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## **FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997**

The Food and Drug Administration Modernization Act of 1997 (FDA Modernization Act or 1997 Act) amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the biological products provisions in section 351 of the Public Health Service Act (PHS Act). The provisions of the 1997 Act affect all products regulated by FDA. Some provisions of the new law apply specifically to particular categories of regulated products (e.g., new drugs, biological products, and medical devices). Other provisions apply broadly to all regulated products. This analysis contains separate sections summarizing the provisions in the 1997 Act that deal with drugs, biological products, and medical devices, and the provisions that affect all regulated products.

Covington & Burling has been deeply involved in all aspects of the drafting and the congressional consideration of this legislation from its inception to enactment. The Firm has prepared this analysis in a form that permits the reader to select those portions of the 1997 Act that are of particular interest.

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**I. Introduction**

Since the enactment of the Federal Food, Drug, and Cosmetic Act in 1938,<sup>1</sup> the statute has been amended more than a hundred times to add, revise, and delete regulatory requirements. One attempt to recodify the entire FD&C Act failed in the early 1950s<sup>2</sup> and has not been attempted since. No legislation has attempted to achieve reform in all aspects of FDA's regulatory jurisdiction. Comprehensive approaches to reform drug regulation in the late 1970s<sup>3</sup> and food regulation in the early 1980s<sup>4</sup> were unsuccessful. All reform has therefore come in the form of narrowly targeted statutes and by FDA administrative action.

Following the congressional elections of November 1994, the new Republican majority reached consensus that comprehensive FDA reform would be a major priority. Numerous hearings were conducted in both the House and the Senate. Legislation was introduced in the Senate in December 1995<sup>5</sup> and was reported out of committee in March 1996.<sup>6</sup> Three parallel House bills were introduced in March 1996 (one each for drugs (including biological products),<sup>7</sup> food,<sup>8</sup> and devices<sup>9</sup>) and were the subject of hearings but were not reported out of committee. Because 1996 was a presidential election year, there was simply not enough time for Congress to complete action on what was unquestionably comprehensive legislation. Congress did, however, enact three parts of the reform legislation as separate statutes: (1) the FDA Export Reform and Enhancement Act of 1996,<sup>10</sup> (2) the Food Quality Protection Act of 1996,<sup>11</sup> and (3) the Animal Drug Availability Act of 1996.<sup>12</sup>

Following the November 1996 elections, Congress returned to this issue. This time, however, there was a new dimension and a greater urgency to the matter. Congress had enacted the Prescription Drug User Fee Act (PDUFA) in 1992,<sup>13</sup> with a five-year life that expired at the end of September 1997. The congressional leadership concluded that the FDA reform legislation considered in 1996 would be tied to reenactment of PDUFA for another five years.

FDA reform legislation was introduced in the Senate in June 1997,<sup>14</sup> was reported out of committee a month later,<sup>15</sup> was debated on the floor of the Senate beginning on September 5,<sup>16</sup> and was passed by a vote of 98-2 on September 24.<sup>17</sup> Bills were introduced in the House for drugs (including biological products) in April,<sup>18</sup> for medical devices in May,<sup>19</sup> and for food in September.<sup>20</sup> All three bills were reported out of committee in October, with separate reports for each.<sup>21</sup> The three bills were combined and passed by the House without debate under a suspension of the rules on October 7.<sup>22</sup>

As passed by the Senate and the House, both the form of the FDA reform legislation and many of the specific provisions were substantially different. These differences were reconciled during meetings that extended throughout October and into November. After marathon sessions in early November, the Conference Committee completed its work and issued its report<sup>23</sup> and the legislation was passed by both Houses of Congress on Sunday, November 9, just before the end of the session.<sup>24</sup> President Clinton signed the legislation on November 21, 1997.<sup>25</sup>

The final legislation largely took the form of the bill passed by the House on September 24, and included most of the provisions that were included in the House bill but not in the Senate bill. Many of the provisions in both bills were modified by the Conference Committee. The final version of the legislation therefore requires close analysis to determine its meaning and impact.

The FDA Modernization Act is divided into the following five titles:

#### Title I: Improving Regulation of Drugs

Title II: Improving Regulation of Devices

Title III: Improving Regulation of Food

Title IV: General Provisions

Title V: Effective Date

The provisions included in this legislation represent a clear compromise between the strong reform sought by some and the preservation of current practices sought by others. Viewed as a whole, the 1997 Act represents a substantial change in the existing law. It includes extremely important statutory amendments throughout the FD&C Act that will require major change in current FDA policy and practice. It is therefore of vital importance to the entire regulated industry.

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## **II. Prescription Drug User Fees**

Sections 101-107 in Subtitle A of Title I of the FDA Modernization Act reauthorize the Prescription Drug User Fee Act (PDUFA) for an additional five years. These provisions were derived from section 101 of the House bill and sections 701-707 of the Senate bill. PDUFA has been regarded as a successful experiment in improving government through private funding tied to performance commitments on the part of the agency. There was agreement among industry, FDA, and Congress that PDUFA should be reauthorized.

Under the 1997 Act, the user fees levels are raised and the mechanism for annually adjusting the fees is modified. The "water line" minimum level of non-user fee funds appropriated to FDA is changed. Relatively minor technical changes are made in the user fee requirements and processes. The FDA performance goals are made more ambitious.

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### **A. User Fee Levels and Adjustments**

Total fee levels are set under section 103(f)(3) of the FDA Modernization Act at \$106,800,000 for fiscal year (FY) 1998, \$109,200,000 for FY 1999 and FY 2000, \$114,000,000 for FY 2001, and \$110,100,000 for FY 2002, with adjustments for inflation and FDA workload. This will raise a total of almost \$550,000,000 over five years.

As under prior law, one-third of the total fee revenues are to be collected from each category of fees: (1) applications and supplement fees, (2) establishment fees, and (3) product fees. Under the original PDUFA, target fee revenues were increased to account for inflation each year, but not for the FDA workload. If the number of applications increased by ten percent, the per-application fee would be correspondingly reduced because the total revenues were fixed. The new law changes this by setting the individual application fees, rather than the total fee revenues, at a fixed level. The full application fee is set under section 103(b)(1)(A) at \$250,704 in FY 1998, \$256,338 in FY 1999 and FY 2000, \$267,606 in FY 2001, and \$258,451 in FY 2002, with the supplemental application fee being one-half of the full fee.

As the number of applications rises or falls, the amount of fees collected will rise or fall accordingly, thereby building in an automatic workload adjustment desired by FDA. Establishment and product fees will be adjusted under section 103(c)(3) based on the

application fee revenues to maintain the equal division among the three categories. In addition, section 103(c)(2)(D) changes the inflation adjustment mechanism so that it is made on a compounded basis, reflecting the total changes from the baseline period. Section 102(6) changes the inflation baseline from August 1992 to April 1997.

FDA estimates the appropriate fee levels each year, but the amount collected can exceed the levels appropriated depending on the actual number of applications, products, and establishments. Section 103(f) gives FDA new authority to retain excess amounts collected in one year and use them to reduce fees in the next year, rather than refunding the excess amounts. FDA is also permitted to transfer user fee moneys among certain appropriations accounts, as long as the funds are used solely for the process of reviewing human drug applications.

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## **B. Maintenance of Appropriations and Expenditures ("Water Line")**

An important part of the original PDUFA agreement was that user fees would not substitute for general fund appropriations. Rather, they would be added on top of the funds that FDA would otherwise receive and that FDA would otherwise be spending on the drug approval process.

In order to implement this understanding, Congress established "water line" appropriations and expenditure levels that had to be achieved in order to permit FDA to collect and retain user fees each year. The 1992 water line was formed by two related provisions. Section 736(f) of the FD&C Act provided that general fund appropriations for FDA each year must equal or exceed the 1992 appropriations level, as adjusted for inflation or changes in overall domestic discretionary budget authority. Section 736(g)(2)(B) provided that user fees must be used to increase the amount devoted to the drug application review process above the 1992 level, subject to the same adjustment factor as the appropriations level.

Changes in the water line were a major issue during the 1997 reauthorization process. Significant limitations on discretionary domestic spending have been enacted as part of the Balanced Budget Act. Concerns were therefore expressed that appropriations would not be sufficient to satisfy the water line, especially in the out years of the new five-year PDUFA reauthorization period. FDA, however, insisted on protecting its appropriations base, and industry insisted on ensuring that user fees remain additive to general fund revenues devoted to the drug approval process.

Congress ultimately agreed with these positions. Sections 103(e) and 103(f)(2) keep both of the water line provisions intact, changing only the base year from FY 1992 to FY 1997 (excluding user fees in the latter year). The Conference Committee Managers Statement (page 1) stated its expectation that "the appropriators will make every effort to meet the trigger so that FDA is allowed to collect and expend user fees. However, it must be acknowledged that particularly in the fifth year of the [Balanced Budget Act], budgetary pressures on all discretionary spending will be great. " The Conference Committee Managers Statement (page 2) also noted that, beginning in FY 1998, the appropriators "will require FDA to submit a directed operating budget" with a "functional breakdown of how appropriated dollars are spent," to improve congressional oversight of FDA's expenditures.

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## **C. Technical Changes**

The new law makes the following relatively minor technical changes in the user fee program:

- The exclusion from user fees for large volume parentals is modified so that it does not encompass therapeutic biologics, conforming the law to current FDA practice, of charging fees for these products (sections 102(1)(B) and (2)(B)).
- Fees are not charged for "interim" biological products licensed only for further manufacturing. Only the application for the final product is assessed a fee (sections 102(1)(B) and (2)(B)).
- Fees are not charged in connection with non-commercial products of federal or state governmental entities (sections 102(1)(B) and (2)(B)).
- The definition of "final dosage form" is changed to refer to a finished dosage form that does not require "substantial" further manufacturing. If a manufacturer completes all but the final step and then transfers the product to a second company for that step, the first manufacturer is considered the manufacturer of the final dosage form and its establishment is considered the place at which the manufacturing takes place (section 102(3)).
- The definition of "prescription drug establishment" is changed so that it no longer has to be under the management of a company listed as an applicant in a prescription drug application. Accordingly, contract manufacturing establishments are subject to fees (section 102(4)).
- The definition of "process for the review of human drug applications" is changed so that user fees can be used for third party reviews by FDA contractors (section 102(5)).
- The entire application fee is due up-front, when the application is submitted, rather than delaying fifty percent of the fee until after an action letter has issued. A conforming change is made in the refund procedure when an application is not accepted for filing (sections 103(a)(2)(A) and (B)).
- Applications for orphan drugs are statutorily exempt from fees, unless there are non-orphan indications in the application. This replaces the current discretionary waiver approach (section 103(a)(2)(C)).
- Supplements to add pediatric indications are exempt from fees (section 103(a)(2)(C)).
- The mechanism for assessing and collecting establishment fees is modified. The fees are assessed against applicants based on all of the establishments identified in their applications. If an establishment is named in more than one application, the fee is prorated among all of the relevant applications and applicants (section 103(a)(3)).
- The law is conformed to FDA practice of requiring both product and establishment fees by January 31 each year (section 103(a)(4)(A)).
- The exclusion from product and relevant establishment fees of drugs after they become subject to generic competition under ANDAs is extended to include antibiotics and drugs approved under the pre-1984 version of ANDAs. This corrects an oversight in the 1992 version of PDUFA (section 103(a)(4)(B)).

- The small business exception is liberalized to exempt a small business from paying any fee at all for its first application (sections 103(d)(5) and (6)).
- A statute of limitations is added for requests for fee waivers, reductions, or refunds. These must be made in writing within 180 days after the fee is due, except that requests relating to fees assessed under prior law must be made within one year of enactment of the PDUFA reauthorization (section 103(g)).

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## **D. FDA Performance Goals**

As in 1992, the FDA performance goals are referred to in the statute but are set forth separately. The 1997 performance goals are more ambitious than in 1992, both in terms of the time periods for review of applications and also with respect to other goals that are intended to shorten drug development times.

For "standard" NDAs, applications for biologics, and efficacy supplements, a goal of ten months rather than the current twelve months will be phased in during the next five years. The goal for "priority" applications will remain at six months. The goal for manufacturing supplements will be reduced from six months to four months during the next five years. A new goal of acting on resubmissions with relatively minor new information will start at six months and be phased down to two months over five years.

The other new goals relate to (1) meeting management, including time periods for scheduling meetings, (2) time periods for responses by the agency to sponsor submissions following imposition of a clinical hold, (3) informal appeals within the agency to resolve major disputes on procedural and scientific matters, (4) protocol assessment and agreement, including a procedure under which FDA can make binding commitments as to the adequacy of study design that can be altered only in light of new public health concerns, (5) development of a paperless INDNDA process by fiscal year 2002, and (6) simplification of action letters. As in 1992, all of the goals apply both to prescription drugs and to applications for drugs marketed initially as nonprescription drugs or switched from prescription to nonprescription status.

It will be important to monitor whether FDA is able to meet its performance goals and what effect these goals ultimately have on shortening the drug development process. Section 104 provides for annual reports on FDA's performance in meeting its goals and on its use of user fee funds.

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## **III. New Drugs and Biological Products**

Subtitle B of Title I of the FDA Modernization Act contains twenty-one provisions that apply to new drugs and biological products.

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### **A. Pediatric Studies of Drugs**

Section 111 of the FDA Modernization Act adds a new section 505A to the FD&C Act to provide an additional six months of market exclusivity for pharmaceutical manufacturers that conduct acceptable studies in children of drugs identified by FDA for which pediatric

information would be beneficial. It is derived from section 618 of the Senate bill and section 102 of the House bill. "Exclusivity" means the period during which FDA cannot approve an abbreviated NDA for the same drug that relies on the safety and effectiveness data in the original company's full NDA.

