

October 9, 2007

Food and Drug Administration Amendments Act of 2007

On September 27, 2007, the President signed into law the Food and Drug Administration Amendments Act of 2007 (FDAAA).¹ This law, containing eleven titles, reauthorizes (and amends) both the prescription drug user fee program and the medical device user fee program. It also reauthorizes and amends the pediatric exclusivity and pediatric assessment programs applicable to new drugs. It contains new provisions designed to provide incentives to device manufacturers to create medical devices specifically designed to meet the needs of pediatric patients. It provides FDA enhanced authorities regarding the safety of approved drugs, expands the NIH registry of clinical trials, requires creation of a database for results of those trials, and addresses conflicts of interest on FDA advisory committees. Another title addresses the safety of human and pet food. The law contains a variety of additional amendments to the Federal Food, Drug, and Cosmetic Act (FDCA).

This memorandum summarizes the provisions of the FDAAA applicable to pharmaceutical products. The summary tracks the organization of the legislation.

TITLE I – PRESCRIPTION DRUG USER FEE AMENDMENTS OF 2007

A. PDUFA IV

This title reauthorizes FDA's prescription drug user fee program through fiscal year 2012. The reauthorization includes expanded user fees for post-approval drug safety programs (ranging from \$25 million in fiscal year 2008 to \$65 million in fiscal year 2012), a general increase in the fees to be paid, and revised workload and inflation adjusters, which are expected to increase fees further in the out years subject to certain caps. A "reverse trigger" could reduce fee levels in the out years, but would only apply where FDA's total appropriations and appropriations allocated to drug review activities have increased over fiscal year 2008 amounts (adjusted for inflation). If such appropriations increase, then the user fee amounts would be reduced by the amount of "excess" appropriations.

Under the new legislation, user fees may be utilized for postmarketing drug safety activities for all products without any time limitation — under current law, user fees may only be used for drug safety activities for drugs approved after October 1, 2002, and for the first two or three years following a drug's approval.

The law also contains various other specific changes to the user fee program, such as extending user fees to all 505(b)(2) applications, providing that lyophilized products are "final dosage forms" subject to annual product fees, providing for partial fee refunds for applications that are withdrawn before FDA has accepted or refused them for filing, exempting qualifying orphan drugs

¹ The legislation began as S. 1082 in the Senate and H.R. 2900 in the House. Pre-conference discussions led to a new version of the legislation, which the House passed as H.R. 3580 on September 19, 2007, and which the Senate passed without change on September 20, 2007.

from annual establishment and product fees, clarifying that discontinued products are not subject to annual product fees, and establishing special rules for positron emission tomography drugs.

The FDA performance goals that will apply under the reauthorized PDUFA program (PDUFA IV) are set out in a so-called “goals letter” now posted on the FDA Web site.² The basic performance goals for the review of standard and priority NDAs and BLAs are unchanged. However, new goals have been established for the review of proposed proprietary drug names. The goals letter also sets out targets for actions to enhance and modernize the drug safety system.

B. DTC User Fees

In addition to extending and modifying in part the existing user fee program, section 104 of the FDAAA adds section 736A to the FDCA to authorize FDA to assess new user fees for the review of direct-to-consumer (DTC) television advertising voluntarily submitted to the agency for advisory review prior to broadcast.³ Under this new program, companies seeking voluntary advisory review of DTC television advertisements must pay a one-time fee into an operating reserve fund and a separate fee each fiscal year for each advertisement to be reviewed. The per advertisement fee is capped at \$83,000 for fiscal year 2008, and is subject to adjustment going forward, including based on inflation and FDA workload. The program includes a process under which companies notify FDA at the start of each fiscal year as to how many advertisements they plan to submit for advisory review, additional fee levels for excess submissions and late payments, and fee-setting provisions comparable to the existing drug user fee program. The law provides that the program will not go into effect, or will terminate in subsequent years, if adequate fee levels are not generated.

Performance goals for the FDA's advisory review of DTC television advertisements are also set out in the agency's PDUFA IV goals letter. In particular, FDA commits to review and provide advisory comments within 45 days on 50 percent of the original submissions in Fiscal Year 2008, improving to 90 percent of the original submissions by Fiscal Year 2012.

C. PDUFA V

Both the existing user fee program and the new DTC fee program are authorized until 2012. FDA must make available to the public a transcript of the agency's negotiations with industry and other stakeholders before presenting recommendations for PDUFA V to the Congress.

TITLE IV — PEDIATRIC RESEARCH EQUITY ACT OF 2007

Section 402 of the FDAAA reauthorizes the mandatory pediatric study provisions of the Pediatric Research Equity Act (PREA).⁴ The mandatory study requirements associated with new applications (full or supplemental) under the PREA are not changed substantially, except that new status reports are required where studies are deferred. FDA's authority to require pediatric studies for marketed drugs in the absence of a new filing is expanded somewhat, with a streamlined procedure and somewhat lower standards that must be met for the agency to invoke this authority. For all required pediatric studies, there is broader public information dissemination, for example, of the

² Available at www.fda.gov/oc/pdufa4/pdufa4goals.html.

³ FDAAA § 104 (FDCA § 736A).

⁴ *Id.* § 402 (FDCA § 505B).

grounds for granting a waiver based on difficulties developing a pediatric formulation, FDA's review of the pediatric assessments, labeling changes, and certain other information.

The same sunset that applies to the pediatric exclusivity provisions (October 1, 2012) applies to the mandatory pediatric study authority.

Section 403 of the FDAAA creates a new section 505C of the FDCA under which FDA is to form an internal pediatric committee to review pediatric plans, assessments, deferrals, and waivers.⁵ The law directs the Institute of Medicine and the GAO to issue reports regarding pediatric issues.

TITLE V — BEST PHARMACEUTICALS FOR CHILDREN ACT OF 2007

Section 502 of the FDAAA reauthorizes the pediatric exclusivity and NIH pediatric study provisions of the Best Pharmaceuticals for Children Act (BPCA) with modifications.⁶ Most significantly, for all drugs pediatric exclusivity will be applied to existing patents and exclusivity periods only where FDA accepts the pediatric studies and awards pediatric exclusivity at least nine months prior to the expiration of the patent or exclusivity period. A proposal to reduce exclusivity from six months to three months for drugs with \$1 billion in annual sales was not included in the enacted legislation.

Other changes to current law include expanded public disclosure of information about the pediatric studies, an extended period of time for FDA to review pediatric submissions (180 days instead of 90 days, as under current law), special adverse event reporting provisions, use of the new internal review committee at FDA to consider pediatric written requests and studies, and a streamlined process for FDA to refer drugs to the NIH for study or to invoke its mandatory study authority where a sponsor does not conduct studies under the pediatric exclusivity provisions. These provisions will sunset in 2012. The law directs the IOM to study issues related to pediatric exclusivity within three years.

