and may not be altered unless it is shown that FDA's determination could be contrary to the public health.

Revised section 513(i)(1) of the FDC Act requires FDA to consider the extent to which reliance on postmarket controls may expedite the classification of devices under section 513(f)(1). In addition, in making determinations of substantial equivalence with respect to devices with differing technological characteristics, FDA must request only that information necessary for demonstrating substantial equivalence, and in so doing, shall consider the least burdensome means of demonstrating substantial equivalence.

FDA's determination of a device's intended use must be based on the proposed labeling of the device submitted in the 510(k) premarket notification. However, if the Director of the Center for Devices and Radiological Health, after providing opportunity for a consultation with the submitter of the notification, determines in writing that there is a reasonable likelihood that a device will be used for an intended use not identified in the proposed labeling and that such use may result in harm, the director may require a statement in the labeling that provides appropriate information regarding such off-label use. This written determination, to be provided to the submitter within ten days of the date of notification of the director's concerns, must specify the limitations on the use of the device not included in the proposed labeling. In this written determination, FDA also must find the device substantially equivalent if the labeling for the device conforms to the specified limitations and the device is substantially equivalent under section 513(i)(1)(A).

The Modernization Act also amends section 515(d)(1)(A) of the FDC Act to require FDA to consider only the conditions of use identified in the proposed labeling in a PMA to determine whether or not there is a reasonable assurance of safety and effectiveness, so long as the proposed labeling is neither false nor misleading. In determining whether the labeling is false or misleading, FDA must evaluate all material facts pertinent to the proposed labeling.

Another addition to section 515(d) exempts from the supplemental application requirement any modifications in manufacturing procedures or methods for which the holder of an approved PMA has submitted appropriate notice to FDA. Such notice must describe the change in detail, summarize the data and information supporting the change, and confirm that the change has been made pursuant to the requirements of section 520(f). The holder of the approved application may distribute the device 30 days after FDA receives such notice, unless the holder has received notification from the agency that such notice is inadequate and describes the information or action required for acceptance of the change. If the agency finds that a supplemental application is required, it must review the supplement within 135 days of receipt. The time used by FDA to review the notice of manufacturing change will be deducted from the 135-day supplement review time if the notice meets appropriate content requirements for PMA supplements.

Finally, FDA must approve a supplement for an incremental design change affecting safety or effectiveness if nonclinical data demonstrate that the design modification enhances the capacity, function, or performance of the device, as intended, and clinical data from the approved PMA and any supplement thereto provide a reasonable assurance of safety and effectiveness for the modified device. FDA has the right to require additional clinical data when necessary to provide a reasonable assurance of safety and effectiveness.

Sec. 206. Premarket notification.

The Modernization Act amends section 510(k) of the FDC Act to exempt from the 510(k) notification requirement all class I devices, except for those intended for a use that is of substantial importance in preventing impairment of human health, and those presenting a potential unreasonable risk of illness or injury. It also exempts those class II devices which FDA determines, either on its own initiative or by petition of an interested party, do not require a 510(k) notification.

New section 510(m) of the FDC Act requires FDA to publish in the Federal Register, within 60 days of enactment, a list of each type of class II device that is exempt from the 510(k) notification requirement. Exempt status of listed devices is effective upon the date of publication. Beginning the first day after the publication of such list, FDA may, either on its own initiative or by petition of any interested person, exempt a type of class II device from the 510(k) notification requirement. FDA must publish notice of its intent to exempt such device (or of the petition), provide a 30-day public comment period, and publish within 120 days after issuance of the notice an order setting forth its final determination regarding the exempt status of the device. If FDA fails to respond to a petition within 180 days of receipt, the petition is deemed granted.

Section 513(f) of the FDC Act has been amended to provide that FDA may not withhold an initial classification determination because of a manufacturer's failure to comply with a requirement unrelated to the substantial equivalence determination. This includes the GMP regulations, unless there is "a substantial likelihood that the failure to comply with such regulations will potentially present a serious risk to human health."

Finally, FDA must issue, within 270 days of enactment, a guidance specifying the general principles the agency will consider in determining when a specific intended use of a device is not reasonably included within a general use of such device for purposes of a determination of substantial equivalence under section 513(f) or section 520(l) of the FDC Act.

Sec. 207. Evaluation of automatic class III designation.

Section 513(f) of the FDC Act has been amended to provide to an unclassified device an opportunity to escape automatic class III designation. A person who submits a 510(k) notification for an unclassified device may request, within 30 days of receiving notice from FDA of the device's class III designation, that FDA reclassify the device. The written request must provide detailed reasons for the recommended classification. FDA has 60 days from the date of submission of the request to issue a classification order regarding that device. Any device classified pursuant to this section shall be a predicate device for purposes of determining substantial equivalence under section 513(f)(1). A device classified as a class III device under this section will be deemed to be

adulterated unless it is approved pursuant to a PMA under section 515, or is exempt from approval pursuant to an IDE under section 520(g).

FDA must publish in the Federal Register any classification order made pursuant to a request for designation within 30 days after issuance of such order.

Sec. 208. Classification panels.

The Modernization Act amends section 513(b) of the FDC Act to further define the role of classification panels. Classification panels recommend to FDA which devices should be subject to general controls, special controls such as performance standards, or premarket approval. They also review many PMAs and certain reclassification petitions.

New section 513(b)(6) provides that the person whose device is under review by the panel must have the same access as FDA to the data and information submitted to the panel, the opportunity to submit to the panel information based on data or information which appears in the PMA, and the same opportunity as FDA to participate in panel meetings. New section 513(b)(6) also requires that panel meetings allow for open and free participation by interested persons and provide sufficient time for presentations and for responses by those persons with differing views whose devices are the subject of the panel review.