There is widespread agreement that it would be desirable to develop additional information on the use of drugs in pediatric populations. At present, section 505A is intended to provide adequate incentives for manufacturers to conduct these studies.

The critical feature of section 505A is that it is intended to provide additional exclusivity not just for pediatric indications or formulations, but for the adult indications and formulations as well. This is needed to make the incentive sufficient. Exclusivity targeted solely to pediatric indications would be useless and exclusivity for pediatric formulations is of little value. The exclusivity was therefore extended to the entire drug (i. e. , all uses and formulations with the same active ingredient).

*Section 505A* amends the existing exclusivity provisions in section 505 of the FD&C Act, which were added as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Waxman-Hatch Act). Those provisions are as follows:

1. Following the approval of an NDA for a new chemical entity (NCE) (i. e. , the first approval of a new drug), an abbreviated NDA cannot be submitted to FDA for five years from the date of approval of the NDA (section 505(j)(4)(D)(ii)).

There is one exception to this rule (in the same statutory clause). If the abbreviated NDA applicant wants to challenge a patent on the drug, it can submit the abbreviated NDA after four years. Under this exception, however, FDA cannot approve the abbreviated NDA until seven and a half years after NDA approval if a patent infringement suit is brought.

2. Following the approval of an NDA or supplemental NDA for a new indication or other change in an already-approved drug, FDA cannot approve an abbreviated NDA for the same change for three years (sections 505(j)(4)(D)(iii) and (iv)).

3. If there are patents on the drug, and the abbreviated NDA applicant does not want to challenge them, FDA cannot approve an abbreviated NDA until the patents have expired (section 505(j)(4)(B)(ii)). This is

known as a "paragraph III" certification (section 505(j)(2)(A)(vii)(III)). If the patents have already expired, the applicant makes a "paragraph II" certification, and the abbreviated NDA can be approved without any waiting period (sections 505(j)(2)(A)(vii)(II) and (j)(4)(B)(i)).

4. If the abbreviated NDA applicant does want to challenge one or more patents, it makes a "paragraph IV" certification (section 505(j)(2)(A)(vii)(IV)). If a patent infringement suit is then brought, FDA cannot approve the abbreviated NDA for thirty months (two and a half years). If the patent holder wins the case, FDA cannot approve the abbreviated NDA until after the patent expires (section 505(j)(4)(B)(iii)).

The five-year and three-year exclusivity provisions described in points 1 and 2, and the patent provisions in points 3 and 4, are independent of one another. Sometimes the exclusivity will run longer, and sometimes the patents will run longer. To make sure that any additional exclusivity period is meaningful, both sets of periods must be extended. In

any particular case, only one will be operative, because the other will run out first. The term of the patent itself is not extended. It is only the period during which FDA cannot approve an abbreviated NDA that is extended.

In addition to abbreviated NDAs, "follow-on" companies can submit what are called "section 505(b)(2) applications" or sometimes "paper NDAs." These also rely on the data in the original NDA. They are subject to the same exclusivity and patent provisions as are abbreviated NDAs. Section 505A therefore makes the identical changes in these provisions (codified in sections 505(b) and 505(c)) as are made for abbreviated NDAs in section 505(j). With this background, an analysis of section 505A can be provided.

*Section 505A(a)* applies when pediatric studies are requested by FDA for a drug that is not yet approved. If the studies are completed and accepted, six months of additional exclusivity is provided, as follows.

(1)(A)(i) For an NCE, the period during which an abbreviated NDA cannot be submitted is extended from five to five and a half years. If the abbreviated NDA applicant wishes to challenge a patent, the period is extended from four to four and a half years, and the corresponding period during which FDA cannot approve the abbreviated NDA if litigation is brought is extended from seven to seven and a half years. See point 1 above.

(1)(A)(ii) For a drug that is not an NCE, the period during which an abbreviated NDA cannot be approved is extended from three to three and a half years. See point 2 above.

(1)(B) In addition to extensions of the Waxman-Hatch periods, any applicable orphan drug exclusivity period is extended from seven to seven and a half years.

(2)(A) If the drug is subject to a patent that is not being challenged by the abbreviated NDA applicant (a paragraph III certification), the period during which FDA cannot approve the abbreviated NDA is extended until six months after the patent expiration. If the pediatric studies are done before the patent expires, the same rule applies even if the patent thereafter expires and the abbreviated NDA has submitted a paragraph II certification. See point 3 above.

(2)(B) If the drug is subject to a patent that is being challenged through a paragraph IV certification and the patent holder wins, the period during which FDA cannot approve the abbreviated NDA is extended until six months after the patent expires. See point 4 above.

*Section 505A(b)* requires FDA to develop a list of already-approved drugs for which additional pediatric information would be useful.

*Section 505A(c)* is identical to subsection (a), except that it applies to already-approved drugs on the subsection (b) list rather than to drugs that have not yet been approved.

*Section 505A(d)* describes the procedures and requirements for agreeing with FDA to conduct pediatric studies, for submitting the study reports to FDA, and for FDA to accept them. The Conference Committee Managers Statement (page 3) explained the intent that qualifying studies can be conducted either before or after a request from FDA has been made.

*Section 505A(e)* applies when an abbreviated NDA might be filed with FDA or approved after the pediatric study reports have been submitted to FDA but before the agency determines whether they meet the requirements for acceptance. Under these circumstances, FDA shall delay accepting or approving the abbreviated NDA for up to ninety days while it decides whether to accept the pediatric studies. If the agency does accept the studies, the six months of exclusivity is deemed to have been running during this delay period.

*Section 505A(f)* requires FDA to publish its determinations that the pediatric study requirements have been met, thus giving notice to abbreviated NDA applicants and potential applicants that the additional six-month exclusivity periods will apply.

*Section 505A(g)* defines "pediatric studies" to mean at least one clinical investigation, which may include a pharmacokinetic study, in pediatric age groups in which the drug is expected to be used.

*Section 505A(h)* applies when an NDA holder has received six months of exclusivity for pediatric studies and then seeks or obtains approval of a new use or other change in the drug. It is possible that FDA might then list this new version or use of the drug as eligible for additional pediatric studies. Under these circumstances, the NDA holder would be eligible for six months of additional exclusivity to be added to the three-year period that is available under subsection (c)(1)(B) (see point 2 above), but the NDA holder could not get the further protection of prohibiting FDA approval for six months beyond patent expiration (see points 3 and 4 above).

*Section 505A(i)* harmonizes the statutory exclusivity provision with FDA's proposed regulations, under which the agency could require pediatric studies to be performed, 62 Fed. Reg. 43900 (August 15, 1997). Any study required by FDA pursuant to its regulations is deemed to satisfy the requirements for exclusivity under section 505A.

*Section 505A(j)* is a sunset provision. In general, exclusivity may not be granted unless NDA for the drug has been submitted on or before January 1, 2002. After that date, exclusivity is available only if (1) the drug was in commercial distribution on the date of enactment of the FDA Modernization Act, (2) the drug was on the subsection (b) list as of January 1, 2002, (3) FDA determines that there is continuing need for pediatric and that the drug may provide health benefits in that population, and (4) all of the requirements of section 505A are met.

*Section 505A(k)* requires a report from FDA to Congress by January 1, 2001, concerning the effectiveness of the program under section 505A, the adequacy of the incentives, the economic impact of the program, and suggestions for changes.

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## **B. Expediting Study and Approval of Fast Track Drugs**

*Section 112* of the FDA Modernization Act adds a new section 506<sup>26</sup> to the FD&C Act to expedite the development and approval of new drugs that address unmet medical needs relating to serious or life-threatening conditions, referred to in the legislation as "fast track products." It comes from section 613 of the Senate bill and section 103 of the House bill. This section essentially codifies FDA's existing accelerated approval regulations in 21 C. F. R. 314.500 et seq., under which drugs for serious or life-threatening conditions can be approved based on surrogate endpoints, and expands it to include clinical endpoints as well. House Drug Report, page 55. The legislation also includes the limitations and

conditions in the regulations relating to phase IV study requirements, FDA review of promotional materials prior to use, and expedited withdrawal procedures. Phase IV studies will usually be required, while the provision for prior review of promotion should be applied only until FDA is assured that the sponsor is compliant with the law. House Drug Report, page 56.

*Section 506(a)* provides that sponsors may request "fast track" designation concurrently with filing of the IND or at any time thereafter. FDA must act on requests within thirty days.

*Section 506(b)* includes the various standards for approval, limitations, and conditions, taken from the FDA accelerated approval regulations, with the addition of clinical endpoints.

*Section 506(c)* provides for submission and review of a "rolling" NDA for a fast track drug. To expedite the review process, FDA may begin reviewing portions of the NDA as they are ready rather than waiting for the complete application to be submitted and filed. The user fee deadlines, however, will be calculated based on the date the application is complete.

*Section 506(d)* directs FDA to make persons aware of the fast track provisions, to encourage development of suitable surrogate endpoints, and to develop within one year a guidance document on fast track products.

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### **C. Information Program on Clinical Trials for Serious or Life-Threatening Diseases**

Section 113 of the FDA Modernization Act adds a new subsection (j) to section 402 of the PHS Act, 42 U. S. C. 282, to establish a coordinated program within NIH to provide information on research relating to serious or life-threatening diseases. It is based on section 808 of the Senate bill and section 105 of the House bill.

The program must include a data bank of information on clinical trials, comprised of a registry of trials, with information on study purpose, eligibility criteria, trial sites, and a contact person. The sponsor must forward information to the data bank within twenty-one days after approval of a protocol for a trial to test effectiveness. User fees cannot be used to support the data bank.

Information on a trial will be excluded from the data bank if the sponsor provides a detailed certification that disclosure of information would substantially interfere with timely enrollment of subjects, unless the Secretary responds with a detailed written determination to the contrary.

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### **D. Health Care Economic Information**

Section 114(a) of the FDA Modernization Act amends section 502(a) of the FD&C Act, which deals with misbranding, by adding a new provision on health care economic information. The provision is derived from section 612 of the Senate bill and section 109 of the House bill.

There is a growing demand from managed care organizations and others for this type of

information. FDA has applied its traditional "substantial evidence" requirement to the clinical safety and effectiveness component of cost-effectiveness and similar claims. This has created a significant barrier to the dissemination of information that is useful and reliable, and that meets contemporary scientific standards for cost-effectiveness data, but that does not satisfy the "two adequate and well-controlled study" requirement used for purely clinical claims.

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## **1. Standard of Evidence**

The amendment to section 502(a) responds to these concerns by requiring that health care economic information be based on "competent and reliable scientific evidence. " This is intended to encompass whatever standards "are widely accepted by experts" in the relevant fields, both economic and clinical. House Drug Report, page 67. The House Drug Report (page 66) cites a Federal Register notice published by the Federal Trade Commission, 49 Fed. Reg. 30999 (August 2, 1984), in connection with its reference to the standard. In this notice, the FTC describes its requirements for substantiation of advertising claims, including the requirement that the advertiser have a "reasonable basis" for its claims. This is a more lenient standard than the substantial evidence test traditionally applied by FDA.

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## **2. Definition**

"Health care economic information" is defined as "any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention. "

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## **3. Approved Indications**

The amendment to section 502(e) expressly modifies the misbranding provisions. Information that complies with this provision will not be considered "false or misleading. " While the provision does not amend the new drug approval requirements of section 505 of the FD&C Act, it does state that the requirements of section 505(a) and section 351(a) of the PHS Act "shall not apply to health care economic information" provided in accordance with this paragraph. Thus, FDA cannot bring an unapproved new drug charge against a manufacturer if it complies with this provision.

Health care economic information is covered by this provision only if it "directly relates to an indication approved" in the drug's NDA or other marketing application. The "directly relates" standard is not further defined or elucidated in the statute, but the House Drug Report (page 66) offers the following example:

. . . economic claims based on preventing disease progression would ordinarily not be considered to be directly related to an approved indication for the treatment of symptoms of a disease, for a drug in which the use in prevention of disease progression has not been approved. For example, rheumatoid arthritis drugs are approved for the treatment of symptoms and not for the prevention of deformity. Therefore, economic claims based in part

on an assumption of prevention of deformity would not be considered directly related to the approved indications for these drugs.

Similarly, economic claims based on prolonging patient survival would not be considered directly related and would not, therefore, be permitted under this subsection, for agents approved for the symptomatic treatment of heart failure, but not approved for prolonging survival in heart failure patients.

The Report (page 66) goes on to state that manufacturers can use "reasonable assumptions about health care economic consequences derived from, but not explicitly cited in, the approved indication . . . "

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#### **4. Audiences**

Health care economic information is covered by this provision when it is provided to formulary committees and similar groups responsible for selecting drugs for managed care organizations and similar entities.

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#### **5. Submission and Access**

The House Report (page 67) indicates Congress's expectation that health care economic information covered by this provision will be submitted to FDA at the time of first use under existing postmarket reporting requirements, 21 C. F. R. 314.81(b)(3). The provision states that data substantiating a health care economic claim must also be made available to FDA upon request. This may have been added because of some uncertainty as to whether the agency had authority to obtain the data under the inspection provisions of section 704(a)(1) of the FD&C Act in view of the exceptions in that section for FDA access to pricing, financial, and research data.

Section 114(b) of the FDA Modernization Act also directs the Comptroller General to conduct a study of the implementation of this section and to submit a report to Congress within four and a half years after enactment.