Section 503 of the FDAAA expands existing NIH programs intended to develop pediatric researchers specifically to include pediatric pharmacologists.⁷

TITLE VI — REAGAN-UDALL FOUNDATION

A. Reagan-Udall Foundation

Section 601 of the FDAAA adds sections 770 to 772 to the FDCA, establishing a nonprofit corporation, the Reagan-Udall Foundation for the Food and Drug Administration. The Foundation will serve three purposes: to modernize medical, veterinary, food, food ingredient, and cosmetic product development; to accelerate innovation; and to enhance product safety.⁸

⁵ *Id.* § 403 (FDCA § 505C).

⁶ *Id.* § 502 (FDCA § 505A and PHS § 409I).

⁷ *Id.* § 503 (PHSA §§ 452G(2) & 487F(a)(1)).

⁸ FDCA § 770(b).

Section 770(c) of the FDCA describes the Foundation's duties. Taking into consideration the Critical Path reports and priorities published by FDA, the Foundation will identify unmet needs in the development, manufacture, and evaluation of the safety and effectiveness of devices, biologics, and drugs, and the safety of food, food ingredients, and cosmetics. It will establish goals in order to meet these unmet needs. In consultation with the Secretary, it will identify intramural and extramural research and development programs relating to these goals and priorities. It will also award grants to, and enter into contracts or collaborative agreements with, scientists and entities (which may include universities and industry) to advance these goals and priorities. It will release and publish information and data — and to the extent practicable license, distribute, and release material, reagents, and techniques — to maximize, promote, and coordinate the availability of material, reagents, and techniques for use by FDA, nonprofit organizations, and academic and industrial researchers, to further these goals and priorities. It is to ensure that actions are taken to obtain patents for inventions developed by the Foundation or with Foundation funds. It will also ensure that executed licenses, memoranda of understanding, material transfer agreements, contracts, and related instruments promote the broadest conversion to commercial and noncommercial applications of licensed and patented Foundation inventions, in order to further its goals.⁹

Subsections (d) through (h) of section 770 describe the Foundation's board of directors, incorporation, nonprofit status, executive director, and administrative powers.¹⁰ The latter include the authority to take whatever actions are necessary to obtain patents and licenses for devices and procedures developed by the Foundation and its employees. Subsections (i) through (k) address acceptance of funds from other sources (including private entities) and personnel issues.¹¹ Subsection (l) requires grant recipients and contractors to submit reports to the Foundation and requires the Foundation to provide annual reports to the Commissioner and to Congress on the activities of the Foundation.¹² Additional provisions address funding issues,¹³ and section 771 specifies that the Foundation should be no more than 20 miles from the District of Columbia, if practicable.¹⁴ Section 772 requires the Commissioner to submit annual reports to Congress and contains additional provisions relating to extramural grants and scientists and physicians who provide services to the Foundation on a voluntary and uncompensated basis.¹⁵

B. Office of the Chief Scientist

Section 602 adds section 910 to the FDCA, which creates an Office of the Chief Scientist within the Office of the Commissioner.¹⁶ The Secretary must appoint a Chief Scientist to lead the office.¹⁷ The duties of the office include overseeing and ensuring the quality and regulatory focus

⁹ *Id.* § 770(c).

¹⁰ *Id.* § 770(d)-(h).

¹¹ *Id.* § 770(i)-(k).

¹² *Id.* § 770(l).

¹³ *Id.* § 770(m)-(n).

¹⁴ *Id.* § 771.

¹⁵ *Id.* § 772.

¹⁶ *Id.* § 910.

¹⁷ *Id.* § 910(b).

of FDA's intramural research programs and ensuring that this intramural research does not duplicate research efforts supported by the Reagan-Udall Foundation.¹⁸

C. Critical Path Public-Private Partnerships

Section 603 adds section 566 to the FDCA, authorizing the Secretary to enter into collaborative agreements, known as Critical Path Public-Private Partnerships, in order to implement the agency's Critical Path Initiative.¹⁹ The purpose of these partnerships is to develop innovative collaborative projects in research, education, and outreach, in order to foster medical product innovation and enhance product safety.²⁰ Eligible entities are limited to institutions of higher education and tax-exempt organizations described in section 501(c)(3) of the Internal Revenue Code.²¹ Each entity must provide assurances that it will not accept funding for a Critical Path Public-Private Partnership project from an organization that manufactures or distributes FDA-regulated products, unless it provides additional assurances about the impact of this funding on the results of its project with the Secretary.²² The Secretary must submit annual reports to Congress on partnership activities in the prior year.²³

TITLE VII — CONFLICTS OF INTEREST

Section 701 of the FDAAA repeals section 505(n)(4) of the FDCA, which governs conflicts of interest on committees that provide FDA advice regarding clinical trials of drugs and approval of new drug applications (NDAs) and biologics license applications (BLAs).²⁴ It adds a new section 712 to the FDCA, which will govern management of conflicts of interest on FDA advisory committees.²⁵ An "advisory committee" is defined as any advisory committee under the Federal Advisory Committee Act that provides advice or recommendations to the Secretary regarding activities of FDA.²⁶ Title VII does not repeal or amend 18 U.S.C. § 208, which governs federal employee conflicts of interest more broadly and also applies to FDA advisory committee members. The amendments made by section 701 of the FDAAA take effect on October 1, 2007.²⁷

D. Recruitment and Appointments

The Secretary must engage in recruitment activities in order to recruit individuals to serve as advisory committee members.²⁸ These activities must include seeking input from professional medical and scientific societies to determine the most effective informational and recruitment activities

¹⁸ *Id.* § 910(b).

¹⁹ *Id.* § 566.

²⁰ *Id.* § 566(a).

²¹ *Id.* § 566(b)(1).

²² *Id.* § 566(c).

²³ *Id.* § 566(d).

²⁴ FDAAA § 701(b).

²⁵ FDCA § 712.

²⁶ *Id.* § 712(a)(1).

²⁷ FDAAA § 701(c).