FDA will review the conclusions and recommendations of the panel and make a final determination. FDA must provide written notification to those who are affected by the decision and, for those decisions which differ from the panel's recommendations and conclusions, FDA must include the reasons for the difference.

New section 513(b)(8) relieves the classification panel from the annual chartering and annual report requirements of the Federal Advisory Committee Act, and new section 513(b)(5) provides that panel meetings must be scheduled so that FDA may meet statutory deadlines.

Sec. 209. Certainty of review timeframes; collaborative review process.

A new section 510(n) of the FDC Act provides that FDA must review a 510(k) premarket notification and make a classification determination no later than 90 days after receiving the notification.

Section 515(d) of the FDC Act has been amended to require FDA to meet with a PMA applicant within 100 days of the date of submission of the complete application, if the applicant so requests, to discuss the status of the application, unless FDA and the applicant jointly establish a different meeting schedule. Prior to the meeting, FDA must provide to the applicant a written description of any deficiencies in the application identified by FDA at that point, and identify the information required to correct the deficiencies. Further, FDA must notify the applicant promptly regarding any other deficiency subsequently identified during the course of review, and any additional information required for the agency to complete the review that was not part of the pre-meeting description.

Sec. 210. Accreditation of persons for review of premarket notification reports.

New section 523 of the FDC Act requires FDA to accredit, within one year of enactment, entities and individuals to review 510(k) notifications and make initial classification recommendations. Excluded from the scope of devices reviewable by accredited third parties are all class III devices; class II devices intended to be permanently implantable, life sustaining, or life supporting; and class II devices requiring clinical data in their premarket notifications. However, the yearly number of devices in the third category is limited by a complicated mathematical formula.

FDA must establish and publish in the Federal Register requirements for accreditation within 180 days of enactment. FDA must respond to a request for accreditation within 60 days of receipt of the request. The accreditation of any person or entity shall specify the activities for which the person or entity is accredited. FDA may suspend or withdraw accreditation after providing notice and an opportunity for an informal hearing, if such person is substantially out of compliance with the requirements of this section, poses a threat to public health, or fails to act in a manner consistent with the purposes of this section.

New section 523(b)(3) specifies certain minimum qualifications for accredited parties. A party may not be a federal employee; must be an independent organization which is neither owned or controlled by, nor has any organizational, material, or financial affiliation, with any device manufacturer, supplier, or vendor; must be a legally constituted entity permitted to conduct the activities for which it seeks accreditation; and must not engage in the design, manufacture, promotion, or sale of devices. Further, a qualified party must conduct its operations in accordance with generally accepted professional and ethical business practices, and shall confirm in writing that it will certify the accuracy of reported information; ensure that it has the competence and capacity to perform any work done; treat any information received, records, reports, and recommendations as proprietary in nature; promptly respond to complaints about the activities for which it is accredited; and guard against financial conflicts of interest. FDA will periodically visit the site of an accredited party to audit its performance, and reserves the right to take other necessary and appropriate measures to ensure that the accredited party continues to adhere to the standards of accreditation.

If a submitter of a 510(k) elects to have an accredited party review its report, it may choose from at least two accredited parties identified by FDA. An accredited party shall provide written notification to FDA of the reasons for any recommendation regarding a 510(k) notification or initial classification. Within 30 days of such notification, FDA shall make a determination on the initial classification. If FDA rejects the recommendation from an accredited party regarding the initial classification of a device, FDA shall provide to both the accredited party and the submitter of the 510(k) notification a statement of written reasons for the ultimate decision.

Compensation for accredited parties is to be determined by agreement between the accredited party and the submitter of the 510(k) notification, and is to be paid by the latter.

The pilot accreditation program will terminate the earlier of: five years after FDA notifies Congress that at least two accredited parties are available to review at least 60 percent of all 510(k) submissions; or four years after FDA notifies Congress that FDA has made classification determinations regarding accredited party recommendations for at least 35 percent of all devices eligible for accredited party review.

Section 704 of the FDC Act has been amended to impose certain recordkeeping requirements for accredited parties. Accredited parties must keep records documenting training of employees, procedures used to handle confidential information, compensation arrangements, and procedures governing avoidance of conflicts of interest. A party must permit any designated FDA official to copy and verify such records at reasonable times.

A new section 301(y) has been added to the FDC Act prohibiting the submission by an accredited party of a report or recommendation that is false or misleading in any material respect; the disclosure by an accredited party of any confidential commercial information or trade secret furnished by the submitter of the 510(k) notification; or the receipt of a bribe, or the doing of any other corrupt act, by an accredited party.

Finally, other provisions require the submission of reports to Congress evaluating the program.

Sec. 211. Device tracking.

The Modernization Act amends section 519(e) of the FDC Act with respect to a device manufacturer's obligation to track devices. Previously, the tracking requirement applied to any device, the failure of which would be reasonably likely to have serious adverse health consequences, and which was a permanently implantable device or a life-sustaining or life-supporting device used outside a device user facility. The Modernization Act replaces this requirement with a provision authorizing FDA to select which devices will be subject to the tracking requirement. FDA, by order, may impose the tracking requirement on devices: the failure of which would be reasonably likely to have serious adverse health consequences; intended to be implanted in the human body for more than one year; or that are life sustaining or life supporting and used outside a device user facility.

Any patient receiving a device for which tracking is required may refuse to release, or refuse permission to release, his or her name, address, social security number, and other identifying information for tracking purposes.

Sec. 212. Postmarket surveillance.