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### **E. Clinical Investigations**

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#### **1. Substantial Evidence**

Section 115(a) of the FDA Modernization Act amends section 505(d) of the FD&C Act to clarify that data from one adequate and well-controlled study, together with confirmatory evidence, may, in the discretion of FDA, constitute substantial evidence of effectiveness. This provision was in both section 408 of the Senate bill and section 110 of the House bill. This removes what FDA has often interpreted as a rigid two-study requirement under the FD&C Act. The new standard applies to all drugs, not just those for serious or life-threatening diseases.

The House Drug Report (page 67) states that this provision is intended "to codify current FDA practice. " It notes that the agency "has approved many new drugs on the basis of one well-controlled investigation, where other evidence was available to confirm the effectiveness of the drug. " The provision vests significant discretion in FDA to determine the circumstances under which one study will be acceptable. The House Drug Report (page 68) emphasizes that "the quality of the data and information about a drug, rather than the number of studies performed," should determine whether it is approvable.

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## **2. Women and Minorities**

Section 115(b) of the FDA Modernization Act amends section 505(b)(1) of the FD&C Act to provide that FDA shall consult with NIH and representatives of the pharmaceutical industry to review and develop guidance on the inclusion of women and minorities in clinical trials. This provision was in section 110 of the House bill. There was no comparable provision in the Senate bill. The reference to consultation with the pharmaceutical industry was added by the Conference Committee. The Conference Committee Managers Statement (page 3) noted specifically that this provision "does not require participation of women and minorities in any particular trial. "

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## **F. Manufacturing Changes for Drugs**

Section 116(a) of the FDA Modernization Act adds a new section 506A to the FD&C Act that is intended to reduce the number of postmarket manufacturing changes requiring FDA approval and otherwise to make it easier to implement manufacturing changes for approved drugs and biologics. This provision comes from section 614 of the Senate bill and section 111 of the House bill. FDA's requirements for submission and approval of supplements to authorize changes in the manufacturing process for approved drugs in 21 C. F. R. 314. 70 have long been regarded as unduly burdensome.

*Section 506A(a)* states that this new section applies to all post-approval manufacturing changes for new drugs and biological products.

*Section 506A(b)* requires that before distributing a drug made following any process change, the manufacturer must validate the effect of the change on identity, strength, quality, purity, and potency insofar as those factors may relate to safety or effectiveness. This requirement applies to all changes, whether major or otherwise.

*Section 506A(c)* provides that a manufacturer must file and obtain FDA approval of a supplemental NDA before implementing a major manufacturing change. A "major manufacturing change" is one that FDA has determined to have substantial potential adversely to affect identity, strength, quality, purity, and potency as they may relate to safety or effectiveness. These include changes in the approved qualitative or quantitative formulation (unless exempted by FDA), changes determined by FDA to require completion of a clinical trial demonstrating equivalence, or changes determined by FDA to have a substantial potential to adversely affect safety or effectiveness.

*Section 506A(d)* authorizes FDA to require that other changes be implemented either without submission of a supplement (similar to changes described in the annual report under current FDA regulations) or only after a supplement has been filed (similar to a "changes-being-effected" under current FDA regulations). For those changes not requiring a supplement, FDA may specify that they be reported in the annual report or on such other

date as the agency may require. With respect to changes-being-effected supplements, distribution may begin thirty days after submission unless FDA requires prior approval during that period, or it may begin immediately upon submission for specific categories of changes identified by the agency. If a supplement is disapproved, FDA has the discretionary authority to order the manufacturer to cease distribution. No authority is provided for FDA to order a recall of drugs already in distribution.

Section 116(b) of the FDA Modernization Act sets forth the effective date for new section 506A. Existing regulations may remain in effect for up to twenty-four months after enactment. The new rules will take effect either on the effective date of implementing regulations or twenty-four months after the date of enactment, whichever occurs first.

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## **G. Streamlining Clinical Research on Drugs**

Section 117 of the FDA Modernization Act amends section 505(i) of the FD&C Act to add specific provisions about the information required to be submitted to FDA as part of the investigational new drug (IND) application and the power of FDA to prevent or halt an investigation by a clinical hold. These provisions come from section 112 of the House bill. There were no comparable provisions in the Senate bill.

FDA's IND paperwork requirements for sponsors and investigators to initiate clinical research have been regarded as unduly burdensome. Many clinical studies are now conducted overseas for this reason. Sponsors have also been frustrated over the ease with which FDA may stop investigations through a formal or informal clinical hold and the difficulties they have in persuading the agency to lift such a hold.

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### **1. IND Requirements**

*Section 505(i)(2)* provides that an initial IND application must include information on study design, "adequate reports of basic information", certified by the applicant to be accurate, necessary to assess safety, adequate chemistry, manufacturing and controls information, and "primary data tabulations from animal or human studies. " A clinical investigation may begin thirty days after FDA receives an IND submission meeting these requirements. This builds on recent FDA guidance that has significantly reduced the size of IND submissions.

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### **2. Clinical Holds**

*Section 505(i)(3)* establishes procedural and substantive requirements for clinical holds. FDA may at any time prohibit a clinical investigation from starting or continuing by issuing a clinical hold. FDA must specify the basis for a clinical hold and confirm its determination in writing. The basis for the hold must include "the specific information available to the Secretary which served as the basis for such clinical hold. "

The standard for issuing a clinical hold is that the drug "represents an unreasonable risk to the safety" of the subjects of the investigation or other reasons established by FDA regulation. The IND regulations issued by FDA are required to provide that investigators will inform subjects that drugs are being used for investigational purposes and will obtain consent "except where it is not feasible or it is contrary to the best interests" of the

subjects.

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## **H. Data Requirements for Drugs and Biologics**

Section 118 of the FDA Modernization Act requires FDA, within twelve months of enactment, to issue a guidance that described when abbreviated reports may be submitted in lieu of full reports for clinical and nonclinical studies required to be included in an NDA or biologics license application. This provision was in section 615 of the Senate bill and section 113 of the House bill. It responds to the regulated industry's concern that drug development and approval times have increased in the United States in part because of the increasing demands of NDA reviewers for individual case report forms and other detailed supporting data, whereas reviewers in other countries rely to a much greater extent on summary or abbreviated study reports. As stated in the House Drug Report (page 70), the "elimination of extra or unnecessary data will result in a consistent and uniform approach throughout the agency, reduce the cost of NDAs, speed up the submission of these applications, reduce wasted time in FDA review of applications, and, thus, result in more efficient and effective development and review of product applications. " The Report (page 70) states that, while a pivotal study should be reported "in sufficient detail for agency reviewers to properly evaluate the study," other information "should be submitted in abbreviated or summary form. "

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## **I. Content and Review of Applications**

Section 119(a) of the FDA Modernization Act amends section 505(b) of the FD&C Act to improve the process for FDA review of NDAs and biological product applications. Parallel amendments are made in section 505(j) for abbreviated NDAs. These provisions come from section 114 of the House bill. There were no comparable provisions in the Senate bill. The House Drug Report (page 72) states that these provisions are intended "to provide for a predictable and dependable structure through which the FDA and sponsors . . . can communicate effectively regarding requirements that must be met to secure marketing clearance or approval. "

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### **1. Standards for Agency Reviewers**

*Section 505(b)(4)(A)* provides that FDA must issue guidance for reviewers relating to "promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards. " These standards must "apply equally to all individuals" who review applications.

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### **2. Agreement on Clinical Trial Design**

*Section 505(b)(4)(B)* requires FDA to meet with a sponsor upon reasonable written request for the purpose of reaching agreement on the design of pivotal trials. The Conference Committee Managers Statement (page 3) states, however, that FDA "may refuse to meet if the sponsor does not provide [sufficient] information" or if the agency "determines that such meeting is premature or would not be useful. " Agency minutes must be prepared and made available to the sponsor.

*Sections 505(b)(4)(C) and (D)* state that any agreement on study design at such a meeting must be put in writing. After testing begins, it cannot be changed unilaterally by FDA unless the director of the reviewing division issues a written decision that "a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun." Upon request, the director must meet with the sponsor to document the scientific issue on which this decision is based.

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### **3. Relationship to Field Activities**

*Section 505(b)(4)(E)* provides that a decision by the reviewing division is binding on field and compliance personnel unless such personnel "demonstrate to the reviewing division why such decision should be modified." Accordingly, determinations by headquarters chemists regarding appropriate manufacturing specifications and controls should not be subject to modification by field investigators who attempt to impose more stringent requirements by relying on their view of current GMP requirements.

*Section 505(b)(4)(F)* states that no action of the reviewing division may be delayed based on the results of a preapproval inspection or other information from field personnel, or the lack of information from the field (such as delays in conducting such an inspection), "unless the reviewing division determines that a delay is necessary to assure the of a safe and effective drug."

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### **4. Abbreviated New Drug Applications**

Section 119(b) of the FDA Modernization Act amends section 505(j) of the FD&C Act to make parallel changes in the process for reviewing and approving abbreviated NDAs.

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### **J. Scientific Advisory Panels**

Section 120 of the FDA Modernization Act adds a new section 505(n) to the FD&C Act to provide for the use of scientific advisory committees to provide expert scientific advice and recommendations to FDA regarding the clinical investigation and approval for marketing of new drugs and biological products. This provision came from section 115 of the House bill. There was no comparable provision in the Senate bill. The House Drug Report (page 73) states that this provision is intended "not merely to create additional administrative requirements for either FDA or its scientific advisors, but to make the advisory committee system more responsive to the needs of the FDA, sponsors and manufacturers, and patients."

FDA is required for the first time to establish advisory committees to provide advice on clinical investigations and approvals. Appointment and oversight authority cannot be delegated below the level of the Center Director.

Standards and requirements are established for committee membership, conflicts of interest, education and training, and pay. Consumer and industry representatives must be members of each advisory committee. For each drug reviewed, at least two members of the committee must have expertise in the particular disease or condition for which the drug is proposed to be indicated.

Meetings must be held at sufficiently regular intervals so that any matter will be reviewed within sixty days of being ready for review. Meetings may be held through the use of electronic communications. FDA must make a final decision within ninety days of receiving a recommendation from an advisory committee, or FDA must provide the reasons why it could not reach a decision.

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## **K. Positron Emission Tomography**

Section 121 of the FDA Modernization Act amends section 201 of the FD&C Act to add a new definition of a "compounded positron emission tomography drug" and amends section 501(a) to establish a new framework for the regulation of PET drugs. NDAs and abbreviated NDAs will not be required for licensed practitioners to compound PET drugs in accordance with United States Pharmacopeia (USP) standards until four years after the date of enactment or two years after FDA establishes approval procedures and GMP requirements, whichever occurs later. These provisions were in section 619 of the Senate bill and section 118 of the House bill.

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## **L. Requirements for Radiopharmaceuticals**

Section 122 of the FDA Modernization Act requires FDA to promulgate regulations governing the approval of radiopharmaceuticals. Proposed regulations must be issued within 180 days of enactment of the FDA Modernization Act, and final regulations within eighteen months of enactment. This provision was in section 609 of the Senate bill and section 119 of the House bill.

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## **M. Modernization of Regulation**

Section 123 of the FDA Modernization Act amends section 351 of the PHS Act to eliminate the requirement of separate product and establishment licenses, thus expanding FDA policy in 21 C. F. R. 601. 2 under which some types of biological products need have only one license. These provisions were in section 610 of the Senate bill and section 120 of the House bill.

Under the new law, applicable to all biological products, a product must be the subject of an approved biologics license. The standard for approval of a license is that the product is "safe, pure, and potent" and the manufacturing facility "meets standards designed to assure" that the product is safe, pure, and potent.

FDA is directed to harmonize, to the extent possible, the review and approval requirements for biological products and new drugs subject to full NDAs. The reference to full NDAs is intended to make clear that harmonization does not extend to applying the Waxman-Hatch provisions governing ANDAs to biological products. There remains no abbreviated application or approval process for biological products.

The new law also amends the PHS Act to make clear that the FD&C Act applies to biological products, except that a product with an approved license under section 351 of the PHS Act does not require an NDA under section 505 of the FD&C Act. This clarifies that all of the provisions applicable to new drugs under the FDA Modernization Act also apply to biological

products.

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## **N. Pilot and Small Scale Manufacture**

Section 124 of the FDA Modernization Act amends section 505(c) of the FD&C Act to provide that a drug manufactured in a pilot or other small scale facility can be used to establish safety and effectiveness and to obtain approval prior to scale-up, unless FDA determines that a full scale facility is necessary to ensure safety or effectiveness. This provision came from section 608 of the Senate bill and section 121 of the House bill. It confirms and expands a policy that FDA has recently implemented to permit the approval of biological products manufactured in pilot and other small scale facilities. Previously, FDA had generally required that products used in pivotal testing be manufactured in a full scale production facility.

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## **O. Insulin and Antibiotics**

Section 125 of the FDA Modernization Act repeals the outdated approval and batch certification requirements for insulin and antibiotics in sections 506 and 507, respectively, of the FD&C Act. Products in both categories will now be subject to the NDA requirements of section 505 that apply generally to new drugs. The provision comes from section 122 of the House bill. There was no comparable Senate provision.

Section 125(c) of the FDA Modernization Act preserves current law relating to exports, under which unapproved insulin and antibiotic products can be exported under section 801 (e) of the FD&C Act, without regard to the more restrictive requirements of section 802 for other unapproved new drugs.

Section 125(d) of the FDA Modernization Act addresses the important question of the effect of the repeal of section 507 of the FD&C Act on the application of the Waxman-Hatch exclusivity and patent provisions to antibiotics. FDA had accepted and approved abbreviated applications for antibiotics (Form 6) before enactment of the Waxman-Hatch Act in 1984, without regard to any exclusivity or patent considerations. Congress did not change this policy when it enacted the abbreviated NDA procedures for new drugs. Now that antibiotics are subject to section 505, the Waxman-Hatch procedures will apply for any antibiotic NDA first submitted to FDA after the date of enactment of the FDA Modernization Act.