²⁸ FDCA § 712(b)(1).

and may include developing a process through which entities that receive funding from NIH, AHRQ, the CDC, or the VA can identify persons for FDA to contact regarding nominations.²⁹

When considering a term appointment to an advisory committee, the Secretary must review the expertise of the candidate and the financial disclosures made by that candidate pursuant to the Ethics in Government Act of 1978, in order to reduce the likelihood that an appointed individual will later require a written determination under 18 U.S.C. § 208(b)(1), a written certification under 18 U.S.C. § 208(b)(3), or a waiver under the new section 712(c)(2) of the FDCA, for service on the committee at a meeting of the committee.³⁰

E. Disclosures, Prohibition, and Waivers

Prior to every meeting of an advisory committee regarding a particular matter (as that phrase is used in 18 U.S.C. § 208) each member of the committee who is a full-time government employee or a special government employee must disclose to the Secretary all financial interests in accordance with 18 U.S.C. § 208(b).³¹ No member of an advisory committee may participate with respect to a particular matter before the committee if the member (or an immediate family member of that member) has a financial interest that could be affected by the advice given to the Secretary with respect to that matter.³² The Secretary may waive this prohibition, if necessary to afford the advisory committee essential expertise, to permit a member to participate as either a voting member or a non-voting member.³³ The Secretary is to determine the percentage of “exceptions” in fiscal year 2007 — defined as waivers under section 505(n)(4) of the FDCA as in effect on the day before enactment of the FDAAA, determinations under 18 U.S.C. § 208(b),³⁴ and certifications under 18 U.S.C. § 208(b)(3) — as a percentage of meeting slots.³⁵ The number of “exceptions” in fiscal year 2008 cannot exceed 95 percent of this base percentage, and the number must decrease each year until it reaches 75 percent in fiscal year 2012.³⁶

No later than 15 days prior to an advisory committee meeting for which the Secretary has made a written determination, a written certification, or a waiver determination, the Secretary must disclose on the FDA website the type, nature, and magnitude of the financial interests of any member to whom such a determination, certification, or waiver applies as well as the Secretary’s reasons for the determination, certification, or waiver.³⁷ If a financial interest becomes known to the Secretary fewer than 30 days prior to the meeting, the Secretary must make these disclosures as soon as practicable after the determination, certification, or waiver decision is made, but in no event later than the date of

²⁹ *Id.* § 712(b)(1).

³⁰ *Id.* § 712(b)(2).

³¹ *Id.* § 712(c)(1). “Financial interest” has the meaning assigned that phrase in 18 U.S.C. § 208(a).

³² *Id.* § 712(c)(2)(A).

³³ *Id.* § 712(c)(2)(B).

³⁴ These are made pursuant to 18 U.S.C. § 208(b)(1).

³⁵ FDCA § 712(c)(2)(C).

³⁶ *Id.* § 712(c)(2). The term “exception,” when used in relation to fiscal year 2008 and later, is presumably meant to include waivers under section 712(c)(2), rather than waivers under section 505(n)(4), which the FDAAA repeals and replaces. The term is, however, defined only once. See *id.* § 712(c)(2)(C)(i).

³⁷ *Id.* § 712(c)(3)(A).

the meeting.³⁸ The obligation to disclose applies notwithstanding section 107(a)(2) of the Ethics in Government Act, but the Secretary is not required to disclose information protected by an exemption from the Freedom of Information Act (FOIA) or by the Privacy Act.³⁹

The Secretary must ensure that the public record and transcript of every advisory committee meeting includes the disclosures described in the preceding paragraph.⁴⁰ In addition, the Secretary must make annual reports to Congress on advisory committee vacancies and nominees as well as waivers and disclosures.⁴¹ The Secretary must also review and update as necessary, at least once every five years, FDA's guidance regarding conflict of interest waiver determinations with respect to advisory committees.⁴²

TITLE VIII — CLINICAL TRIAL DATABASES

Current federal law requires the registration of clinical trials only for drugs intended for the treatment of serious or life-threatening diseases or conditions.⁴³ Title VIII of the FDAAA rewrites section 402(j) of the Public Health Service Act (PHSA) to include an expanded clinical trial registry data bank and a clinical trial results data bank.

F. Expanded Clinical Trial Registry Data Bank

1. Registry Data Bank

Under the revised section 402(j)(2) of the PHSA, the registry data bank must include all “applicable” drug clinical trials. “Applicable” drug clinical trials include all controlled clinical investigations of a product subject to section 505 of the FDCA or section 351 of the PSHA, other than “phase I” clinical investigations. The FDAAA directs the Secretary, acting through the Director of NIH, to expand the registry data bank to include descriptive information, recruiting information, location and contact information, and administrative data (essentially, the study identification number and corresponding IND) for each covered trial. The descriptive information consists of the following for a trial: a brief title and summary (intended for the lay public), the primary purpose, the study design, the study phase, the study type, the primary disease or condition being studied (or the focus of the study), the intervention name and type, the study start date, the expected completion date, the target number of subjects, and the outcomes (including the primary and secondary outcome measures). The recruitment information consists of the eligibility criteria for the trial, the trial and site recruitment status, and whether there is expanded access for those who do not qualify for enrollment in the trial.

The Director of NIH must ensure that the public may search entries in the registry data bank using one or more of the following criteria: (1) the disease or condition being studied, (2) the treatment being studied, (3) location, (4) the age group being studied, (5) the study phase of the clinical trial, (6) the sponsor, (7) the recruitment status of the clinical trial, and (8) the National Clinical

³⁸ *Id.* § 712(c)(3)(B).

³⁹ *Id.* § 712(c)(3).

⁴⁰ *Id.* § 712(d).

⁴¹ *Id.* § 712(e).

⁴² *Id.* § 712(f).

⁴³ See PHSA § 402(j) (codified at 42 U.S.C. § 282(j)).

Trial number or other study identification. By March 2009, the Director of NIH must also allow searching by the safety issue being studied.

Information must be submitted for all clinical studies initiated after, or ongoing as of, December 26, 2007. The sponsor (or principal investigator, when designated as the responsible party) must submit the required clinical trial information to the Director of the NIH no later than 21 days after the first patient is enrolled in the clinical trial, except that no submissions are required before December 26, 2007. The sponsor must inform the Director within 30 days of any changes in enrollment status and when the clinical trial has been completed.

2. Linking Registry Data Bank to Clinical Trial Results

Under the new PHS section 402(j)(3), by December 26, 2007, the Secretary must ensure that the registry data bank includes links to the following results information for all clinical trials that form the primary basis of an efficacy claim or are conducted after a drug is approved: (1) for drugs considered at an advisory committee, any posted FDA summary document regarding the applicable drug clinical trial; (2) any FDA assessment of the results of a pediatric trial posted in accordance with the PREA or BPCA; (3) any FDA public health advisories regarding the drug that is the subject of the applicable trial; and (4) the FDA action package for approval document required under FDCA § 505(l)(2). The results must also include Medline citations to any publications regarding each applicable clinical trial and, if available, the entry for the drug that is the subject of an applicable drug clinical trial in the National Library of Medicine database of structured product labels. The Secretary may include results data bank entries for clinical trials submitted prior to the enactment of the FDAAA.

By September 27, 2008, the Secretary, again acting through the Director of NIH, shall expand the registry data bank to include additional information regarding clinical trial results for approved products. This additional information shall consist of: (1) a table of the demographic and baseline data collected for the trial overall and each arm of the trial to describe the study participants and drop outs; (2) the primary and secondary outcome measures, with the results of tests showing the statistical significance of the measures; (3) a point of contact for scientific information on the trial; and (4) whether there exists an agreement limiting the rights of the principal investigator to publish or discuss the results of the trial.