Under former section 522 of the FDC Act, postmarket surveillance was mandatory for devices introduced into interstate commerce after January 1, 1991, that (1) were permanent implants the failure of which might cause serious, adverse consequences or death, (2) were intended to support or sustain life, or (3) presented a potential serious risk to health. Under the Modernization Act, postmarket surveillance for such devices is no longer mandatory. FDA may require, by order, postmarket surveillance for a device if it is necessary to protect the public health.

A device manufacturer required to conduct postmarket surveillance must, within 30 days of receiving notice from FDA, submit for the agency's approval a plan for the required surveillance. Within 60 days of receiving such plan, FDA must determine if the person designated to conduct surveillance is appropriately qualified and experienced, and if the plan will result in collection of data useful for determining the occurrence of unforeseen adverse events. FDA may require a prospective surveillance period of up to 36 months. Any determination by FDA that a longer period is necessary shall be made by mutual agreement or, failing a mutual agreement, through the dispute resolution process described in new section 562 of the FDC Act.

Sec. 213. Reports.

The Modernization Act revises section 519(a) of the FDC Act to eliminate the obligations of "distributors" to submit medical device reports. Manufacturers and importers remain subject to this requirement. However, FDA must promulgate regulations requiring distributors to maintain records and to make them available to FDA upon request. The Modernization Act also revokes section 519(d) of the FDC Act, thereby eliminating the requirement to file annual certifications concerning the number of reports filed with FDA.

Further, section 510(g) has been amended to exempt "wholesale distributors" of devices from the establishment registration and listing requirements, provided they do not manufacture, repackage, process, or relabel a device. A "wholesale distributor" is defined as a "person (other than the manufacturer or the initial importer) who distributes a device from the original place of manufacture to the person who makes the final delivery or sale of the device to the ultimate consumer or user."

The Modernization Act also revises section 519(b) which contains the requirement for reports by device user facilities. Specifically, a summary of reports by user facilities is now required on an annual, rather than a semiannual, basis. These reports are now required each year on January 1.

The Modernization Act directs the implementation by regulation of a new system, the "Sentinel System," which will limit user reporting under section 519(b)(l)-(4) to a subset of user facilities. This subset will provide a representative profile of reports for device deaths and serious illnesses or serious injuries. The current user reporting system will continue to apply to all device user facilities during the planning phase of the new system and possibly during the transition phase, at FDA's discretion.

Sec. 214. Practice of medicine.

The Modernization Act adds a new section 906 to the FDC Act to provide that the FDC Act shall not interfere with a practitioner's authority to prescribe or administer to a patient any legally marketed device for any condition or disease provided there is a valid practitioner-patient relationship. However, under new section 906, FDA still has the authority to impose restrictions on the sale, distribution, or labeling of a device as part of a substantial equivalence determination, established as a condition of approval, or by regulation. The new law provides that it does not alter any current prohibition on the promotion of unapproved uses of a legally marketed device.

Sec. 215. Noninvasive blood glucose meter.

Section 215 of the Modernization Act contains Congress' findings that a safe, effective, noninvasive blood glucose meter would enhance the health of diabetics.

Sec. 216. Use of data relating to premarket approval; product development protocol.

Revised section 520(h) of the FDC Act provides that any information contained in a PMA -- including information from clinical and preclinical tests and studies demonstrating safety and effectiveness, but excluding descriptions of methods of manufacture, product composition, and other trade secrets -- may be used by FDA six years after approval of such application to: approve another

device; determine whether a product development protocol has been completed for another device; establish a performance standard or special control under the Act; or classify or reclassify a device. The publicly available safety and effectiveness information may form the evidentiary basis for any of the above agency actions.

The Modernization Act also amends section 515(f)(2) of the FDC Act to revise FDA's obligations upon receipt of a product development protocol (PDP). Under the new provision, if FDA determines that a PDP appears appropriate under section 515(f), FDA may refer the proposed protocol to the appropriate panel under section 513 for a recommendation on whether the protocol should be approved, and must refer such protocol upon the submitter's request (unless FDA finds that the proposed protocol and accompanying data substantially duplicate a protocol previously reviewed by the panel).

Sec. 217. Clarification of the number of required clinical investigations for approval.

The language in section 513(a)(3)(A) of the FDC Act, providing that the effectiveness of a device shall be determined "on the basis of well-controlled investigations, including clinical investigations," has been amended to state "on the basis of well-controlled investigations, including 1 or more clinical investigations." This change clarifies that one clinical investigation may be sufficient for a demonstration of effectiveness.

TITLE III: IMPROVING REGULATION OF FOOD

Sec. 301. Flexibility for regulations regarding claims.

The Modernization Act adds a new section 403(r)(7) to the FDC Act to authorize FDA to make proposed rules on health claims and nutrient content claims effective immediately upon the date of publication, pending consideration of public comment and publication of a final regulation.

Sec. 302. Petitions for claims.

Section 403(r)(4)(A)(i) of the FDC Act provides that not later than 100 days after FDA receives a petition for approval of a health claim, FDA must either issue a final decision denying a health claim petition, or file the petition for further action. The Modernization Act amends this section to provide that if FDA does not take either one of those actions, the petition will be deemed to be denied, unless an extension is mutually agreed upon by FDA and the petitioner.

Section 403(r)(4)(A)(i) also provides that, once FDA has filed the petition for further action, the agency has 90 days within which to deny the petition or publish a proposed regulation approving the claim. The Modernization Act amends this section to provide that if FDA does not take either action within the 90 days, the petition shall be deemed to be denied, unless an extension is mutually agreed upon by FDA and the petitioner.