Antibiotics approved by FDA under section 507 of the FD&C Act before the date of enactment are considered to be subject to approved NDAs and abbreviated NDAs (depending on whether they were approved through the full or abbreviated process under section 507). The Waxman-Hatch protections will not apply to any application for an antibiotic if the antibiotic was the subject of any application under section 507 received by FDA before the date of enactment of the FDA Modernization Act. FDA is authorized to publish a list of such drugs.

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## **P. Elimination of Certain Labeling Requirements**

Section 126 of the FDA Modernization Act makes two changes in drug labeling

requirements. First, prescription drugs are permitted to bear the symbol "Rx only" instead of the old longer statement "Caution: Federal Law prohibits dispensing without prescription. " Second, the obsolete labeling provisions in section 502(d) of the FD&C Act relating to labeling of "habit forming" drugs are repealed. These provisions were in section 802 of the Senate bill. There were no comparable provisions in the House bill.

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## **Q. Application of Federal Law to Practice of Pharmacy Compounding**

Section 127 of the FDA Modernization Act adds a new section 503A to the FD&C Act to permit pharmacy compounding under specified circumstances. The provision is derived from section 809 of the Senate bill. There was no comparable provision in the House bill. The Conference Committee Managers Statement (page 4) expresses the purpose of this provision: "It is the intent of the conferees to ensure continued availability of compounded drug products as a component of individualized therapy, while limiting the scope of compounding so as to prevent manufacturing under the guise of compounding. "

*Section 503A(a)* provides that a drug product may be compounded without complying with the requirements for GMPs, adequate directions for use, or NDA approval if is compounded by a licensed pharmacist or physician for an identified individual patient based on the unsolicited receipt of a valid prescription that a compounded drug is necessary for the patient. The drug must be compounded only (1) upon receipt of the prescription or (2) beforehand in "limited quantities," based on a history of prescriptions within an established relationship between the pharmacist and the patient or the patient's physician.

*Section 503A(b)* requires that the drug product must be compounded from bulk drug substances that comply with USP standards, are components of approved drugs (if no USP monograph exists), or are listed by FDA (if neither of the first two standards applies). The pharmacist must not "compound regularly or in inordinate amounts . . . any drug products that are essentially copies of a commercially available drug product. "

A drug is "essentially a copy" if there is no "significant difference" from the commercially available drug. According to the Conference Committee Managers Statement (page 4), this standard cannot be used as a "mere pretext. " For example, "minor changes in strength . . . that are not known to be significant" would not qualify. FDA also can take into account other circumstances, such as whether the prescribing physician "is receiving financial remuneration or other financial incentives to write prescriptions for compounded products. "

A drug product cannot be compounded if it is on a list promulgated by FDA of drugs that are demonstrably difficult to compound. Compounding can only be performed in a State that has entered into a memorandum of understanding with FDA addressing "the distribution of inordinate amounts of compounded drug products interstate" or, if there is no such memorandum of understanding, if the interstate distribution of compounded drugs does not exceed five percent of the pharmacist's total prescriptions dispensed.

*Section 503A(c)* prohibits the compounding pharmacy from advertising or promoting the compounding of any particular drug or class or type of drug. The general availability of a compounding service may be advertised.

*Section 503A(d)* requires FDA to issue implementing regulations. The agency must consult an advisory committee unless the issuance of regulations without such consultation is necessary to protect the public health.

*Section 503A(e)* states that this section does not apply to PET drugs or radiopharmaceuticals, which are governed by sections 121 and 122 of the FDA Modernization Act, respectively.

*Section 503A(f)* provides that "compounding" does not include mixing, reconstituting, and other acts in accordance with the manufacturer's directions.

Section 127(b) of the FDA Modernization Act establishes the effective date for this section one year after enactment of the FDA Modernization Act. The Conference Committee Managers Statement (page 5) states that FDA should undertake to promulgate implementing regulations during this period.

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## **R. Reauthorization of Clinical Pharmacology Program**

Section 128 of the FDA Modernization Act amends section 2 of Public Law 102-222, 105 Stat. 1677 (1991), to reauthorize the FDA clinical pharmacology training program established under that statute through fiscal year 2002. This provision comes from section 812 of the Senate bill. There was no comparable provision in the House bill.

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## **S. Reports of Postmarketing Approval Studies**

Section 130 of the FDA Modernization Act adds a new section 506B to the FD&C Act dealing with postmarketing phase IV studies to which manufacturers have agreed as a condition of NDA approval. This provision came from section 810 of the Senate bill. There was no comparable provision in the House bill. Other phase IV studies, which the manufacturer has not agreed with FDA to conduct as a condition for NDA approval, are not covered by the provision.

*Section 506B(a)* requires sponsors to make annual reports to FDA on the progress of their required phase IV studies. This applies both to new studies and to existing phase IV commitments. Initial reports for the latter studies must be made within six months of the issuance of implementing regulations.

*Section 506B(b)* states that information in these reports shall be made public to the extent necessary to identify the sponsor, to establish the status of the study, and to identify any reasons for failing to carry out the study.

*Section 506B(c)* directs FDA to publish an annual report in the Federal Register on the status of these studies and to submit a report to Congress by October 1, 2001.

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## **T. Notification of Discontinuance**

*of a Life Saving Product*

Section 131 of the FDA Modernization Act adds a new section 506C to the FD&C Act requiring notice to FDA from the sole manufacturer of life-supporting products six months before the manufacturer discontinues production. This provision came from section 131 of the House bill. There was no comparable provision in the Senate bill.

Section 506C applies to drugs that are life-supporting, life-sustaining, or intended for use in the prevention of debilitating disease or condition, except for recombinant products that replace products originally derived from human tissue. The manufacturer may request a reduction in the six-month notification period for these drugs for good cause, such as biomaterials shortages, liability problems, or substantial economic hardship. FDA is required to distribute information on the discontinuance of these drugs to appropriate physicians and patient organizations to the maximum extent practicable.

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## **U. Other Relevant Provisions**

Many other provisions of particular relevance to new drugs and biological products are set forth in Title IV of the new law. These are discussed in Part VI of this analysis.

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## **IV. Nonprescription Drugs and Cosmetics**

Five provisions of the FDA Modernization Act focus specifically on nonprescription drugs and one provision applies to cosmetics.

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### **A. National Uniformity for Nonprescription Drugs**

Section 412(a) of the FDA Modernization Act adds a new section 751 to the FD&C Act to establish national uniformity for nonprescription drugs. This provision is derived from section 807 of the Senate bill and section 129 of the House bill. The Senate Report (pages 63-67) and the House Drug Report (pages 79-80) contain extensive legislative history on this provision.

*Section 751(a)* states the general rule that, except as otherwise provided, no State (including a political subdivision) may establish any requirement that relates to the regulation of a nonprescription drug and that is different from or in addition to, or that is otherwise not identical with, a requirement under the FD&C Act, the Poison Prevention Packaging Act of 1970, or the Fair Packaging and Labeling Act. The Conference Committee Managers Statement (pages 13-14) emphasizes that national uniformity does not apply to State advertising laws patterned after the Federal Trade Commission Act that deal with claims substantiation, fair balance, and misleading or deceptive advertising.

*Section 751(b)* provides that FDA may, by regulation, grant an exemption from the general rule of national uniformity, after notice and opportunity for written and oral presentation of views, under such conditions as may be prescribed in the regulation. The State must demonstrate that its requirement protects an important public interest that would otherwise be unprotected, would not cause any drug to be in violation of federal law, and would not unduly burden interstate commerce. FDA is required to make a decision on an exemption application not later than 120 days after receiving the application.

*Section 751(c)* provides that national uniformity shall not apply to any State requirement that relates to the practice of pharmacy or any State requirement that a drug be dispensed only upon the prescription of a licensed practitioner. The scope of national uniformity is defined to include any requirement relating to public information or any other form of public communication relating to a warning of any kind for a drug.

*Section 751(d)* excludes from national uniformity a drug that is not approved through a new drug or antibiotic drug application or a final OTC drug monograph. This exclusion does not apply where one of the three federal statutes or an implementing regulation establishes federal requirements relating to the same subject as the State requirement. All requirements established by a State public initiative or referendum enacted prior to September 1, 1997, are explicitly excluded from national uniformity. Thus, California Proposition 65 is excluded from national uniformity but all future similar State requirements will be subject to national uniformity.

*Section 751(e)* states that this new section does not modify or otherwise affect the product liability law of any State.

*Section 751(f)* provides that nothing in this section shall prevent a State from enforcing a requirement that is identical to a requirement of the FD&C Act.

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## **B. Records Inspection for Nonprescription Drugs**

Section 412(b) of the FDA Modernization Act amends section 704(a)(1) of the FD&C Act to extend the authority of FDA to inspect company records to include human nonprescription drugs to the same extent that this authority now exists for prescription drugs. The Conference Committee Managers Statement (page 13) endorses FDA Compliance Policy Guide 130.300, which establishes the FDA policy of not ordinarily requesting company quality assurance audit reports in order to encourage the regulated industry to conduct these self-audits. The Statement also emphasizes that the new records inspection authority applies only to products determined to be nonprescription drugs and not to products that are solely cosmetics.

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## **C. Active and Inactive Ingredient Labeling for Nonprescription Drugs**

Section 412(c) of the FDA Modernization Act amends section 502(e)(1) of the FD&C Act to make two changes with respect to nonprescription drug labeling. First, the label is required to bear quantity or the proportion of each active ingredient. Previously, the label was required to bear only the name of each active ingredient. Second, the label must bear the name of each inactive ingredient listed in alphabetical order on the outside container of the retail package, and on the immediate container if determined to be appropriate by FDA. The provision specifically states that no trade secret shall be required to be divulged. Cosmetic drugs, which are required to state the cosmetic ingredients in descending order or predominance, are excluded from the requirement that inactive ingredients be listed in alphabetical order.

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## **D. Nonprescription Sunscreen Drugs**

Section 121 of the FDA Modernization Act provides that FDA must issue regulations for nonprescription sunscreen drugs not later than eighteen months after the date of enactment. This provision was in section 813 of the Senate bill. There was no comparable provision in the House bill. The Conference Committee Managers Statement (page 6) states that various technical and scientific issues may take longer than eighteen months to resolve and that the conferees do not intend that all regulation in this area be complete or comprehensive by a specified date.

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## **E. National Uniformity for Cosmetics**

Section 412(d) of the FDA Modernization Act adds a new section 752 to the FD&C Act to establish national uniformity for cosmetics. This provision is derived from section 807 of the Senate bill and section 129 of the House bill.

*Section 752(a)* states the general rule that, except as otherwise provided, no State (including a political subdivision) 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 FD&C Act, the Poison Prevention Packaging Act of 1970, or the Fair Packaging and Labeling Act.

*Section 752(b)* provides that FDA may, by regulation, grant an exemption from the general rule of national uniformity under the same requirements and conditions that are established in Section 751(b) for nonprescription drugs.

*Section 752(c)* provides that national uniformity for packaging and labeling includes any specific requirement relating to the same aspect of the cosmetic as a requirement specifically applicable to the particular cosmetic or class of cosmetics under the FD&C Act for packaging or labeling, including any State requirement relating to public information or any other form of public communication.

*Section 752(d)* states that this new section does not modify or otherwise affect the product liability law of any State.

*Section 752(e)* provides that this section shall not apply to a State requirement adopted by a State public initiative or referendum enacted prior to September 1, 1997. Thus, California Proposition 65 is excluded from national uniformity but all future similar State requirements will be subject to this section.

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## **V. Medical Devices**

Title II of the FDA Modernization Act affects all aspects of medical device regulation -- clinical trials, device classification, review of marketing applications, postmarketing reporting and device tracking, labeling, and global harmonization of device manufacturing requirements.

This part of the analysis summarizes those provisions of the 1997 Act that specifically refer to medical devices. Rather than proceeding serially through each section of the 1997 Act, this part groups the sections by topic, in order to permit a conceptual understanding of the changes to current device law.

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### **A. Investigational Devices**

Section 201 of the 1997 Act amends section 520(g) of the FD&C Act to require FDA to issue certain regulations concerning investigational devices.

First, FDA must issue regulations, within one year of enactment, to permit manufacturers to make certain modifications (including manufacturing changes) to an investigational device without the need for a new investigational device exemption (IDE) application or supplement, provided that the modification is not a "significant change in design or in basic principles of operation. " This provision was in both the House (§ 202) and Senate (§ 601) bills.

Second, FDA must also permit, without the need for an additional IDE approval, changes to clinical protocols that do not affect (1) the validity of the clinical data or the likely benefit-to-risk relationship, (2) the scientific soundness of the investigational plan, or (3) the rights or safety of the human subjects. The sponsor may make changes in the device or protocol if it determines the applicable conditions are met and gives FDA notice not later than 5 days after making the change or modification. This provision is patterned on section 202 of the House bill.

The 1997 Act also directs FDA to review a clinical trial protocol for any class III or any implantable device, prior to a submission to an institutional review board (IRB) or for an investigational device exemption (IDE), for the purpose of reaching agreement with the applicant regarding the investigational plan. If the applicant so requests in writing, FDA must meet with the applicant within 30 days of the request. Agreements between FDA and the manufacturer regarding the clinical plan shall be part of the administrative record and shall not be changed except (1) with the written agreement of the sponsor/applicant, or (2) upon a decision by the Director of the Office of Device Evaluation (ODE) "that a substantial scientific issue essential to determining the safety or effectiveness of the device involved has been identified. " These provisions are based on section 202 of the House bill.