By March 27, 2009, the Secretary shall by regulation determine the best method for including in the data bank information on serious and frequent adverse events for a drug. Default rules will apply if no such regulation is finalized by September 27, 2009.

By September 27, 2010, the Secretary, through the Director of NIH, shall by regulation further expand the registry data bank to include for all approved products a technical and non-technical summary of the trial and its results, along with the full protocol or related information for the trial, and “[s]uch other categories as the Secretary determines appropriate.” The regulations must also consider whether to extend these requirements to clinical trials for unapproved products.

Results data must generally be submitted to the data bank within 1 year of the actual or estimated completion date of the trial, whichever is earlier. FDA may in its regulations increase this deadline to 18 months. In addition, upon the certification of a sponsor, results need not be submitted until 30 days after a new drug or new use is approved related to the clinical trial at issue, provided that results must be submitted within two years of any such certification. Information must be updated at least annually, and certain details must be updated more frequently if they change.

The Secretary may grant extensions for good cause or waivers if extraordinary circumstances exist and the waiver is in the public interest, consistent with the protection of public health, or in the interest of national security.

3. Coordination and Compliance

At the time of submission of an application for a drug or biological product, the applicant must include a certification that all applicable requirements of PHSA § 402(j) have been met. Where available, the certification must include the appropriate National Clinical Trial control numbers. Federal agencies cannot release funds under research grants to grantees who have not complied with the requirements of the clinical trial registry data bank. If an applicable clinical trial is funded in whole or in part by a grant from HHS, including the FDA, NIH, or the Agency for Healthcare Research and Quality, any grant or progress report forms required under such grant must include a certification that the sponsor has made all required submissions to the Director of the NIH for inclusion in the registry database. If the head of one of these agencies verifies that the grantee has not submitted the appropriate clinical trial information, the agency head must provide notice to the grantee and allow the grantee 30 days to correct such non-compliance and submit the required clinical trial information.

Failure to submit required clinical trial information and submission of false or misleading information, is a prohibited act and subject to civil monetary penalties under the FDCA. Public notice of violations will also be posted.

G. Preemption and Rule of Construction

Section 801(d) of the FDAAA states that upon the expansion of the registry and results data bank by regulation, no state or local government may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database.

Section 801(d) of the FDAAA also states that the fact of submission of clinical trial information relating to an unapproved use of a drug, if submitted in compliance with PHSA § 402(j), may not be construed by the Secretary or in any administrative or judicial proceeding as evidence of a new intended use of the drug, or as labeling or misbranding of the drug.

TITLE IX — ENHANCED AUTHORITIES REGARDING POSTMARKET SAFETY OF DRUGS

A. Subtitle A — Postmarket Studies and Surveillance

Section 901 of the FDAAA adds a new section 505(o) to the FDCA, which gives the Secretary the authority to mandate postmarket studies and clinical trials as well as postmarket labeling changes. Determinations by the Secretary under section 505(o) must be made by individuals “at or above the level of individuals empowered to approve a drug (such as division directors within the Center for Drug Evaluation and Research).”⁴⁴ Section 901 also adds sections 505(p) and 505-1, which govern risk evaluation and mitigation strategies (REMS).

⁴⁴ FDCA § 505(o)(5).

1. Postmarket Studies and Clinical Trials

Section 505(o) of the FDCA authorizes the Secretary to require any person that holds an approved NDA for a prescription drug or a BLA for a biological product that is a drug, and any person with such an application pending, to conduct a postmarket study or clinical trial.⁴⁵ A study or trial may be required to assess a known serious risk related to the use of the drug, to assess signals of serious risk related to use of the drug, or to identify an unexpected serious risk when available data indicate the potential for a serious risk.⁴⁶

The Secretary may not require a postmarket study, however, unless he or she determines that ordinary pharmacovigilance reports under section 505(k)(1) and the new active postmarket risk identification and analysis system under section 505(k)(3) will not be sufficient to accomplish these goals. The Secretary may not require a postmarket clinical trial unless a postmarket study or studies will be insufficient to meet these goals.⁴⁷

The decision to require a study or trial may be based on information regarding chemically related or pharmacologically related drugs.⁴⁸ The Secretary must notify an applicant of this requirement by the target dates set forth in the agency's user fee reauthorization goals letter.⁴⁹ The Secretary may impose this requirement after approval of the product in question only if the Secretary becomes aware of new safety information, which is defined to mean information about a serious risk or an unexpected serious risk associated with use of the drug, or information about the effectiveness of the approved REMS of the drug.⁵⁰ The responsible person may appeal a requirement to conduct a study or trial, using dispute resolution procedures established by the Secretary in regulation and guidance.⁵¹

The responsible person must submit a timetable for completion of each study or trial required under section 505(o), as well as periodic reports to the Secretary on the status of the study or trial in question.⁵² Failure to comply with the timetable or to submit the periodic reports is a violation of section 505(o), unless the responsible person demonstrates "good cause" for the noncompliance.⁵³ The Secretary may coordinate the timetable for completion of the study or trial with efforts by marketing authorities in other countries to identify and assess the serious risks of the drug.⁵⁴ In this

⁴⁵ *Id.* § 505(o)(1)-(3). These persons are referred to, in subsection (o), as "responsible persons."

⁴⁶ *Id.* § 505(o)(3)(B). The phrases "serious risk" and "signal of a serious risk" are defined in section 505-1(b) of the FDCA.

⁴⁷ *Id.* § 505(o)(3)(D).

⁴⁸ *Id.* § 505(o)(3)(A).

⁴⁹ *Id.* § 505(o)(3)(E)(i).

⁵⁰ *Id.* §§ 505(o)(3)(C) and 505-1(b)(3).

⁵¹ *Id.* § 505(o)(3)(F).

⁵² *Id.* § 505(o)(3)(E)(ii). The obligation to report periodically also applies to any other study undertaken by the responsible person to investigate a safety issue.

⁵³ *Id.* § 505(o)(3)(E). The Secretary may determine what constitutes "good cause."