This section has been amended also to provide that FDA has 540 days (18 months) to complete the rulemaking for the health claim once the proposed rule is published. If FDA does not complete the rulemaking within the 540 days, it must provide to Congress an explanation of why it did not do it.

Sec. 303. Health claims for food products.

The Modernization Act amends section 403(r)(3) of the FDC Act to add new subparagraphs (C) and (D), authorizing companies to make certain health claims without FDA approval in a regulation. These health claims must be the subject of a "published ... authoritative statement, which is currently in effect," by "a scientific body of the U.S. 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) or the National Academy of Sciences or any of its subdivisions. . . ." § 403(r)(3)(C)(i).

This type of health claim is subject to the requirement of section 403(r)(3)(A)(ii); that is, the claim may be made only if the food "does not contain, as determined by [FDA] by regulation, any nutrient in an amount which increases to persons in the general population the risk of a disease or health-related condition which is diet related, taking into account the significance of the food in the total daily diet." § 403(r)(3)(C)(iii) and (r)(3)(A)(ii). FDA has already established these

"disqualifying nutrient levels" in 21 C.F.R. § 100.14(a)(5). In addition, the health claim may not be false, or misleading by failing "to reveal facts material in the light of" the claim. § 403(r)(3)(C)(iii), (a), and 201(n).

Nevertheless, FDA remains the final arbiter on whether the health claim may be made. At least 120 days before the first introduction into interstate commerce of the food bearing the health claim, FDA must be notified that such claim will be made. § 403(r)(3)(C)(ii). The notification to FDA must include "a balanced representation of the scientific literature relating to the relationship between a nutrient and a disease or health-related condition to which the claim refers." § 403(r)(3)(C)(ii).

These FDA-unauthorized health claims may be made only until (a) FDA issues a regulation prohibiting or modifying the claim or finding that the requirements to make the claim have not been met, or (b) a district court finds in an enforcement proceeding that the requirements to make the claim have not been met. § 403(r)(3)(D)(i)-(ii). FDA may publish the proposed regulation prohibiting or modifying the claim following new section 403(r)(7), which authorizes FDA to make the proposed rule effective immediately upon the date of publication. § 403(r)(3)(D)(i).

Sec. 304. Nutrient content claims.

The Modernization Act adds new section 403(r)(2)(G)-(H) to the FDC Act, two provisions nearly identical to those for FDA-unauthorized health claims, but applicable to nutrient content claims.

A scientific body of the U.S. Government must publish "an authoritative statement, which is currently in effect, which identifies the nutrient level to which the claim refers." § 403(r)(2)(G)(i). However, the nutrient content claim must use a term established by FDA in its regulations. § 403(r)(2)(G)(iii). Under the amendments made by the Modernization Act, if a scientific body of the U.S. government issues an "authoritative statement" establishing a recommended daily allowance or Daily Value for the nutrient, then a nutrient content claim for that nutrient may be made based on that Daily Value using the terms defined in FDA's regulations.

As in the case of FDA-unauthorized health claims, the FDA-unauthorized nutrient content claim may be made only until FDA issues a regulation modifying or prohibiting the claim, or until a district court finds in an enforcement proceeding that the requirements to make the claim have not been met. § 403(r)(2)(H)(i)-(ii). FDA may propose this regulation prohibiting or modifying the claims also using new section 403(r)(7), which authorizes FDA to make the proposed rule effective immediately upon the date of publication. § 403(r)(2)(H)(i).

Sec. 305. Referral statements.

The Modernization Act amends section 403(r)(2)(B) of the FDC Act to eliminate the requirement that nutrient content claims be accompanied by a statement referring the consumer to the panel where the nutrition information is located. A referral statement will be required only if FDA determines that a particular level of a nutrient in a food increases the risk of a disease or health-related condition which is diet related. FDA has already established these levels in 21 C.F.R. § 101.13(h). In addition, the referral statement does not need to indicate the panel where the nutrition information is located (e.g., "see nutrition information for fat content").

Sec. 306. Disclosure of irradiation.

A new section 403C of the FDC Act provides that FDA may not require that a labeling statement that discloses that a food has been intentionally subject to radiation be more prominent than the declaration of ingredients.

Sec. 307. Irradiation petition.

This section, which is not to be codified in the FDC Act, requires FDA to make a final determination on any pending petition for the irradiation of red meat within 60 days following the date of enactment.

Sec. 308. Glass and ceramic ware.

A provision not intended to be codified in the FDC Act provides that, prior to January 1, 2003, FDA may not ban as an unapproved food additive lead- and cadmium-based enamel on glass and ceramic ware that have less than 60 millimeters of decorating area below the external rim and that are not, by design, representation, or custom of usage, intended for use by children, unless FDA determines that the enamel is unsafe. In addition, after January 1, 2003, if FDA bans such lead- and cadmium-based enamel, it may do so only by regulation and the ban may not come into effect before one year after the date of publication of the final rule.

Sec. 309. Food contact substances.

The Modernization Act amends section 409 of the FDC Act to allow the use of certain indirect "food additives" without an FDA food additive regulation authorizing such use. The new provisions apply to a food additive that is a "food contact substance," which is defined as "any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food." § 409(h)(6). This amendment generally endorses FDA's 1995 "threshold of regulation" regulation for indirect food additives. 21 C.F.R. § 170.39.

A new section 409(h) provides that (instead of a food additive petition) a manufacturer may file with FDA a "notification" containing the information that forms the basis for the manufacturer's determination that the intended use of the food contact substance is safe under the existing safety standard for approval of food additives in section 409(c)(3)(A). § 409(h)(1). Unless FDA determines, within 120 days of receipt of the notification, that the manufacturer's determination is incorrect, and informs the manufacturer of such determination, the notification "shall become effective," allowing the marketing of the substance for the intended use subject of the notification. § 409(h)(2)(A). FDA's determination constitutes final agency action subject to judicial review. § 409(h)(2)(B).