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## **B. Performance Standards**

Section 204 of the 1997 Act adds a subsection (c) to section 514 of the FD&C Act. This provision is based on section 205 of the House bill and section 205 of the Senate bill. It authorizes FDA to recognize, in whole or in part, an appropriate standard established by a nationally or internationally recognized standards-development organization. Manufacturers may certify compliance with such standards for the purpose of meeting an applicable premarket submission requirement or other requirement under the FD&C Act.

FDA must publish, in the Federal Register, a notice listing the recognized standards. FDA can withdraw recognition of a standard if it determines the standard is no longer appropriate for meeting a requirement applicable to devices under the FD&C Act.

A manufacturer who elects to rely on a standard shall provide a declaration of conformity to FDA, certifying that the device is in conformity with the standard. FDA shall accept such a declaration unless it finds that the standard is not applicable to the particular device under review, or the submitted data and information do not demonstrate that the device conforms to the standard.

A manufacturer who submits a declaration of conformity with a listed standard can be required, at any time, to submit the data and information relied upon in making the declaration. The falsification of a declaration of conformity, or the refusal to submit the underlying data or information, is a prohibited act under section 301 (as amended). In addition, a device is adulterated if it fails to conform in all respects to the standard.

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## **C. 510(k) Notification**

The 1997 Act makes numerous changes affecting 510(k) notification, including expanding the number of devices that are exempt from 510(k), authorizing third-party review of 510(k) notifications, and specifying standards for the review of data and information in a 510(k).

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### **1. Exemptions**

Section 206(a) of the 1997 Act adds new sections 510(l) and 510(m) to the FD&C Act. These provisions are patterned after section 207(a) of the House bill and section 603 of the Senate bill.

Under new section 510(l), class I devices shall be exempt from the 510(k) notification requirement, except those devices that are intended for a use of substantial importance in preventing impairment of human health, or that present a potentially unreasonable risk of illness or injury.

For class II devices, pursuant to new section 510(m), FDA must publish in the Federal Register, within 60 days of enactment, a list of each type of class II device that will be exempt from 510(k) requirements. Such exemption will be effective on the date of publication. Beginning one day after that publication, any person may petition FDA to exempt additional types of class II devices from 510(k) requirements. FDA may also exempt additional class II devices on its own initiative. FDA shall publish notice of the intended exemption and provide opportunity for public comment. FDA must publish a final determination regarding the exemption within 120 days after issuance of the notice of intent. If FDA fails to respond to a petition within 180 days of receiving it, the petition shall be deemed to be granted.

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### **2. Review Time**

Section 209(a) of the 1997 Act adds section 510(n) to the FD&C Act, directing FDA to review and make a determination on a 510(k) notification not later than 90 days after receiving it. This provision is derived from section 405(a) of the Senate bill.

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### **3. Predicate Devices**

Section 206(c) of the 1997 Act amends section 513(i) to direct FDA to specify the principles it will use in determining when a marketed device which is labeled for a general use cannot be the predicate device for a new device labeled with more specific claims. FDA must issue such guidance, within 270 days of enactment of this legislation, describing when a specific intended use is not reasonably included within a general use for purposes of determining substantial equivalence. Similar provisions were in the House (§ 207(c)) and Senate (§ 407) bills.

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### **4. Scope of Review**

Section 205(b) of the 1997 Act amends section 513(i) of the FD&C Act, which defines "substantial equivalence," by adding several new provisions.

In reviewing a 510(k), FDA shall consider the extent to which reliance on postmarket controls may expedite device classification and marketing clearance under the 510(k) process. In addition, when a new device has different technological characteristics than the predicate device, FDA shall only request "information that is necessary to making substantial equivalence determinations" and that constitutes "the least burdensome means of demonstrating substantial equivalence." These provisions are based on section 206(b) of the House bill and section 404(b) of the Senate bill.

In resolving differences between the House and Senate bills, perhaps the most controversial device provision related to FDA's ability to consider off-label uses in reviewing a 510(k). This issue was addressed in section 206(b) of the House bill and section 404(b) of the Senate bill.

Section 205(b) of the 1997 Act resolves the controversy in favor of the provisions in the House bill. FDA's determination of the intended use, for purposes of determining substantial equivalence, shall be based upon the proposed labeling submitted in the 510(k). However, if the Director of ODE determines that there is a "reasonable likelihood that the device shall be used for an intended use not identified in the proposed labeling" and "such use could cause harm," FDA can require an appropriate statement in the labeling concerning the off-label use, such as a proscription or contradiction. FDA must give notice within 10 days of such a determination to the manufacturer, to permit an opportunity for consultation concerning such use. Although the agency can specify labeling limitations, it cannot refuse to clear the device for marketing based on concerns about potential harm from the unlabeled use. These provisions relating to consideration of unlabeled uses shall sunset in 5 years. At such time, Congress can consider the effect of these provisions, such as whether they helped to get devices to the market more quickly and with adequate protection of the public health.

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## **5. Effect of Other Statutory Requirements on**

### *510(k) Review*

Section 206(b) of the 1997 Act amends section 513(f) of the FD&C Act. It prohibits FDA from refusing to clear a 510(k) notification for a device based on a manufacturer's failure to comply with statutory requirements unrelated to a substantial equivalence determination, such as good manufacturing practice (GMP) regulations. An important exception, however, is when FDA determines that "there is a substantial likelihood that the failure to comply with such [GMP] regulations will potentially present a serious risk to human health." This provision is based primarily on section 207(b)(2) of the House bill; a provision was also in section 406 of the Senate bill.

This provision is generally aimed at prohibiting FDA from re-instituting its prior policy of maintaining a "reference list" of firms believed not to be in GMP compliance and denying any and all 510(k) clearances for such firms, as well as prohibiting ad hoc agency determinations to deny 510(k) clearances for a device where a firm is alleged to have unrelated GMP violations. The intent is to avoid using the 510(k) process as an enforcement tool for GMP requirements.

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## **6. Changing Automatic Class III Designation For A Non-SE Device**

Under section 513 of the FD&C Act, an FDA determination that a device is not substantially equivalent (non-SE) has left that device in class III until it is reclassified.

Section 207 of the 1997 Act amends section 513(f) to permit the 510(k) submitter to request a review of that automatic class III classification within 30 days of receiving the non-SE determination. Both the House (§ 207(b)(1)) and Senate (§ 604) bills had similar provisions.

The submitter shall provide data and information to FDA to support the requested classification of the device into class I or II. FDA must then determine the appropriate classification of the device based on the classification criteria in section 513, and issue that determination within 60 days of receiving the submitter's request to review and classify. If FDA determines the device should remain in class III, a premarket approval application will be required. A classification determination under this provision shall be published in the Federal Register within 30 days.

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## **7. Third-Party Review**

Section 210 of the 1997 Act adds a new section 523 to the FD&C Act to embody a pilot program for third-party review of 510(k) notifications. Section 210 of the House bill and section 204 of the Senate bill provided for a third-party review program.

Not later than 180 days after enactment, FDA shall accredit organizations that will be authorized to review 510(k) notifications and make recommendations to FDA on the initial classification. Not later than 30 days after receiving the accredited organization's written recommendation, FDA shall make a determination on the 510(k). If FDA makes a different determination than the organization, FDA must provide the 510(k) submitter with a detailed statement explaining the reasons for the change.

These accredited organizations cannot perform a review for a class III device, or for a class II device which is intended to be permanently implanted or which is life-supporting or life-sustaining. Nor can they review a class II device for which clinical data must be submitted in the 510(k); for this group of devices, the number of them less the number of the other devices excluded from third-party review may not exceed 6 percent of the number which equals the total number of 510(k)s submitted in a year less the number of 510(k)s excluded. The ratio just described is subject to adjustment to exclude class III devices reclassified to class II, and include class II devices exempt from 510(k) requirements. The Conference Committee's Joint Explanatory Statement (page 7) simply states that the excluded category of class II devices for which clinical data are required "is limited in size to not more than six percent of all 510(k) submissions. " Not later than 3 years after enactment, FDA shall report to Congress its determination as to whether Congress should remove the limitation on review of 510(k)s for class II devices for which clinical data are required.

The Act specifies the qualifications and requirements applicable to organizations seeking accreditation. Within 180 days of enactment, FDA must publish in the Federal Register criteria to accredit or deny accreditation. FDA shall also conduct on-site audits of accredited organizations, which will be subject to FDA inspection under section 704 of the FD&C Act. FDA may suspend or withdraw accreditation of any organization that is not in substantial compliance or that poses a threat to public health.

FDA's accreditation authority under these provisions shall terminate at the earliest of (1) 5 years after FDA notifies Congress that at least 2 accredited organizations are available to review 60 percent of the 510(k) notifications, or (2) 4 years after FDA notifies Congress that it has made determinations with respect to at least 35 percent of the devices reviewed by accredited organizations. As described in the Conference Committee's Joint Explanatory Statement (page 7), this section "provides for the termination of the pilot program after [FDA] has met specified targets for inclusion of eligible devices. "

The Comptroller General is required to submit a report to Congress not later than 5 years after enactment describing the extent to which the accreditation program has been implemented. In addition, not later than 6 months prior to the date that FDA's accreditation authority will terminate, the Comptroller General shall submit a report to Congress describing the use of accredited organizations and evaluating the extent to which their actions either promoted or were contrary to the purposes of the FDCA.

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## **D. Premarket Approval Application(PMA)**

The 1997 Act affects the submission and review of a premarket approval application (PMA) in several important respects.

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### **1. Presubmission Meeting**

Section 209(b) of the 1997 Act amends section 513(a) of the FD&C Act to require FDA to meet with a manufacturer prior to submission of a PMA. Section 209 of the House bill and section 302 of the Senate bill had similar provisions.

The purpose of the meeting is to determine the type of clinical data that will be necessary to demonstrate the effectiveness of a device for its proposed conditions of use. Within 30 days following the meeting, FDA shall specify in writing any clinical data necessary to establish a reasonable assurance of device effectiveness. The data can be from "one or more" well-controlled investigations. FDA shall consider, in consultation with the applicant, "the least burdensome appropriate means" that would have "a reasonable likelihood of resulting in approval. " FDA's determination as to the necessary data shall be binding on the agency, "unless such determination . . . could be contrary to the public health. "

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### **2. Scope of Review**

Section 205(c)(1) of the 1997 Act amends section 515(d) of the FD&C Act to direct FDA to "rely on the conditions of use included in the proposed labeling" as the basis for determining whether there is a reasonable assurance of safety and effectiveness for a PMA device, provided the proposed labeling is neither false nor misleading. FDA shall "fairly evaluate all material facts pertinent to the proposed labeling" in determining whether it is false or misleading. This provision was in section 206(c)(1) of the House bill and section 404(a) of the Senate bill.

Section 205(a) of the 1997 Act amends section 513(a) to direct FDA, in making a determination on the effectiveness of a device, to consider whether the extent of effectiveness data that otherwise would be required for PMA approval can be reduced

through reliance on postmarket controls. This provision is based on section 206(a) of the House bill.

Section 217 of the 1997 Act amends section 513(a)(3) to clarify that "one or more clinical investigations," and not necessarily more than one, is the requirement applicable to evidence of effectiveness for a device. Both the House (§ 206(a)) and Senate (§ 408) bills contained similar provisions.

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### **3. Collaborative Review Process**

Section 209(b) of the 1997 Act amends section 515(d) of the FD&C Act to encourage a collaborative process for PMA review. This provision is based primarily on section 302 of the Senate bill; section 209 of the House bill also addressed this issue.

Upon written request, FDA is required to meet with the applicant not later than 100 days after a PMA has been filed as complete, for the purpose of discussing the review status of the application. Prior to the meeting, FDA shall provide in writing a description of any deficiencies that have been identified at that point, based on an interim review of the entire application. In addition, FDA must promptly notify the applicant in writing of any additional deficiency subsequently identified.

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### **4. PMA Supplements**

Section 205(c)(2) of the 1997 Act amends section 515(d) of the FD&C Act to require submission of a PMA supplement for any change to a device that affects safety or effectiveness. However, a preapproval supplement is not required if the change is a modification in a manufacturing procedure or method of manufacturing, and the PMA holder submits a written notice describing the change, summarizing the data and information supporting the change, and informing FDA that the change has been made in accordance with GMP requirements. Such notice must be submitted 30 days before distributing a device subject to the manufacturing change. The devices may be distributed after 30 days, unless FDA acts within that time to notify the PMA holder that the notice is not adequate and describes the additional information required. If FDA requires a preapproval supplement, the agency must review it within 135 days of its receipt. House bill section 206(c)(2) and Senate bill section 601(c) were similar.

The Act also specifies requirements for FDA review of PMA supplements relating to an incremental change to the design of a device that affects safety or effectiveness. FDA shall approve such a supplement if (1) nonclinical data demonstrate that the design modification creates the intended additional capacity, function, or performance of the device, and (2) clinical data, from the approved application and any supplement to it, provide a reasonable assurance of safety and effectiveness for the changed device. FDA may require additional clinical data to evaluate the design modification if needed. Again, this provision is similar in both the House and Senate bill provisions cited above.

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### **5. Data From Previous Device Studies**

Section 201(b) of the 1997 Act amends section 515(d) to require FDA to accept in a PMA,

under certain conditions, "statistically valid and reliable data" and other information from previous clinical investigations of a prior generation of a device or of another device. FDA must accept the data or information if either of these conditions is met:

- (a) they are derived from investigations of an earlier version of the device, the device was modified after the investigation but before the PMA was submitted, and the modification is not a significant change in design or basic principles of operation that would invalidate the data or information; or
- (b) they relate to an approved device that is available for marketing under the FDCA and are relevant to the design and intended use of the device that is the subject of the pending PMA.