⁵⁴ *Id.* § 505-1(h)(8). This coordination must occur in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug. *Id.* Further, it is authorized only if the Secretary deems the country's drug approval and risk management processes "comparable" to those in the United States. *Id.*

case, notice to the responsible person is required, and this process may not be the sole source of delay of action on an application or supplement.⁵⁵

Title IX and the changes made by Title IX are not to be construed as affecting the authority of the Secretary to request pediatric studies under section 505A or to require them under section 505B.⁵⁶

2. Safety Labeling Changes

Section 505(o) also requires the Secretary promptly to notify responsible persons if the Secretary becomes aware of new safety information that the Secretary believes should be included in the drug's labeling.⁵⁷ Following this notification, the responsible person has 30 days to either: (a) submit a supplement proposing changes to the labeling to reflect the new safety information, or (b) notify the Secretary that the responsible person does not believe that a labeling change is necessary and explain the reasons for this conclusion.⁵⁸ The Secretary must act promptly on any supplement submitted.⁵⁹ If the Secretary disagrees with the proposed labeling changes (or with the conclusion that no change is necessary), the Secretary must initiate discussions to reach agreement on whether and how the labeling should be modified to reflect the new safety information.⁶⁰ These discussions may not extend for more than 30 days after the responsible person's response, unless the Secretary finds an extension warranted.⁶¹

Within 15 days of the conclusion of these discussions, the Secretary may issue an order requiring the responsible person to make the labeling changes the Secretary deems appropriate to address the new safety information.⁶² The responsible person must submit a supplement for those changes within 15 days of this order.⁶³ Within five days of receipt of the order, however, the responsible person may appeal using dispute resolution procedures established by the Secretary in regulation and guidance.⁶⁴ If the responsible person does not submit a supplement within 15 days, and if there is no appeal or dispute resolution proceeding pending at that time, the responsible person will be considered in violation of section 505(o).⁶⁵ The Secretary may accelerate all of the timelines discussed above upon the conclusion that a labeling change is necessary to protect the public health.⁶⁶

⁵⁵ *Id.* § 505-1(h)(8), (h)(9).

⁵⁶ FDAAA § 901(d).

⁵⁷ FDCA § 505(o)(4)(A). If the issue relates to a drug that is marketed only under an ANDA, i.e., because the reference product is no longer marketed, the Secretary must notify the holder of the approved ANDA. *Id.*

⁵⁸ *Id.* § 505(o)(4)(B).

⁵⁹ *Id.* § 505(o)(4)(C).

⁶⁰ *Id.* § 505(o)(4)(C).

⁶¹ *Id.* § 505(o)(4)(D).

⁶² *Id.* § 505(o)(4)(E).

⁶³ *Id.* § 505(o)(4)(E).

⁶⁴ *Id.* § 505(o)(4)(F).

⁶⁵ *Id.* § 505(o)(4)(G). Moreover, if the Secretary concludes at the end of dispute resolution that a supplement must be submitted, the responsible person has 15 days to do so or be deemed in violation of section 505(o). *Id.*

⁶⁶ *Id.* § 505(o)(4)(H).

The paragraph on safety labeling changes, which is paragraph (4) of section 505(o), may not be construed to affect the responsibility of the responsible person to “maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21” of the Code of Federal Regulations, and any successor regulations.⁶⁷

3. REMS

a) Submission

A new drug applicant (including an ANDA applicant) for a prescription drug and an applicant for a biological product that is a new drug must submit — as part of its application — a proposed REMS if the Secretary determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks of the drug.⁶⁸ This decision must be made in consultation with the office responsible for reviewing the drug and the office responsible for postmarket safety of the drug.⁶⁹ And it must take into account the estimated size of the population likely to use the drug, the seriousness of the disease or condition to be treated, the expected benefits of the drug with respect to that disease or condition, the expected or actual duration of treatment, the seriousness of any known or potential adverse events, and whether the drug is a new molecular entity.⁷⁰

If a REMS is not required when an application is approved, the Secretary may later require submission of a REMS proposal only if he or she: (1) becomes aware of new safety information, and (2) makes a determination that a REMS is necessary to ensure that the benefits of the drug outweigh the risks of the drug.⁷¹ “New safety information” means information, about a serious risk or an unexpected serious risk associated with the use of the drug, that the Secretary has become aware of since the drug was approved.⁷² It can be derived from a clinical trial, an adverse event report, a postmarket study, peer-reviewed biomedical literature, the postmarket risk identification and analysis system under section 505(k) of the FDCA, or other scientific data deemed appropriate by the Secretary.⁷³ This same standard governs applications approved before the effective date of the new section.⁷⁴ The holder of the approved application has 120 days to submit a proposed REMS, unless the Secretary specifies a different deadline, which must be reasonable, to protect the public health.⁷⁵

Determinations by the Secretary under section 505-1(a) — i.e., whether to require a REMS — must be made by individuals “at or above the level of individuals empowered to approve a

⁶⁷ *Id.* § 505(o)(4)(l).

⁶⁸ *Id.* § 505-1(a)(1); *see also id.* § 505-1(b)(2) (defining “covered application”).

⁶⁹ *Id.* § 505-1(a)(1).

⁷⁰ *Id.* § 505-1(a)(1).

⁷¹ *Id.* § 505-1(a)(2)(A). This decision must be made in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug.

⁷² *Id.* § 505-1(b)(3).

⁷³ *Id.* § 505-1(b)(3).

⁷⁴ *Id.* § 505-1(a)(2)(A).

⁷⁵ *Id.* § 505-1(a)(2)(B).

drug (such as division directors within the Center for Drug Evaluation and Research.⁷⁶ In addition, they are not subject to dispute resolution before the Drug Safety Oversight Board (DSOB).⁷⁷

b) Content

Every proposed REMS must include a timetable for submission of assessments of the strategy.⁷⁸ It must include additional elements — a Medication Guide, patient package insert, or a plan for communication to healthcare providers — if the Secretary makes the relevant findings.⁷⁹ The requirement to develop a Medication Guide will be governed, as it is now, by 21 C.F.R. part 208.⁸⁰ A patient package insert may be required if the Secretary determines that it may help mitigate a serious risk of the drug.⁸¹ A communication plan may be required if the Secretary determines that it might support implementation of an element of the REMS.⁸² This communication plan may include sending letters to healthcare providers, disseminating information about the REMS to encourage implementation or to explain safety protocols, and disseminating information through professional societies.⁸³

The Secretary may also require “elements to assure safe use” of a drug (i.e., use and distribution restrictions), upon a determination that: (1) the drug, which has been shown effective, but which is associated with a serious adverse drug experience, can be approved only if, or would be withdrawn unless, these elements are required to mitigate a specific serious risk listed in its labeling, and (2) if the drug was initially approved without this restriction in place, other potential REMS elements (described in the preceding paragraph) are not sufficient to mitigate this risk.⁸⁴ These restrictions must be: (1) commensurate with the specific serious risk listed in the drug’s labeling; (2) posted publicly by the Secretary, within 30 days of their imposition, with an explanation of how they will mitigate the observed safety risk; (3) not unduly burdensome on patient access to the drug; and (4) to the extent practicable, in conformity with restrictions for other drugs with similar, serious risks, and designed to be compatible with established distribution, procurement, and dispensing systems for drugs.⁸⁵

The Secretary must seek input from patients, physicians, pharmacists, and other healthcare providers about how restrictions under this subsection can be standardized so that they are not unduly burdensome on patient access to drugs and so that they minimize (to the extent practicable) the burden on the healthcare delivery system.⁸⁶ The Secretary must also annually evaluate

⁷⁶ *Id.* § 505-1(a)(4).