FDA is authorized to promulgate regulations to "identify the circumstances" under which a food additive petition must be filed "and shall consider criteria such as the probable consumption . . .

and potential toxicity of the food contact substance in determining the circumstances in which a petition" is necessary. House Report 105-306 at 19. FDA has already established these criteria in the "threshold of regulation" regulation. 21 C.F.R. § 170.39(a). New section 409(i) requires FDA to establish by regulation the procedure by which it will deem a notification of a food contact substance "to be no longer effective."

FDA must begin accepting and reviewing notifications under this section not later than April 1, 1999, provided it receives appropriations sufficient to fund the program.

TITLE IV: GENERAL PROVISIONS

Sec. 401. Dissemination of information on new uses.

Currently, FDA generally does not permit manufacturers to disseminate any materials -- including reprints of peer-reviewed articles or independent reference texts -- that discuss unapproved uses of approved drugs or devices, except in certain narrowly defined circumstances.

The Modernization Act adds new sections 551 to 557 to the FDC Act, expanding the circumstances in which manufacturers are permitted to disseminate information on unapproved uses, while preserving the incentives to add new indications to the labeling. The new provisions apply to dissemination of information on unapproved uses of drugs, biologics, and medical devices.

Manufacturers may disseminate two types of written information on uses not described in the approved labeling. They are:

(1) Unabridged reprints of peer-reviewed articles that report on clinical investigations and that are published in scientific or medical journals. § 552. The journals must, among other things, be of national scope and reputation and be indexed in the National Library of Medicine. § 552(a)(1).

(2) Unabridged reference publications containing information about clinical investigations. The reference publication must be generally available where medical texts are sold and may not be written, edited, or significantly influenced by a manufacturer. § 552(a)(1).

The information may be distributed only to a health care practitioner, pharmacy benefit manager, health insurance issuer, group health plan, or federal or state government agency. § 551(a). Thus, dissemination of off-label information to patients is not permitted.

The reprint or text must be accompanied by a prominent statement disclosing, among other things, that the information concerns an unapproved use, that there are approved treatments for the use (if applicable), and the names of any authors who have received compensation or have a significant financial interest in the manufacturer. The reprint or text must also be accompanied by the approved labeling and a bibliography of previously published articles concerning the unapproved use. § 551(b)(6).

The product that is the subject of the reprint or reference text must be lawfully marketed. In addition, the clinical research discussed in the materials must have been conducted by the disseminating manufacturer, or, if not, the manufacturer must have obtained permission to distribute the information from the manufacturer who conducted the research. § 551(b)(1) and (3).

Sixty days prior to dissemination, the manufacturer must submit to FDA a copy of the information to be distributed and any clinical trial information on safety and effectiveness of the new use, along with a summary of such information. § 551(b)(4). The submission must also include a certification regarding supplements, as described in the next section.

With one exception described in the next section, FDA approval to distribute is not required. However, if FDA (after notice to the manufacturer and an opportunity for a meeting) determines that the material is not objective and balanced, the agency may require the manufacturer to accompany the reprint or text with additional information on safety and effectiveness that is necessary to provide objectivity and balance. This may include information that the manufacturer has submitted to FDA or any other information that FDA may make publicly available. § 551(c)(1). FDA may, in addition, require the manufacturer to include an "objective statement" that relates to safety and effectiveness. § 551(c)(2).

In order to distribute off-label information, a manufacturer who has completed the studies needed for a supplemental application for the new indication but has not yet submitted the application must include in the pre-distribution submission to FDA (described above) a certification that the studies have been completed and that a supplement will be submitted to FDA within six months after the dissemination. § 554(b). Manufacturers who have not yet conducted such studies must submit to FDA a protocol and proposed schedule for conducting studies necessary for a supplemental application for the new use, and a certification that a supplement will be submitted within 36 months (or a longer time agreed to by FDA) after the dissemination. The manufacturer may not disseminate the information unless FDA has first determined that the proposed protocol is adequate and the investigational schedule reasonable. Following the dissemination, the manufacturer must submit periodic reports to FDA describing the status of the studies. § 554(c).

As an alternative to either of the above certifications, a manufacturer may submit an application for exemption from the certification requirement, which must be approved by FDA before dissemination of the reprint or text may occur. FDA may approve an application for exemption only if it would be either unethical for the manufacturer to conduct research to support a supplement (for example, where the new use has become the standard of care), or economically prohibitive to do so (for example, where statutory exclusivity would not be available or the patient population for the indication is small). § 554(d).

FDA must take action on an application for exemption within 60 days after receipt. If FDA fails to do so, the application is deemed to be approved, but FDA may at any time terminate the deemed approval and order the dissemination to cease. §§ 554(d)(3) and 555(b)(3).

In addition to requiring additional information to accompany a proposed dissemination as discussed above, FDA may take corrective action after the dissemination occurs. If FDA determines based on new data that the product may not be effective for the unapproved use or may present a "significant risk to public health," FDA may, after consulting with the manufacturer, order the manufacturer to cease the dissemination or to take other actions necessary to protect the public health. In addition, FDA may order cessation and/or corrective action if the manufacturer has not complied with the requirements for dissemination; if a manufacturer that has certified that it will submit a supplement within six months has not done so; if a manufacturer that has certified that it

will conduct studies necessary for a supplement does not pursue the studies with due diligence; or if a supplement that is eventually submitted by a disseminating manufacturer does not demonstrate the safety and effectiveness of the new use. § 555(a)(1) and (b).