This provision is from section 601(c) of the Senate bill.

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## **6. Use Of The PMA Data Of Other Manufacturers**

Section 216(a) of the 1997 Act amends section 520(h) of the FD&C Act to authorize FDA to use data and information from any manufacturer's PMA six years after its approval. This provision is from section 403 of the Senate bill.

FDA can use PMA information that includes data from clinical and preclinical studies demonstrating safety or effectiveness, but cannot use "descriptions of methods of manufacture and product composition and other trade secrets. " FDA can use the information (1) to approve another device, (2) to determine whether a product development protocol (PDP) has been completed for another device, (3) to establish a performance standard or special controls, or (4) to classify or reclassify another device.

When FDA uses PMA data or information for one of the authorized agency actions, the summary of safety and effectiveness (SSE) for that PMA shall constitute the evidentiary support for FDA's action.

These provisions replace the provisions relating to approval of the fourth device of a kind. As a conforming amendment, the judicial review provisions of section 517 are amended to delete reference to decisions under section 520(h)(4)(B), relating to the identification of the fourth device of a kind.

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## **7. Expedited Review For Certain Devices**

Section 202 of the 1997 Act amends section 515(d) of the FD&C Act to direct FDA to "provide review priority" for certain devices that can provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. These include devices (1) representing breakthrough technologies, (2) for which no approved alternatives exist, (3) which offer significant advantages over existing approved alternatives, or (4) the availability of which is in the best interest of patients. This provision is from section 203 of the House bill.

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## **8. Representation Of Approval**

Section 421 of the 1997 Act repeals section 301(l) of the FD&C Act, which prohibited manufacturers from representing truthfully in labeling that a device has an approved PMA. This provision was in both the House (§ 218) and Senate (§ 409) bills.

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## **E. Product Development Protocol**

Section 216(b) of the 1997 Act amends section 515(f) of the FD&C Act, which establishes the product development protocol (PDP) process, to make review by an advisory panel optional. Under the amendment, (1) FDA, on its own initiative, may refer a proposed protocol to a panel for a recommendation respecting approval, or (2) FDA shall refer the protocol to a panel upon the request of the submitter (unless the proposed protocol substantially duplicates a PDP previously reviewed by a panel). This provision had no counterpart in the House or Senate bills.

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## **F. Humanitarian Use of Devices**

Section 203 of the 1997 Act amends section 520(m) of the FD&C Act, which establishes the humanitarian device exemption, in several respects. Section 204 of the House bill and section 103 of the Senate bill had provisions relating to humanitarian devices.

First, FDA must issue an order granting or denying an application requesting humanitarian use of a device within 75 days after receiving an application for such use.

Second, the Act provides a new exception from the requirement for prior IRB approval of a humanitarian use, where a physician determines in an emergency situation that the delay could cause serious harm or death to a patient. In such a situation, the physician must notify the IRB's chair after the use of the device.

Third, the Act deletes the current language of paragraph (5), which limits the term of a humanitarian use exemption granted to a device. Instead, FDA may require the applicant to demonstrate continued compliance with the requirements for the exemption if the agency believes either that the criteria for exemption are no longer satisfied or that it is otherwise necessary to protect the public health. FDA may suspend or withdraw a humanitarian device exemption only after notice and an opportunity for an informal hearing.

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## **G. Postmarketing Requirements And Reporting**

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### **1. Device Tracking**

Section 211 of the 1997 Act amends section 519(e) of the FD&C Act, effective 90 days after enactment, to repeal the statute's mandatory tracking requirement in favor of providing FDA with some discretion in determining whether to require tracking of a device. This provision is based on section 212 of the House bill and section 605(b) of the Senate bill.

FDA may issue an order to require tracking of a class II or class III device meeting one of these criteria: (1) the failure of the device would be reasonably likely to have serious adverse health consequences; (2) the device is intended to be implanted for more than one year; or (3) the device is life-sustaining or life-supporting and used outside a device user facility. A device is subject to tracking requirements only if it is the subject of such an order.

The Act also authorizes a patient who receives a device subject to tracking to refuse to release, or to refuse permission to release, the patient's name, address, social security number, or other identifying information for the purpose of tracking. This provision is from section 605(a) of the Senate bill.

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## **2. Postmarket Surveillance**

Section 212 of the 1997 Act amends section 522 of the FD&C Act to repeal the mandatory requirement for postmarket surveillance in favor of providing FDA with discretion in determining whether to require it. This provision is based on provisions in section 213 of the House bill and section 606 of the Senate bill.

FDA may issue an order to require a manufacturer to conduct postmarket surveillance for a device which is class II or class III and meets one of these criteria: (1) the failure of the device would be reasonably likely to have serious adverse health consequences, (2) the device is intended to be implanted for more than one year, or (3) the device is life-sustaining or life-supporting and used outside a device user facility.

Within 30 days of receiving an order requiring postmarket surveillance, a manufacturer is required to submit to FDA, for agency approval, a plan for the required surveillance. Within 60 days of receipt of the plan, FDA must determine if the plan is adequate for "the collection of useful data that can reveal unforeseen adverse events or other information necessary to protect the public health. "

FDA may order a prospective surveillance period of up to 36 months. If FDA believes a longer period is necessary, that must be arranged by mutual agreement of the manufacturer; absent such agreement, FDA must utilize the dispute resolution process established in new section 562 of the FD&C Act. This provision is from section 213(b) of the House bill.

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## **3. Medical Device Reporting**

Section 213(a) of the 1997 Act amends section 519 of the FD&C Act to repeal the requirement for submission of medical device reports (MDR) by distributors. The Act directs FDA to issue regulations requiring distributors to maintain records relating to device safety and effectiveness. Similar provisions were in section 215 of the House bill and section 607 of the Senate bill.

The Act also repeals the requirement for distributors to report on corrections or removals of a device. This provision also was in both the House and Senate bills.

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## **4. User Facility Reporting**

Section 213(c) of the 1997 Act amends the user facility reporting requirements in section 519(b) of the FD&C Act.

Device user facilities will be required to submit on an annual (rather than semi-annual) basis a summary of the user reports they submitted in the prior year.

FDA is directed to issue regulations establishing a "sentinel system," under which user facility reporting will apply only to a "subset of user facilities that constitutes a representative profile of user reports for device deaths and serious illnesses or serious injuries. " Until this system is implemented, the current requirements continue to apply to all device user facilities. Not later than 2 years after enactment, FDA shall submit a report to Congress describing the plan for a sentinel system and the progress toward its implementation. This provision is based on section 215(c)(2) of the House bill.

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## **5. Registration Requirements**

Section 213(b) of the 1997 Act amends section 510(g) of the FD&C Act to exempt "wholesale distributors" of devices from the requirement for establishment registration, provided that they do not manufacture, repackage, process, or relabel a device. This provision was in section 215(b) of the House bill and section 607(b) of the Senate bill.

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## **H. Administrative Provisions**

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### **1. Classification Panels**

Section 208 of the 1997 Act amends section 513(b) of the FD&C Act to direct FDA to schedule classification panel meetings so as to meet applicable statutory deadlines. This provision is based on section 208 of the House bill.

In addition, a manufacturer whose device is the subject of review by a panel shall be given access to the same data and information submitted to the panel (except for trade secret data), shall be able to submit information to the panel that is based on information in the manufacturer's PMA, and shall have the same opportunity as FDA to participate in panel meetings. Manufacturers whose devices are subject to panel review are to be given adequate time for both an initial presentation and response to the views presented at the meeting. This provision also is from the House bill.

After receiving a panel recommendation, FDA shall make a final decision on a PMA in accordance with section 515(d)(2). If FDA's decision differs from the panel's recommendation, FDA must notify the manufacturer in writing of the reasons for the difference.

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### **2. Practice of Medicine**

Section 214 of the 1997 Act adds section 906 to the FD&C Act to clarify that the statute should not be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer a legally marketed device for any condition or disease within the context of a legitimate patient-practitioner relationship. This provision is based on section 216 of the House bill.

FDA retains authority, however, to establish restrictions on the sale, distribution, or labeling of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. In addition, this section does not affect any existing prohibition on the promotion of unapproved uses of a device.

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### **3. Noninvasive Blood Glucose Meter**

Section 215 of the 1997 Act (without amending the FD&C Act) sets forth certain congressional findings about diabetes and expresses the sense of the Congress that the availability of a safe and effective noninvasive blood glucose meter would enhance the health and well-being of people with diabetes. This provision is from section 221 of the House bill.

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#### **I. Global Harmonization**

Section 410 of the 1997 Act amends the device GMP provisions in section 520(f) of the FD&C Act. It requires that FDA, before adopting GMP regulations, must ensure that the regulations conform, to the extent practicable, in whole or in part, with internationally recognized standards defining quality systems. This provision was in section 214 of the House bill and section 202 of the Senate bill.

The Act also amends section 803 to direct FDA to support the Office of the U. S. Trade Representative in discussions with other countries in order to reduce the burden of regulation and harmonize regulatory requirements to the extent consistent with consumer protection.

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#### **J. Other Relevant Provisions**

Other provisions of particular relevance to medical devices -- such as dissemination of treatment information on unapproved uses, and expanded access to unapproved therapies and diagnostics -- are set forth in Title IV of the 1997 Act. These are discussed in Part VI this analysis.

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### **VI. General Provisions**

Title IV of the FDA Modernization Act contains twenty-two sections that are characterized in the legislation as "general provisions" because they apply to more than one category of regulated products. Some of these apply only to particular categories of regulated

products, but most apply to all products regulated by FDA.

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## **A. Dissemination of Information on New Uses**

Section 401 adds a new subchapter D to the FD&C Act, consisting of new sections 551-557 authorizing manufacturers to disseminate information on unapproved ("off-label") uses of approved drugs, biological products, and devices. This provision is based on section 811 of the Senate bill and sections 106 and 107 of the House bill.

These provisions respond to the problem created by FDA's highly restrictive prohibition on the dissemination of off-label information. Industry and patient groups have long pointed out that FDA policies prevent the distribution of highly credible current information that is needed for physicians to treat their patients most effectively and in accordance with the latest medical knowledge. First Amendment concerns also have been expressed. FDA has responded that some off-label uses are unsafe or ineffective, and that manufacturers should file supplements so that FDA can review the data. These provisions request a compromise that allows the distribution of some off-label information, but only if the manufacturer complies with a number of restrictions.

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### **1. Section 551 (General Requirements)**

Section 551(a) permits a manufacturer to distribute written information concerning a use not described in the approved labeling under the conditions described in subsection (b). The information can be distributed to practitioners, pharmacy benefit managers, insurers, group health plans, and governmental agencies. It cannot be distributed directly to patients.

*Section 551(b)* sets forth requirements for distributing information under this section:

- The drug, biological product, or device must be approved.
- The information must comply with section 552.
- The information must not be derived from research conducted by another manufacturer, except with its permission.
- The manufacturer must submit the information to FDA sixty days before beginning distribution, together with safety and effectiveness information from clinical trials safety information from reports of clinical experience.
- The manufacturer must comply with section 554, relating to the submission of a supplement covering the use in question.
- The manufacturer must include with the information to be disseminated a prominent statement that the use has not been approved, a copy of the approved labeling, and disclosures relating to authorship and funding, as well as a bibliography.

*Section 551(c)* permits FDA to require the manufacturer to disseminate additional safety and effectiveness information to provide objectivity and balance, as well as an objective statement prepared by FDA itself.

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## **2. Section 552 (Information That May Be Disseminated)**

The only information that a manufacturer may distribute is (1) an unabridged reprint of a, peer-reviewed article published in a scientific or medical journal about a clinical investigation, which would be considered "scientifically sound," or (2) a reference publication containing similar information. To qualify, a reference publication must not have been prepared at the manufacturer's request, significantly influenced or distributed solely by the manufacturer, focus on a particular drug or device, or present materials that are false or misleading.

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## **3. Section 553 (Reports to FDA)**

A manufacturer must submit to FDA on a "biannual"<sup>27</sup> basis a list of articles and reference publications distributed under section 551 and a list identifying the categories of persons that received them. Records must be maintained to facilitate any required corrective action under section 555.

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## **4. Section 554 (Supplements)**

*Section 554(a)* provides that a manufacturer can disseminate information under section 551 only if it has submitted to FDA a supplemental application covering the new use, the manufacturer certifies that it will submit such a supplement, or it has an exemption from the supplement requirement.

*Section 554(b)* states that a manufacturer may satisfy the requirements of this section by submitting a certification to FDA that it has completed the studies necessary for the supplement and that it will submit the supplement within six months of the initial dissemination of information under section 551.

*Section 554(c)* provides that, if the studies have not been completed, the manufacturer must submit a proposed protocol and schedule for the studies to FDA, along with a certification that the supplement will be submitted within thirty-six months of the initial dissemination of information. FDA must make a determination that the proposed protocol is adequate and the schedule is reasonable. The manufacturer must make periodic progress reports to FDA. There is a provision permitting FDA to extend the thirty-six-month period for up to twenty-four additional months if the manufacturer has acted with "due diligence. "

*Section 554(d)* permits the manufacturer to request an exemption from the supplement requirement from FDA if it would be "economically prohibitive" or "unethical" to conduct the studies and submit the supplement. An exemption request will be deemed to be approved if it is not acted on by FDA within sixty days of receipt, but FDA can thereafter terminate the approval.