⁷⁷ *Id.* § 505-1(h)(5)(A)(i).

⁷⁸ *Id.* § 505-1(c).

⁷⁹ *Id.* § 505-1(e)(1). This decision, too, must be made in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug. *Id.* § 505-1(c)(2).

⁸⁰ *Id.* § 505-1(e)(2)(A).

⁸¹ *Id.* § 505-1(e)(2)(B).

⁸² *Id.* § 505-1(e)(3).

⁸³ *Id.* § 505-1(e)(3).

⁸⁴ *Id.* § 505-1(f)(1). This decision, too, must be made in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug. *Id.*

⁸⁵ *Id.* § 505-1(f)(2).

⁸⁶ *Id.* § 505-1(f)(5)(A).

the restriction(s) in place on at least one drug, to determine whether these conditions are met and whether the restrictions assure safe use of the drug.⁸⁷ Based on the input and evaluation described in the previous sentences, the Secretary must issue or modify agency guidance on elements to assure safe use and modify elements in place, as appropriate.⁸⁸

Elements to assure safe use must be linked to a specific serious risk listed in the drug's labeling and, to mitigate that risk, may include requirements: (1) that healthcare providers who prescribe the drug have particular training, experience, or certification; (2) that patients be monitored; and (3) that patients be enrolled in registries.⁸⁹ The elements can also include: (4) that pharmacies and others dispensing the drug be specially certified; (5) that the drug be dispensed to patients only in certain settings, such as hospitals; and (6) that patients have evidence of "safe-use conditions" (e.g., laboratory test results). In the latter three cases, the REMS may also include a system through which the applicant is able to take reasonable steps to monitor and evaluate implementation by healthcare providers, pharmacists, and other parties in the healthcare system responsible for implementation.⁹⁰

A drug subject to use or distribution restrictions may be made available for an unapproved use to treat a serious or life-threatening condition under the mechanisms FDA has in place to implement section 561 of the FDCA, which governs expanded access to unapproved therapies.⁹¹ The Secretary must promulgate regulations explaining how a physician may provide the drug for this purpose.⁹²

During a public health emergency under section 319(a) of the PHS Act, the Secretary may waive any use or distribution restriction with respect to a "qualified countermeasure" under that Act, if he or she determines that waiver is required to mitigate the effects of, or reduce the severity of, the public health emergency in question.⁹³

Finally, no holder of an approved NDA or BLA may "use" a restriction under this subsection to "block or delay" approval of an abbreviated new drug application (ANDA) or 505(b)(2) application or to prevent application of that restriction (under the requirement for a single shared system) to a drug that is the subject of an ANDA.⁹⁴

c) Assessment and Modification

Following approval of a REMS, the application holder may submit an assessment of the REMS (which may include a proposal to modify it) at any time and must submit an assessment at certain other times⁹⁵: (1) when submitting a supplemental application for a new indication;⁹⁶ (2) when

⁸⁷ *Id.* § 505-1(f)(5)(B).

⁸⁸ *Id.* § 505-1(f)(5)(C).

⁸⁹ *Id.* § 505-1(f)(3).

⁹⁰ *Id.* § 505-1(f)(3), (f)(4).

⁹¹ *Id.* § 505-1(f)(6).

⁹² *Id.*

⁹³ *Id.* § 505-1(f)(7).

⁹⁴ *Id.* § 505-1(f)(8).

⁹⁵ The requirement to submit assessments is described in section 505-1(g)(2) and is expressly "subject to paragraph (5)," but there is no section 505-1(g)(5).

required to do so by the REMS timetable; (3) when ordered to do so by the Secretary based on new safety or effectiveness information;⁹⁷ and (4) in the case of a drug subject to an NDA, within 15 days of an order by the Secretary if the Secretary determines that there may be cause to withdraw approval of the NDA under section 505(e).⁹⁸

The timetable for REMS assessment included in the REMS itself must provide for assessment 18 months after the REMS is approved, three years after REMS approval, and in the seventh year after REMS approval. Subject to these minimum requirements, it must specify a frequency for assessment, which may be modified later and, indeed, altogether eliminated after the first three years, if the Secretary determines that serious risks of the drug have been adequately identified and assessed and are being adequately managed.⁹⁹ The Secretary may coordinate the timetable for submission of assessments with efforts by marketing authorities in other countries to identify and assess the serious risks of the drug.¹⁰⁰ In this case, notice to the responsible person is required, and this process may not be the sole source of delay of action on an application or supplement.¹⁰¹

A REMS assessment must include: (1) with respect to any goal for existing use or distribution restrictions, an assessment of the extent to which those restrictions are meeting the goal or whether instead the goal or restrictions should be modified; (2) with respect to any postmarket study required under section 505(o) or otherwise undertaken to investigate a safety issue, the status of the study and whether any difficulties completing the study have been encountered; and (3) with respect to any postmarket clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue, the status of the trial, whether enrollment has begun, the number of participants enrolled, the estimated completion date, whether any difficulties completing the trial have been encountered, and “registration information with respect to requirements” under sections 402(i) and 402(j) of the PHSA.¹⁰²

⁹⁶ The requirement to submit a REMS assessment when submitting a supplement for a new indication for use applies unless: (1) the drug is not subject to section 503(b), i.e., the prescription requirement, and (2) the REMS includes only a timetable for REMS assessment. *Id.* § 505-1(g)(2)(A). Because nonprescription drugs are not subject to REMS in the first instance, the first provision appears to be superfluous.

⁹⁷ Specifically, the Secretary must determine that new safety or effectiveness information indicates that a REMS element must be modified or a new REMS element must be adopted. This decision must be made in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug.

⁹⁸ *Id.* § 505-1(g)(1), (2). Section 903 of the FDAAA amends section 505(e) of the FDCA, adding a statement that the Secretary may withdraw or suspend approval of an application without first ordering a REMS assessment. FDAAA § 903.

⁹⁹ FDCA § 505-1(d).

¹⁰⁰ *Id.* § 505-1(h)(8). This coordination must occur in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug. *Id.* Coordination is authorized only if the Secretary deems the country's drug approval and risk management processes “comparable” to those in the United States.

¹⁰¹ *Id.* § 505-1(h)(8), (h)(9).