Following dissemination, a manufacturer must submit biannual reports to FDA listing the articles and reference texts distributed and the categories of providers that received the materials, and must also notify FDA of any new safety or effectiveness data concerning the new use. §§ 553, 555(a)(2).

Dissemination of off-label information in violation of these provisions is made an unlawful act under section 301 of the FDC Act, subject to injunction and criminal penalties (but not seizure of the product). § 301(z).

FDA is directed to promulgate implementing regulations no later than one year after the date of enactment of the Modernization Act. Modernization Act § 401(c).

The dissemination provisions become effective upon the promulgation of final regulations, but no later than one year following enactment. They cease to be effective on September 30, 2006 or seven years following FDA's promulgation of regulations, whichever is later. Modernization Act § 401(d) and (e).

Sec. 402. Expanded access to investigational therapies and diagnostics.

The Modernization Act adds new section 561(a) to the FDC Act, which provides that, in emergency situations, FDA may authorize the shipment of investigational drugs (including investigational biological products) and investigational devices for the diagnosis, monitoring, or treatment of a serious disease or condition.

In addition, new section 561(b) permits any individual, acting through a licensed physician, to request an investigational drug or investigational device from a manufacturer or distributor. The manufacturer or distributor may provide the physician with the requested investigational product if the following conditions are met: (1) the licensed physician determines that the person has no

comparable or satisfactory alternative therapy and that the probable risk to the patient from the investigational product is not greater than the probable risk from the disease or condition; (2) FDA determines that there is sufficient evidence of the investigational product's safety and effectiveness in the particular case; (3) FDA determines that provision of the investigational product to the physician will not interfere with the initiation, conduct, or completion of clinical investigation to support marketing approval; and (4) the sponsor or clinical investigator submits to FDA a clinical protocol consistent with regulations promulgated describing the use of investigational drugs in a single patient or a small group of patients.

New section 561(c) codifies FDA's regulations for treatment INDs, 21 C.F.R. § 312.34, and treatment IDEs. 21 C.F.R. §§ 812.36 and 812.150.

Under new section 561(d), FDA may, at any time, terminate expanded access for investigational drugs or devices if the requirements of section 561 are no longer met.

Sec. 403. Approval of supplemental applications for approved products.

The Modernization Act requires that FDA establish performance standards for the prompt review of supplemental applications of approved products. In addition, each Center within FDA must designate an individual who will be responsible for encouraging the prompt review of supplemental applications and for working with sponsors to facilitate the development and submission of data to support supplemental applications.

The performance standards are to be published within 180 days following enactment of the legislation. FDA also has 180 days to issue final guidance to clarify the requirements for, and facilitate the submission of data to support the approval of supplemental applications. Specifically, the guidance documents must: (1) clarify when published matter may be the basis for approval of a supplemental application; (2) specify data requirements that will avoid duplication of previously submitted data by recognizing the availability of that data in support of an original application; and (3) define which supplemental applications are eligible for priority review.

Sec. 404. Dispute resolution.

The Modernization Act adds new section 562 to the FDC Act. Within one year of enactment, FDA must promulgate regulations by which a sponsor, applicant, or manufacturer may request review of a scientific controversy, including a review by an appropriate scientific advisory panel or advisory committee, if no specific provision in the FDC Act or a regulation provides a right of review of the controversy. Any review must take place in a timely manner.

Sec. 405. Informal agency statements.

The Modernization Act adds a subparagraph (h) to section 701 of the FDC Act to require FDA to follow predictable and consistent procedures in developing, issuing, and using guidance documents. FDA must develop guidance documents with public participation and ensure that the documents are made available to the public, both in written and electronic form. Though guidance documents are not binding on FDA or the public, the agency must ensure that its employees do not deviate from such guidances without appropriate justification from supervisory personnel.

Any guidance document that sets forth initial interpretations of statutes or regulations, changes in interpretation of policy that are of more than a minor nature, or complex scientific issues or highly controversial issues would require public participation prior to the implementation of the guidance. However, upon determination that prior public participation is not feasible or appropriate, FDA may waive this requirement. For guidance documents that set forth existing practices or minor changes in policy, FDA must allow for public comment upon implementation.

FDA must maintain electronically and publish periodically in the Federal Register a list of guidance documents. Further, there must be an effective appeals mechanism established to address complaints that FDA is not developing and using guidance documents in accordance with this new provision. Also, by July 1, 2000, FDA must promulgate a regulation specifying the policies and procedures of FDA for the development, issuance and use of guidance documents.

Sec. 406. Food and Drug Administration mission and annual report.

The Modernization Act adds a new "Mission" section to the FDC Act, section 903. FDA's mission consists of two parts: (1) FDA must promote public health by promptly and efficiently reviewing clinical research and taking appropriate action on marketing of regulated products in a timely manner; and (2) FDA must protect the public health by ensuring that foods are safe, wholesome, sanitary, and properly labeled; human and veterinary drugs are safe and effective; there is a reasonable assurance of safety and effectiveness of devices intended for human use; cosmetics are safe and properly labeled; and the public health and safety are protected from electronic product radiation. FDA must participate with other countries to reduce the burden of regulation, to harmonize regulatory requirements, and to achieve appropriate reciprocal arrangements. FDA should carry out this "Mission" in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

Not later than one year after enactment, in consultation with appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups, and industry, FDA must develop and publish in the Federal Register a plan bringing FDA into compliance with each of the obligations under this Act. Further, FDA must annually prepare and publish in the Federal Register a report of the agency's performance and solicit public comment on the report.

Sec. 407. Information system.