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## **5. Section 555 (Corrective Actions)**

*Section 555(a)* provides that, if FDA receives new information indicating that the new use may not be effective or may present a "significant risk to public health," the agency may take appropriate action, including ordering the manufacturer to cease dissemination. FDA must consult with the manufacturer before taking action under this subsection. Pursuant to regulations to be promulgated by FDA, manufacturers will be required to report new safety and effectiveness information to FDA.

*Section 555(b)* authorizes FDA to order a manufacturer to cease dissemination if there has been a failure to comply with the statutory requirements, the agency has determined that the supplement is inadequate for approval, the manufacturer has not submitted the supplement within six months as promised or has not acted with due diligence in the completion of studies and submission of the supplement, or FDA has terminated a "approved" exemption from the supplement requirement.

*Section 555(d)* authorizes FDA to order a manufacturer to correct information that has been disseminated.

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## **6. Section 556 (Definitions)**

Several terms are defined. Most significantly, "scientific or medical journal" is defined as a journal with an expert editorial board and policy requiring full disclosure by authors of conflicts of interest, which requires that articles be peer-reviewed in accordance with regular procedures, that is "generally recognized to be of national scope and reputation," that is indexed in the Index Medicus, and that is not in the form of a "special supplement" funded wholly or partly by one or more manufacturers.

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## **7. Section 557 (Rules of Construction)**

*Section 557(a)* codifies the current FDA rule that these provisions do not prohibit manufacturers from responding to unsolicited requests from health care practitioners.

*Section 557(b)* states that information disseminated in accordance with these provisions is not labeling, and such dissemination shall not be considered adulteration, misbranding, or evidence of a new intended use.

*Section 557(c)* states that these provisions do not affect patent rights in any respect.

*Section 557(d)* states that these provisions do not affect the rights of publishers to require authorization or to charge a fee for reprints.

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## **8. Other Provisions**

The dissemination of information in violation of these provisions is made a prohibited act under new section 301(z) of the FD&C Act. FDA is required to promulgate implementing regulations within one year of the enactment of the FDA Modernization Act. These provisions take effect one year after enactment or upon issuance of final implementing regulations, whichever occurs first. These provisions cease to be in effect on September 30, 2006, or seven years after the date of promulgation of implementing regulations,

whichever is later. The Comptroller General must conduct a study and submit a report to Congress by January 1, 2002, on the impact of these provisions on FDA resources. FDA must arrange, through the Institute of Medicine, for a study of the scientific issues raised by these provisions, to be submitted to Congress by September 30, 2005.

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## **B. Expanded Access to Investigational Therapies and Diagnostics**

Section 402 of the FDA Modernization Act adds a new section 561 to the FD&C Act to authorize expanded access to drugs and devices that are still undergoing investigation. This provision largely codifies existing regulations and practice. It is based on section 102 of the Senate bill and section 104 of the House bill.

This section applies to drugs and devices intended for use in "serious" diseases and conditions. The Conference Committee Managers Statement (page 11) expressed its intent that this term be broadly construed:

The conferees note that they purposely used broad language in this section relating to 'serious' conditions, without attempting to define them, in order to permit wide flexibility in implementation. Illnesses that do not cause death, or imminent death, can nonetheless destroy the lives of both patients and their families. The conferees therefore intend that the seriousness of an illness be given broad consideration, to take into account all of the circumstances involved.

The Statement also noted that manufacturers are often understandably reluctant to make investigational products available to seriously and terminally ill patients. This can "jeopardize the approval of their product because these patients' medical progress on any therapy may conflict with or be inconsistent with data from patients in the clinical studies. " The Statement therefore directed FDA to "evaluate ways to address this problem, particularly for terminal patients who have failed existing approved therapies. "

*Section 561(a)* allows FDA to authorize shipments of investigational drugs and devices in emergency situations. The current FDA drug regulations already permit this. 21 C. F. R. § 312. 36.

*Section 561(b)* allows physicians to request a manufacturer to provide an investigational drug or device for a particular patient if (1) the physician determines that there is no comparable or satisfactory therapy and the probable risk from the drug is not greater than the probable risk from the disease, (2) FDA determines there is sufficient evidence of safety and effectiveness to support use in the particular case, (3) FDA determines that providing the drug or device will not interfere with initiation, conduct, or completion of clinical trials, and (4) the sponsor or clinical investigator submits a protocol consistent with the IND or IDE regulations for treatment use in small numbers of patients (21 C. F. R. § 312. 35(b)).

*Section 561(c)* authorizes expanded access of an investigational drug or device under a treatment protocol. This largely codifies FDA's treatment IND regulations in 21 C. F. R. 312. 34 and 312. 35. FDA is authorized to disseminate information about the availability of drugs and devices under the expanded access protocols authorized by this provision.

*Section 561(d)* authorizes FDA to terminate expanded access at any time if the

requirements of this section are no longer being met.

*Section 561(e)* defines "investigational drug," "investigational device," "treatment IND," and "treatment IDE" by reference to FDA's regulations.

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### **C. Approval of Supplemental Applications for Approved Products**

Section 403 of the FDA Modernization Act sets forth requirements relating to FDA approval of supplemental applications for all forms of agency approval of articles under the FD&C Act and the PHS Act. This is accomplished by direct statutory enactment without amendment of the FD&C Act or the PHS Act. Section 108 of the House bill was limited to drugs and biological products, but section 611 of the Senate bill applied broadly to all regulated articles that require FDA approval. The Conference Committee adopted the Senate version of the legislation.

The House Drug Report (pages 63-65) contains legislative history regarding the of supplemental applications for approved new drugs and biological products. It acknowledges that in many instances there is no incentive for the submission of a supplemental application and in fact there may be disincentives. As a result, a significant number of drugs are prescribed in a manner which differs in some respect from the labeling approved by FDA. The Report states that this legislative provision is designed to result in new FDA policy in order to reduce the disincentives to the submissions of these applications by reducing the cost and increasing the efficiency of handling them within the agency.

*Subsection (a)* requires FDA to publish in the Federal Register not later than 180 days after the date of enactment standards for the prompt review of supplemental applications for approved articles.

*Subsection (b)* requires FDA within the same time to issue final guidance to clarify the requirements for, and facilitate the submission of data to support, the approval of supplemental applications. The guidance must clarify when published material may be the basis for approval a supplemental application and must avoid duplication of data submitted in the original application. It must also define those supplemental applications that are eligible for priority review.

*Subsection (c)* requires FDA to designate an individual in each Center (except the Food Center) who will be responsible for encouraging the prompt review of supplemental applications and working with applicants to facilitate submissions.

*Subsection (d)* requires the Secretary of HHS to develop programs and policies that will foster collaboration between FDA, NIH, professional medical and scientific societies, and others, to identify any studies that may support supplemental applications and to encourage sponsors to make supplemental applications or conduct further research in support of a supplemental application based on such studies.

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### **D. Dispute Resolution**

Section 404 of the FDA Modernization Act amends the FD&C Act to add a new section 562 dealing with resolution of scientific controversies relating to drugs, biological products, and

medical devices. As contained in section 116 of the House bill, this provision applied to all regulated products. The Senate bill contained no comparable provision. The Conference Committee adopted the House provision but limited it to drugs, biological products, and devices.

*Section 562* provides that, where there is a scientific controversy between FDA and the sponsor, applicant, or manufacturer and no other provision of the FD&C Act or an FDA regulation provides a right of review, FDA must establish a procedure by regulation under which review may be requested. This procedure must include review by an appropriate scientific advisory committee. FDA must promulgate such regulations within one year after the date of enactment of the FDA Modernization Act.

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## **E. Informal Agency Statements**

Section 405 of the FDA Modernization Act adds new subsection 701(h) to the FD&C Act to govern the use of informal agency statements. Section 401 of the Senate bill required only that FDA promulgate a regulation regarding the development, issuance, and use of guidance documents after evaluating the effectiveness of the good guidance practices (GGP) document that FDA published in the Federal Register on February 27, 1997. Section 117 of the House bill set forth requirements and criteria for all FDA informal statements. The Conference Committee adopted the House provision, with slight changes, and added the Senate requirement at the end.

The House Drug Report (pages 73-74) contains important legislative history with respect to this provision. The report strongly endorses the view that the value of FDA guidance documents is to provide consistency and predictability and emphasizes the importance of assuring that the FDA staff apply the new provision and implementing regulations in a consistent manner.

*Section 701(h)(1)(A)* requires FDA to develop guidance documents with public participation and ensure that such documents are made publicly available both in written form and electronically. These guidance documents do not create or confer any rights for or on any person but they do present the views on FDA on matters under its jurisdiction.

*Section 701(h)(1)(B)* provides that, although guidance documents are not binding on FDA, FDA must ensure that its employees do not deviate from such guidance without appropriate justification and supervisory concurrence.

*Section 702(h)(1)(C)* requires that, for guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are not minor, complex scientific issues, or highly controversial issues, FDA must ensure public participation prior to implementation. An exception is made where FDA determines that prior public participation is not feasible or appropriate, in which case FDA must provide for public comment after implementation begins and must take such comment into account.

*Section 701(h)(1)(D)* provides that, for guidance documents that set forth existing practices or minor changes in policy, FDA may provide for public comment after implementation begins.

*Section 701(h)(2)* requires that guidance documents contain uniform nomenclature and uniform internal procedures for approval. Such documents must be dated and periodically reviewed and, where appropriate, revised.

*Section 701(h)(3)* requires FDA to maintain electronically, and to publish periodically in the Federal Register, a list of guidance documents.

*Section 701(h)(4)* requires FDA to establish an effective appeals mechanism to address complaints that FDA is not developing and using guidance documents in accordance with this subsection. This provision was not contained in the House or Senate bills and was added by the Conference Committee.

*Section 701(h)(5)* requires that FDA promulgate a regulation no later than July 1, 2000, specifying policies and procedures for the development, issuance, and use of guidance documents, consistent with the requirements of new section 701(h), after evaluating the effectiveness of the GGP document published by the agency in the Federal Register on February 27, 1997.

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## **F. Food and Drug Administration Mission and Annual Report**

Section 406 of the FDA Modernization Act amends section 903 of the FD&C Act to establish a statutory mission for FDA and to require an annual plan and annual report. Sections 101 and 501 of the Senate bill and section 123 of the House bill contained differing versions of these requirements. The Conference Committee included all of the provisions of both bills.

*Section 903(b)* establishes an FDA mission statement. The mission of FDA is to promote the public health by taking appropriate action on the marketing of regulated products in a timely manner, and to protect the public health by ensuring that regulated products are safe, effective, and properly labeled. FDA is also required to participate in international harmonization efforts. The agency is required to consult with independent experts, consumers, and industry in carrying out its mission.

*Section 903(f)(1)* requires FDA, after consultation with interested individuals and groups, to publish in the Federal Register within one year after the date of enactment a plan to bring the agency into compliance with each of the obligations established under the FD&C Act. The plan must be reviewed and revised biannually.

*Section 903(f)(2)* requires the agency plan to include objectives and mechanisms to achieve such objectives specifically relating to review of applications and other submissions, maximizing information for consumers and patients, implementing inspection and postmarket monitoring, insuring access to the scientific and technical expertise needed by FDA to meet its obligations, establishing mechanisms by July 1, 1999, for meeting the time period specified in the FD&C Act, and eliminating backlogs in the review of applications by January 1, 2000.

*Section 903(g)* requires FDA to publish an annual report in the Federal Register and to solicit public comment on it. The report must provide detailed statistical information on the performance of the Secretary under the agency plan required by section 903(f), compare the FDA performance with the objectives of the plan and with the statutory obligations of the agency, and identify any regulatory policy that has a significant negative impact on compliance with the plan and the statute and set forth any proposed revision of such policy.

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## **G. Information System**

Section 407 of the FDA Modernization Act adds a new section 741 to the FD&C Act to require FDA to establish an information system regarding all submissions to the agency requesting agency action. The provision makes it clear that such a system must encompass every form of request made to the agency, regardless of its designation. Thus, it includes everything from new drug applications and device premarket notifications to citizen petitions requesting any form of action. The legislation requires FDA to submit a report to Congress on the status of the system, including the projected costs and concerns about confidentiality, not later than one year after the date of enactment.

This provision was taken from section 124 of the House bill. The Senate bill did not contain a comparable provision. The Conference Committee Managers Statement (page 11) states that the conferees intend that the information system shall provide access to the information by the applicant under conditions set by FDA. Such access shall not be provided, however, until appropriate safeguards are in place to ensure the integrity and confidentiality of the information to which access is provided. Once such safeguards are in place, accordingly, applicants will be able directly to access the current status of their matter through this information system. Other persons will not have such access.

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## **H. Education and Training**

Section 408(a) of the FDA Modernization Act establishes new section 742 of the FD&C Act to provide for training and education programs for FDA employees relating to their regulatory responsibilities. It combines a brief provision in section 125 of the House bill with the intramural research training program in section 804 of the Senate bill, resulting in a substantially new provision.

*Section 742(a)* requires FDA to conduct training and education programs for FDA employees relating to the regulatory responsibilities and policies established by the FD&C Act, including programs for scientific training, inspections (including inspection specialization), administrative process and procedure, and integrity issues.

*Section 742(b)* authorizes FDA to establish, through fellowship and other training programs, intramural research training for predoctoral and postdoctoral scientists and physicians.

In addition to these FDA programs, section 408(b) of the FDA Modernization Act amends the PHS Act to establish a separate comparable fellowship and training program in the Centers for Disease Control and Prevention (CDC). New sections 317G of the PHS Act requires CDC to establish fellowship and training programs to train individuals in epidemiology, surveillance, laboratory analysis, and other disease detection and prevention methods, in order to train health personnel to work toward the prevention and control of diseases, injuries, and disabilities.