¹⁰² Section 402(j) is discussed in the section of this memorandum on Title VIII of the FDAAA and requires registration of, and posting of the results from, clinical trials. Section 402(i), which originally contained the clinical trial registry requirement, now relates to a discretionary fund for the Director of NIH.

d) Decision

The Secretary must promptly review each proposed REMS and each REMS assessment.¹⁰³ No later than 60 days after submission of a REMS assessment (or 30 days in the case of an assessment prompted by possible withdrawal of approval), the Secretary must initiate discussions with the responsible party.¹⁰⁴ Unless the responsible person invokes dispute resolution, if modification of the REMS was proposed in a voluntary REMS assessment, or in an assessment (a) required by the REMS itself, (b) required by the Secretary because of new information, or (c) required because grounds for withdrawal of the application may exist, the Secretary must describe the required REMS modification in an order no later than 90 days after discussions began.¹⁰⁵ Unless the responsible person invokes dispute resolution, when a REMS is proposed as part of an initial application, the Secretary must describe the required REMS in the action letter on the application.¹⁰⁶ Each action letter and order is to be made publicly available.¹⁰⁷ An approved REMS remains in effect until the Secretary acts.¹⁰⁸

e) Dispute Resolution

If a proposed REMS is submitted as part of an application for initial approval of the product in question, and if there is a dispute about the strategy, the applicant must use the major dispute resolution procedures set forth in FDA's user fee reauthorization goals letter.¹⁰⁹ In all other cases, a dispute about the REMS must be handled under the dispute resolution process described in section 505-1 of the FDCA.¹¹⁰ (As noted above, however, the Secretary's decision to require a REMS in the first instance is not subject to dispute resolution.) The responsible person may invoke this process no more than 35 days after discussions begin (and no sooner than 15 days after they begin), by requesting in writing that the dispute be reviewed by the DSOB.¹¹¹

Upon receipt of this request, the Secretary must schedule the dispute for review by the DSOB and, within 5 days of doing so, publish notice that the dispute will be reviewed.¹¹² The matter

¹⁰³ FDCA § 505-1(h)(1). This review must be done in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug.

¹⁰⁴ *Id.* § 505-1(h)(2). Initiating the discussion, also, must be done in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug.

¹⁰⁵ *Id.* § 505-1(h)(3)(A)(ii).

¹⁰⁶ *Id.* § 505-1(h)(3)(A)(i). Use of an action letter is also required with respect to a REMS modification included in a voluntary REMS assessment. *Id.* § 505-1(h)(3)(A)(ii), citing "subsection (g)(1)." This contradicts the clause that follows and was probably meant to refer to "subsection (g)(2)(A)" — requiring use of an action letter when a proposed REMS or REMS assessment is included with a supplemental application for a new indication.

¹⁰⁷ *Id.* § 505-1(h)(3)(C).

¹⁰⁸ *Id.* § 505-1(h)(3)(B).

¹⁰⁹ *Id.* § 505-1(h)(4).

¹¹⁰ Request for dispute resolution does not preclude further discussions between the applicant and agency, nor does it preclude the use of administrative appeals within the agency. *Id.* § 505-1(h)(5)(C)(i). Any time before completion of the dispute resolution process, i.e., a decision and order, the Secretary and applicant may reach agreement about the REMS. This agreement, which must involve the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug, terminates the dispute resolution process. *Id.* § 505-1(h)(5)(C)(ii).

¹¹¹ *Id.* § 505-1(h)(5)(A)(i). Section 505-1(j) establishes the DSOB and describes its composition and meetings.

¹¹² *Id.* § 505-1(h)(5)(A)(ii).

must be scheduled for review at one of the next two regular meetings of the DSOB¹¹³ or may be reviewed more promptly at a specially convened meeting.¹¹⁴

No FDA employee who reviewed the drug or participated in an administrative appeal relating to the drug may serve on the DSOB at the meeting in question.¹¹⁵ The DSOB may, however, supplement its membership for the meeting with other individuals with relevant expertise, from FDA or other federal public health or healthcare agencies.¹¹⁶ At the DSOB meeting, both parties may make written and oral presentations.¹¹⁷ The proceeding must be recorded, transcribed, and made public within 90 days of the meeting.¹¹⁸ The transcript must be redacted to protect trade secrets and information protected from disclosure under FOIA and the Privacy Act.¹¹⁹

No later than five days after its meeting, the DSOB must provide a written recommendation on the dispute to the Secretary, and within an additional five days the Secretary must make the DSOB's recommendation public.¹²⁰ The Secretary's final decision must appear in a public order, no later than seven days after receipt of the DSOB recommendation, if it relates to a voluntary REMS assessment, or a REMS assessment (a) required by the REMS itself, (b) required by the Secretary because of new information, or (c) required because grounds for withdrawal of the application may exist.¹²¹ It must appear in an action letter by the action deadline on the application (or seven days after receipt of the DSOB recommendation, if that date is later), if it relates to a REMS proposal submitted with an initial application.¹²² The Secretary will be considered to have met the action deadline for an application if the Secretary: (1) initiated discussions no fewer than 60 days before the action deadline, and (2) complied with the timing requirements relating to scheduling of DSOB review, providing a written recommendation, and issuing an action letter.¹²³ An approved REMS remains in effect until the Secretary acts.¹²⁴

f) Class Effects

The Secretary may defer assessment of an approved REMS (or more than one), in order to convene a public meeting or meetings, when a concern about a serious risk of the drug may

¹¹³ The DSOB must meet at least monthly. *Id.* § 505-1(j)(2)(E).

¹¹⁴ *Id.* § 505-1(h)(5)(B). This might be necessary, for example, to meet an action deadline on the application. Once DSOB review is scheduled and notice has been posted, however, the applicant must terminate any administrative appeals pending (or withdraw the request for DSOB review). *Id.* § 505-1(h)(5)(C)(i).

¹¹⁵ *Id.* § 505-1(h)(5)(J).

¹¹⁶ *Id.* § 505-1(h)(5)(K).

¹¹⁷ *Id.* § 505-1(h)(5)(D).

¹¹⁸ *Id.* § 505-1(h)(5)(E).

¹¹⁹ *Id.* § 505-1(h)(5)(E).

¹²⁰ *Id.* § 505-1(h)(5)(F).

¹²¹ *Id.* § 505-1(h)(5)(G)(ii).

¹²² *Id.* § 505-1(h)(5)(G)(i), citing § 505-1(h)(1), in turn citing § 505-1(g). By citing subsection (h)(1), this provision also requires use of an action letter if the issue arises out of any REMS assessment submitted under subsection (g). This conflicts with the prior clause. The drafters probably meant to require use of an action letter when the REMS assessment is included with a supplemental application for a new indication, i.e., assessments submitted under subsection (g)(2)(A).

¹²³ *Id.* § 505-1(h)(5)(I).