The Modernization Act adds a new section 741 to the FDC Act to require FDA to establish and maintain an information system to track the status of every application or submission (including petitions, notifications, and other requests) requesting agency action. Within one year of enactment, FDA must submit to Congress a report on the status of such information system, including the projected costs of the system and concerns about confidentiality.

Sec. 408. Education and training.

New section 742 of the FDC Act requires FDA to conduct training and education programs for its employees relating to the agency's regulatory responsibilities and policies, including programs for scientific training, section 704 inspections skills training, product specialization training for inspections, and training in administrative process, procedure, and integrity.

Sec. 409. Centers for education and research on therapeutics.

The Modernization Act amends the PHS Act to create a new section 905, "Demonstration Program Regarding Centers for Education and Research on Therapeutics."

Sec. 410. Mutual recognition agreements and global harmonization.

Revised section 520(f)(1)(B) of the FDC Act requires FDA to ensure, before the promulgation of any GMP regulation, that such regulation will conform, to the extent practicable, with internationally recognized quality system standards. Revised section 803 encourages FDA to support the Office of the U.S. Trade Representative, in consultation with the Secretary of Commerce, in promoting harmonization of regulatory requirements pertaining to drugs, biologics, devices, foods, food additives, color additives, and GMPs through mutual recognition agreements. The section requires FDA to publicize a framework for achieving mutual recognition of GMP inspections no later than 180 days after the date of enactment.

Sec. 411. Environmental impact review.

New section 746 of the FDC Act provides that an environmental impact statement prepared in accordance with 21 C.F.R. Part 25 for an action, recommendation, or report made pursuant to the FDC Act is deemed to meet the requirements for a detailed statement under section 102(2)(C) of the National Environmental Policy Act (NEPA). This section generally endorses FDA's final rule of July 29, 1997 reducing the number of cases in which an environmental impact statement or environmental assessment is required. 62 Fed. Reg. 40570.

Sec. 412. National uniformity for nonprescription drugs and cosmetics.

The Modernization Act adds a new section 751 to the FDC Act to provide that no state or political subdivision of a state may establish or continue in effect any requirement "that relates to the regulation" of OTC drugs "that is different from or in addition to, or that is otherwise not identical with," a requirement of the FDC Act, the Poison Prevention Packaging Act (PPPA), or the Fair Packaging and Labeling Act (FPLA). § 751(a). A "requirement" that "relates to the regulation" of OTC drugs includes any requirement "relating to public information or any other form of public communication relating to a warning of any kind." § 751(c)(2).

There is an exception for OTC drugs that are not marketed (a) pursuant to an approved new drug application (including antibiotics), or (b) pursuant to a final FDA regulation "establishing conditions under which the drug is generally recognized as safe and effective and not misbranded" (e.g., an OTC Drug Review final monograph). For these products, states may impose different or additional requirements that do not relate (a) "to the same subject as" a regulation enacted pursuant to the FDC Act, the PPPA, or the FPLA, or (b) to any other requirement of the FDC Act, the PPPA, or the FPLA that may be imposed in the future by any amendment to such laws. § 751(d)(1).

In addition, states may apply for authorization from FDA to impose different or additional requirements for any OTC drug if such requirements would protect an important public interest that would otherwise be unprotected, would not cause any drug to be in violation of any applicable requirement under Federal law, and would not unduly burden interstate commerce. § 751(b)(1). To authorize states to impose such different or additional requirements, FDA must publish a regulation after notice and opportunity for comment.

Section 751 contains a "grandfather" provision that makes it inapplicable to a "requirement adopted by a State public initiative or referendum enacted prior to September 1, 1997" (e.g., California's Proposition 65). § 751(d)(2). In addition, section 751 does not apply to state requirements that relate to the practice of pharmacy or that require that a drug be dispensed only by prescription. § 751(c)(1).

FDA Inspection Authority for OTC Drugs

Section 412 of the Modernization Act also amends section 704(a)(1) of the FDC Act to grant to FDA the authority to inspect for OTC drugs for human use the same things FDA has authority to inspect for prescription drugs. That is, for OTC drugs, FDA is now authorized to inspect "all things ... (including records, files, papers, processes, controls, and facilities)," whereas before FDA could only inspect equipment, finished and unfinished materials, containers, and labeling.

Labeling for OTC Drugs

The Modernization Act amends section 502(e)(1)(A)(ii) of the FDC Act to require that the label for an OTC drug for human use state the quantity of each active ingredient, and, if deemed appropriate by FDA, the proportion of each active ingredient. In addition, a new section 502(e)(1)(A)(iii) has been added requiring all drugs to state "the established name of each inactive ingredient listed in alphabetical order on the outside container of the retail package," and, if deemed appropriate by FDA, also on the immediate container. An exception from the requirement to list inactive ingredients was established for OTC drugs that are also cosmetics. Those products are already required (by the cosmetic labeling regulations) to list their inactive (cosmetic) ingredients in descending order of predominance by weight.

Preemption for Labeling and Packaging of Cosmetics

The Modernization Act adds a new section 752 to the FDC Act to provide that no state or political subdivision of a state may establish "any requirement for labeling or packaging" of a cosmetic "that is different from or in addition to, or that is otherwise not identical with," a requirement "specifically applicable to a particular cosmetic or class of cosmetics" under the FDC Act, the PPPA, or the FPLA. § 752(a). This section applies also to "any State requirement relating to public information or any other form of public communication." § 752(c).

States may apply for authorization from FDA to impose different or additional labeling and packaging requirements for cosmetics if such requirements would protect an important public interest that would otherwise be unprotected, would not cause a cosmetic to be in violation of any applicable requirement under Federal law, and would not unduly burden interstate commerce.