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## **I. Centers for Education and Research on Therapeutics**

Section 409 adds a new section 905 to the PHS Act authorizing a demonstration grant program to establish and operate one or more centers for education and research on therapeutics. This is derived from section 126 of the House bill. There was no comparable provision in the Senate bill.

The lead agency for implementing this section is the Agency for Health Care Policy and Research (AHCPR), which is directed to consult with FDA. The Conference Committee Managers Statement (page 12) states that AHCPR is the lead agency because of "its expertise in the evaluation of the effectiveness of clinical care, its non-regulatory role, and its close working relationship with the health care community in the improvement of the quality of care. "

The activities to be supported by grants under this provision are extremely broad:

- The conduct of clinical and laboratory research to--
  - increase awareness of (i) new uses of drugs, biological products and devices; (ii) ways to improve their effective use; and (iii) risks of new uses and combinations of drugs and biological products.
  - provide objective clinical information to practitioners, pharmacy benefit managers, managed care organizations, insurers, and consumers.
  - improve the quality and reduce the cost of health care through appropriate use of drugs, biological products and devices and through prevention of adverse effects resulting from their use.
- the conduct of research on comparative safety and effectiveness of drugs, biological products, and devices.
- other appropriate activities, except for the review of new drugs.

Grant applications are subject to peer review before being approved.

Appropriations are authorized in the amounts of \$2,000,000 for fiscal year 1998 and \$3,000,000 for each fiscal year from 1999 through 2002.

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## **J. Mutual Recognition Agreements and Global Harmonization**

Section 410 of the FDA Modernization Act contains two provisions designed to encourage conformity of FDA requirements with international standards. It represents the of section 202 of the Senate bill and sections 127 and 214 of the House bill.

*Section 410(a)* of the FDA Modernization Act amends section 520(f)(1)(B) of the FD&C Act to add a new provision to require FDA to insure that the device good manufacturing practice (GMP) requirements conform, to the extent practicable, with internationally recognized standards defining quality systems for medical devices.

*Section 410(b)* of the FDA Modernization Act amends section 803 of the FD&C Act to add a new subsection (c).

*Section 803(c)(1)* requires FDA to support the office of the United States Trade Representative to reduce the burden of regulation and harmonize regulatory requirements if FDA determines that such harmonization continues consumer projections consistent with the purposes of the FD&C Act.

*Section 803(c)(2)* requires similar FDA support in efforts to move toward the acceptance of mutual recognition agreements relating to the regulation of all products under FDA's jurisdiction, including the regulation of GMP, between the European Union and the United States.

*Section 803(c)(3)* requires FDA regularly to participate in meetings with foreign governments to discuss and reach agreement on methods and approaches to harmonize regulatory requirements.

*Section 803(c)(4)* requires FDA to make public a plan that establishes a framework for achieving mutual recognition of GMP inspections not later than 180 days after the date of enactment.

*Section 803(c)(5)* excludes dietary supplements from these new provisions.

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## **K. Environmental Impact Review**

Section 411 of the FDA Modernization Act amends the FD&C Act to add a new section 746 relating to environmental impact analyses and statements. This provision is identical to section 602 of the Senate bill and section 128 of the House bill.

*Section 746* provides that, notwithstanding any other provision of law, an environmental impact statement prepared in accordance with the FDA regulations in 21 C. F. R. part 25 shall be considered to meet the requirements for a detailed statement under section 102 (2)(C) of the National Environmental Policy Act (NEPA) of 1969. The Conference Committee Managers Statement emphasizes that the conferees believe that the new FDA procedures implementing NEPA appropriately eliminate unnecessary paperwork and delays.

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## **L. National Uniformity for Nonprescription Drugs**

These provisions are dealt with separately in part IV of this analysis.

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## **M. Food and Drug Administration Study of Mercury Compounds in Drugs and Food**

Section 413 of the FDA Modernization Act requires an FDA study of mercury compounds in drugs and food. This provision is taken from section 130 of the House bill. There was no comparable provision in the Senate bill. There is no legislative history relating to the reason for this provision.

*Section 413(a)* requires FDA to compile a list of drugs and foods that contain intentionally introduced mercury compounds and provide a quantitative and qualitative analysis of the mercury compounds in that list. This must be completed within two years after the date of enactment.

*Section 413(b)* requires FDA to conduct a study of the effect on humans on the use of mercury compounds in nasal sprays.

*Section 413(c)* requires FDA, by itself or under contract with the NAS Institute of Medicine, to conduct a study of the effect on humans of the use of elemental, organic, or inorganic mercury when offered for sale as a drug or dietary supplement. The study must evaluate the scope of mercury use for these purposes and the adverse effects on the health of children and other sensitive populations. FDA must consult with EPA, the Consumer Product Safety Commission (CPSC), and the Agency for Toxic Substances and Disease Registry (ATSDR), in conducting this study. If FDA concludes that mercury in drugs or dietary supplements poses a threat to human health, the agency is required to promulgate regulations restricting the sale of mercury for such use. Such regulations must be designed to protect the health of children and other sensitive populations but should not unnecessarily interfere with the availability of mercury for use in religious ceremonies.

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## **N. Interagency Collaboration**

Section 414 of the FDA Modernization Act adds a new section 903(c) to the FD&C Act to require interagency collaboration. This provision comes from section 201 of the Senate bill. There was no comparable provision in the House bill.

*Section 903(c)* requires FDA to implement programs and policies that will foster collaboration between FDA, NIH, and other science-based federal agencies in order to enhance the scientific and technical expertise available to FDA in discharging its duties with respect to the development, clinical investigation, and postmarket monitoring of emerging medical therapies, including complementary therapies and advances in nutrition and food science.

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## **O. Contracts for Expert Review**

Section 415 of the FDA Modernization Act amends the FD&C Act to add a new section 907 governing contracts for expert review. This is taken from section 203 of the Senate bill. The House bill did not contain a comparable provision.

*Section 907(a)(1)* authorizes FDA to enter into contracts with any organization or individual with relevant expertise to review and evaluate any application or submission made under the FD&C Act or the PHS Act for the approval or classification of an article, for the purpose of making recommendations to the agency on the matter. Any such contract is subject to the confidentiality provisions of section 708 of the FD&C Act.

*Section 907(a)(2)* provides that FDA may use this authority whenever the agency determines that it will improve the timeliness of the review unless it would reduce the quality or unduly increase the cost. FDA may also use this authority if FDA determines that it will improve the quality of the review, unless it would unduly increase cost. *Section 907(b)* provides that the FDA official responsible for any matter for which expert review is shall review the recommendations of the organization or individual who conducted the expert review and make a final decision regarding the matter in a timely manner. A final decision by FDA on the matter must be made within the applicable prescribed time period established in the FD&C Act or the PHS Act.

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## **P. Product Classification**

Section 416 of the FDA Modernization Act adds a new section 563 to the FD&C Act to provide for classification of products. This provision is taken from section 402 of the Senate bill. The House bill did not contain a comparable provision.

*Section 563(a)* provides that a person who submits an application or other submission under the FD&C Act may request FDA for a determination respecting the classification of the product as a drug, biological product, device, or combination product subject to section 503(g) of the FD&C Act or respecting the FDA organizational component that will regulate the product. Any such request must include a recommended classification or organizational component.

*Section 563(b)* requires FDA to determine the classification or organizational component not later than sixty days after receipt of the request for a determination. FDA may not subsequently modify such statement except with the written consent of the person or for public health reasons based on scientific evidence.

*Section 563(c)* provides that, if FDA fails to meet the sixty-day deadline, the recommendation made by the person submitting the request for a determination shall be considered to be a final determination. That determination may not subsequently be modified by the Secretary except with the written consent of the person or for public health reasons based on scientific evidence.

The Conference Committee Managers Statement (page 14) emphasizes that the authority of FDA to modify product classifications, after they are made, is limited to public health reasons based on scientific information.

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## **Q. Registration of Foreign Establishments**

Section 417 of the FDA Modernization Act amends section 510(i) of the FD&C Act to foreign establishments to register with FDA if they manufacture drugs or devices that are imported or offered for import into the United States. This provision is identical to section 801 of the Senate bill. There was no comparable provision in the House bill.

Registration of foreign establishments under the Drug Listing Act had previously been voluntary. This provision makes it mandatory. This provision also authorizes FDA to enter into cooperative arrangements with officials of foreign countries to determine whether drugs and devices manufactured overseas are subject to refusal of admission into the United States under the FD&C Act.

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## **R. Clarification of Seizure Authority**

Section 418 of the FDA Modernization Act amends section 304(d)(1) of the FD&C Act to provide that any person seeking to export an imported article pursuant to any of the provisions of this subsection shall establish that the article was intended for export at the time the article entered commerce. This provision was included in section 803 of the Senate bill. There was no comparable provision in the House bill. The Senate Report (page 63) makes it clear that this provision applies only to seized and condemned imported articles and does not affect articles proffered for import that are refused entry under section 801(a) of the FD&C Act and properly exported within ninety days of refusal.

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## **S. Interstate Commerce**

Section 420 of the FDA Modernization Act amends section 709 of the FD&C Act to extend the rebuttable presumption of interstate commerce for purposes of enforcement action, which has previously applied only to devices, to include food, drugs, and cosmetics as well. This provision was included in section 806 of the Senate bill. There was no comparable provision in the House bill.

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## **T. Safety Report Disclaimers**

Section 420 of the FDA Modernization Act amends the FD&C Act to add a new section 756 to deal with the status of safety reports submitted to FDA. This provision was taken from section 814 of the Senate bill. It was added as an amendment to the Senate bill offered by Senator Hatch after the bill was reported out of committee, and was accepted during the Senate debate. There was no comparable provision in the House bill.

*Section 756* provides that any report or information relating to the safety of a food, drug, device, dietary supplement, or cosmetic that is submitted or required to be submitted to FDA shall not be construed to reflect necessarily a conclusion that the report constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience. The person submitting the report need not admit, and may deny, that the report constitutes such an admission.

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## **U. Labeling and Advertising Regarding Compliance With Statutory Requirements**

Section 421 repeals section 301(l) of the FD&C Act. It was included in section 409 of the Senate bill and section 218 of the House bill. Section 301(l) prohibited any representation in labeling or advertising that FDA had approved an application for the drug or device or that the drug or device complies with the approval requirements of the FD&C Act.

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## **V. Rule of Construction**

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

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## **VII. Effective Date**

Section 501 of the FDA Modernization Act establishes the general rule, with only five exceptions, that the provisions of the 1997 Act become effective ninety days after the date of enactment, i. e. , on February 19, 1998, ninety days after President Clinton signed the legislation into law. The five exceptions are (1) where a specific provision in the 1997 Act provides a different effective date and (2) section 111 (Pediatric Studies of Drugs), section 121 (Positron Emission Tomography), section 125 (Insulin and Antibiotics), and section

307 (Irradiation Petition), all of which become effective on the date of enactment.

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<sup>1</sup> 52 Stat. 1040 (1938), 21 U.S.C. 301 et seq.

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<sup>2</sup> H.R. Rep. No. 906, 84th Cong., 1st Sess. (1955).

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<sup>3</sup> The Drug Regulation Reform Acts of 1978 and 1979, S. Rep. No. 96-321, 96th Cong., 1st Sess. (1979).

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<sup>4</sup> The Food Safety Amendments of 1971, 127 Cong. Rec. 13969 (June 25, 1981).

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<sup>5</sup> S. 1477, 104th Cong., 1st Sess. (1995).

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<sup>6</sup> S. Rep. No. 104-284, 104th Cong., 2d Sess. (1996).

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<sup>7</sup> H.R. 3199, 104th Cong., 2d Sess. (1996).

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<sup>8</sup> H.R. 3200, 104th Cong., 2d Sess. (1996).

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<sup>9</sup> H.R. 3201, 104th Cong., 2d Sess. (1996).

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<sup>10</sup> 110 Stat. 1321, 1321-313 (1996).

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<sup>11</sup> 110 Stat. 1489 (1996).

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<sup>12</sup> 110 Stat. 3151 (1996).

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<sup>13</sup> 106 Stat. 4491 (1992), 21 U.S.C. 379g, section 735 of the FD&C Act.

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<sup>14</sup> S. 830, 105th Cong., 1st Sess. (1997).

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<sup>15</sup> S. Rep. No. 105-43, 105th Cong., 1st Sess. (1997).

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<sup>16</sup> 143 Cong. Rec. S8837 (September 5, 1997) (daily ed.).

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<sup>17</sup> 143 Cong. Rec. S9811-S9868 (September 24, 1997) (daily ed.).

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<sup>18</sup> H.R. 1411, 105th Cong., 1st Sess. (1997).

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<sup>19</sup> H.R. 1710, 105th Cong., 1st Sess. (1997).

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<sup>20</sup> H.R. 2469, 105th Cong., 1st Sess. (1997).

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<sup>21</sup> H.R. Rep. No. 105-306 (food), H.R. Rep. No. 105-307 (devices), and H.R. Rep. No. 105-310 (drugs), 105th Cong., 1st Sess. (1997).

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<sup>22</sup> 143 Cong. Rec. H8455-H8482 (October 7, 1997) (daily ed.).

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<sup>23</sup> H.R. Rep. No. 105-399, 105th Cong., 1st Sess. (1997).

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<sup>24</sup> 143 Cong. Rec. S12241-12252 and H10452-10478(November 9, 1997) (daily ed.).

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<sup>25</sup> 111 Stat. 2296 (1997).

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<sup>26</sup> Old section 506, dealing with insulin, is repealed by section 125 of the FDA Modernization Act.

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<sup>27</sup> The apparent intent of this provision is for semi-annual reports (once every six months) rather than biannual ones (once every two years), because the reports are to include information from the preceding six-month period.

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