§ 752(b). To authorize states to impose such different or additional requirements, FDA must publish a regulation after notice and opportunity for comment.

New section 752 contains a "grandfather" provision that makes it inapplicable to a "requirement adopted by a State public initiative or referendum enacted prior to September 1, 1997" (e.g., California's Proposition 65). § 752(e).

Sec. 413. Food and Drug Administration study of mercury compounds in drugs and food.

In a section not intended to be codified in the FDC Act, the Modernization Act requires FDA to compile, within two years after the date of enactment, a list of foods and drugs containing intentionally introduced mercury compounds and to conduct a quantifiable and qualitative analysis of the compounds. Further, the section directs FDA to conduct a study of the effect on humans of mercury compounds used in nasal sprays; and to conduct on its own, or by contract with the Institute of Medicine of the National Academy of Sciences, a study of the effect on humans of elemental, organic, or inorganic mercury when offered for sale as a drug or dietary supplement. If FDA determines that the use of mercury in drugs or dietary supplements poses a threat to human health, it must restrict by regulation the sale of mercury intended for such use.

Sec. 414. Interagency collaboration.

The Modernization Act adds a new section 903(c) that requires FDA to implement programs and policies that will foster collaboration between FDA, NIH, and other science-based federal agencies to enhance the scientific and technical expertise available to the Commissioner with respect to the development, clinical investigation, evaluation and postmarketing monitoring of emerging medical therapies, including complementary therapies and advances in nutrition and food science.

Sec. 415. Contracts for expert review.

A new section 907 of the FDC Act authorizes FDA to enter into contracts with expert parties for the purpose of reviewing and evaluating applications and submissions to FDA made pursuant to either the FDC Act or the Public Health Service Act. An expert party who contracts with the agency is expected to make a recommendation on all or part of any application or submission reviewed. It is anticipated that FDA will enter into such contracts whenever such expert review will improve the timeliness and/or quality of review, unless the use of experts would for whatever reason reduce the quality or unduly increase the cost of review. The FDA official in charge of any matter for which expert review is used will review the recommendation of the expert party and make a final decision on the matter within the applicable time limit.

Sec. 416. Product classification.

The Modernization Act adds a new section 563 to the FDC Act allowing the submitter of any application or submission under the FDC Act to request the classification of the product as a drug, biologic, device, or combination product. In submitting a request, the submitter must recommend either a product classification, or a component to regulate the product, as appropriate. Within 60 days of receipt of the request, FDA must provide the submitter with a written statement identifying the reasons for the classification or component designated, and may not modify the statement unless the submitter consents in writing, or unless dictated by public health reasons based on scientific evidence. If FDA fails to respond within the 60-day timeframe, the submitter's recommendation for a classification or regulatory component will be deemed to be a final decision by FDA that may only be modified with the submitter's written consent or for public health reasons based on scientific evidence.

Sec. 417. Registration of foreign establishments.

This provision amends section 510(i) of the FDC Act to require any establishment in a foreign country to register the name and place of business of the establishment with the FDA if that establishment is engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or device that is imported or offered for import to the United States. Moreover, the

provision requires that FDA be provided with the name of the U.S. agent for the establishment. Upon registration, the foreign establishment must also comply with the requirements of section 510(j), which include the listing requirement.

Sec. 418. Clarification of seizure authority.

Section 304(d)(1) of the FDC Act provides that if a seized and condemned article has been imported and the person seeking its release establishes that the violation did not occur after the article was imported and that the person had no cause to believe that the product was violative before it was released from Customs custody, the court "may permit the article to be delivered to the owner for exportation in lieu of destruction upon a showing by the owner that all of the conditions of section 801(e) can and will be met." This provision, however, does not apply where condemnation is based upon certain enumerated violations.

Section 304(d)(1) also provided that if the exportation was made "to the original foreign supplier" of the product, no compliance with section 801(e) was required, and the article could be exported regardless of the nature of the violation. The Modernization Act amends this provision to require compliance with certain requirements of section 801(e)(1). An additional provision has been added to the effect that any person seeking to export a condemned article under this section "shall establish that the article was intended for export at the time the article entered commerce."

Sec. 419. Interstate commerce.

The Modernization Act amends section 709 to make it applicable also to enforcement actions respecting foods, drugs, or cosmetics. Section 709 had provided that in any enforcement action respecting a device, the connection with interstate commerce required for jurisdiction shall be presumed to exist. Thus, the government is no longer required to present in an enforcement action concerning a food, drug, or cosmetic evidence that the product has moved in interstate commerce in order to establish jurisdiction over the product.

Sec. 420. Safety report disclaimers.

The Modernization Act adds a new section 756 to the FDC Act to provide that "a safety report or other information in connection with the safety of a product" that is submitted to FDA "shall not be construed to reflect necessarily a conclusion ... that the report or information constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or otherwise caused or contributed to a death, serious injury, or serious illness." This section applies to "an entity that submits or is required to submit" the information. In addition, the entity that submits the information "need not admit, and may deny," that the product malfunctioned, caused, or contributed to the adverse experience.

Sec. 421. Labeling and advertising regarding compliance with statutory requirements.

The Modernization Act deletes section 301(l) of the FDC Act, which prohibited, in labeling and advertising, any representation or suggestion that FDA had approved a new drug application for a drug, had approved a premarket application for a device, or had approved a new investigational drug application for an investigational drug. Representations that a product has been approved by FDA are now permitted.

Sec. 422. Rule of construction.

Section 422 of the Modernization Act makes clear that nothing in the new law shall be construed to affect the question of whether FDA has authority to regulate tobacco.

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