¹²⁴ *Id.* § 505-1(h)(5)(H).

relate to the pharmacological class to which that drug belongs.¹²⁵ Notice of the deferral must be provided to the holder of the approved application within five days of this decision, the deferral must be published in the Federal Register, and notice of the public meeting(s) and a description of the deferral must be provided to the public.¹²⁶ Following the meeting or meetings, the Secretary may announce in the Federal Register a planned regulatory action (including a modification of the REMS of every drug in the class), seek public comment, and after seeking comment issue an order addressing the regulatory action.¹²⁷ Use of this process to consider a drug class effect may not be the sole source of delay on an application or supplement.¹²⁸

g) Use of Advisory Committees

The Secretary may convene a meeting of one or more FDA advisory committees to review a concern about the safety of a drug or class of drugs, including before a REMS assessment (or assessments) are due, to review a REMS (or more than one), or to review a REMS dispute.¹²⁹

h) Generic Drugs

A drug that is the subject of an approved ANDA is subject to only two elements of the REMS required for the applicable listed drug: (1) any Medication Guide or patient package insert required, and (2) any elements to assure safe use (i.e., use or distribution restrictions) required.¹³⁰ The generic drug and reference drug must use a single, shared system for the latter, although the Secretary may waive this requirement for the generic drug if he or she finds that: (1) the burden of creating a single, shared system outweighs its benefit, or (2) an aspect of the elements for the listed drug is claimed by an unexpired patent or is trade secret and the generic applicant certifies that it was unable to obtain a license.¹³¹ In the case of waiver, the generic applicant may use a different, comparable aspect to assure safe use.¹³² If a generic drug is approved under section 505(j) with respect to a particular listed drug, the Secretary will undertake, for the listed drug, any communication to healthcare providers required under the REMS for the listed drug, and he or she will notify the generic application holder if the REMS is modified.¹³³

4. Enforcement

Section 505(o)(1) of the FDCA states that a responsible person may not introduce a new drug into commerce if the person is in violation of section 505(o)(3) or section 505(o)(4), which relate to postmarket studies, postmarket clinical trials, and safety labeling changes. Section 505(p)

¹²⁵ *Id.* § 505-1(h)(7)(A). This decision must be made in consultation with the office responsible for reviewing the drug and the office responsible for postapproval safety of the drug. *Id.*

¹²⁶ *Id.* § 505-1(h)(7)(B).

¹²⁷ *Id.* § 505-1(h)(7)(D).

¹²⁸ *Id.* § 505-1(h)(9).

¹²⁹ *Id.* § 505-1(h)(6).

¹³⁰ *Id.* § 505-1(i)(1).

¹³¹ *Id.* § 505-1(i)(1)(B). The Secretary may seek to negotiate a voluntary agreement with the owner of the patent, method, or process for a license for the generic applicant to use the aspect in question.

¹³² *Id.* § 505-1(i)(1)(B).

¹³³ *Id.* § 505-1(i)(2).

states that a person may not introduce into commerce a new drug that is a prescription drug, or a biological product that is a drug, if a REMS is required and the person fails to maintain compliance with the REMS or other requirements of section 505-1. In addition, failure to conduct a postmarket study required under section 506 (fast track) or FDA's subpart H (drug) and E (biologic) regulations is deemed a violation of section 505(p)(1).

Section 902 of the FDAAA amends section 502 of the FDCA. Under the new subsections (y) and (z), a drug will be deemed misbranded if: (1) it is subject to an approved REMS and the responsible person fails to comply with a requirement of the REMS, or (2) the responsible person violates a requirement of section 505(o)(3) (relating to postmarket studies and trials) or section 505(o)(4) (relating to safety labeling changes).¹³⁴

Section 902 also amends section 303(f) of the FDCA. Under a new paragraph (4) of section 303(f), a responsible person who violates a requirement of section 505(o), section 505(p), or section 505-1 is subject to a civil money penalty. This penalty may not exceed \$250,000 per violation or \$1 million for all violations adjudicated in a single proceeding. If a violation continues, however, after the Secretary has provided written notice to the responsible person, the penalty may not exceed \$250,000 for the first 30-day period but may double for every 30-day period thereafter, not to exceed \$1 million for any 30-day period, and not to exceed \$10 million for all violations adjudicated in a single proceeding.¹³⁵

5. Prescription Drug Advertising

Section 901 of the FDAAA also adds a new section 503B to the FDCA. Under section 503B, the Secretary may require the submission, for review, of any television advertisement for a drug no later than 45 days before dissemination of the advertisement.¹³⁶ In conducting a review under this section, the Secretary may make recommendations with respect to "information included in the label of the drug," on changes that are necessary to protect "the consumer good and well-being" or changes that are "consistent with prescribing information for the product." In addition, he or she may make recommendations with respect to "information included in the label of the drug," if appropriate and if information exists, on statements for inclusion in the advertisement "to address the specific efficacy of the drug as it relates to specific population groups," such as the elderly, children, and racial and ethnic minorities.¹³⁷ The preceding provisions do not authorize the Secretary to make or direct changes in the material submitted.¹³⁸ Section 503B does, however, authorize the Secretary to require specific disclosures in advertising. Specifically, if the Secretary determines that an advertisement would be false or misleading without a specific disclosure about a serious risk listed in the labeling of the drug involved, he or she may require inclusion of that disclosure in the advertisement.¹³⁹ The

¹³⁴ *Id.* § 502(y), (z).

¹³⁵ *Id.* § 303(f)(4).

¹³⁶ *Id.* § 503B(a). Nothing in section 503B is to be construed as affecting requirements under section 502(n) of the FDCA, 21 C.F.R. § 314.550 and § 601.45 and their successor regulations (promotional materials relating to subpart H/E products), or 21 C.F.R. § 314.640 and § 601.94 and their successor regulations (promotional materials relating to products approved under the Animal Rule). *Id.* § 503B(f).

¹³⁷ *Id.* § 503B(b). In formulating these recommendations, the Secretary must take into consideration the impact of the advertised drug on elderly populations, children, and racially and ethnically diverse communities. *Id.* § 503B(d).

¹³⁸ *Id.* § 503B(c).

¹³⁹ *Id.* § 503B(e)(1).

Secretary may also require an advertisement to include, for a period of up to two years following approval or licensure of the product, disclosure of the date of approval, if he or she determines that the advertisement would otherwise be false or misleading.¹⁴⁰

Section 901 also amends section 502(n) of the FDCA. As amended, section 502(n) will state that in the case of a direct-to-consumer (DTC) television or radio advertisement for a prescription drug, if the advertisement states the name of the drug and its conditions of use, the “major statement” relating to side effects and contraindications must be presented in a “clear, conspicuous, and neutral manner.”¹⁴¹ Section 901 also directs the Secretary, within 30 months of enactment of the FDAAA, to “by regulation establish standards for determining” whether the major statement is presented in the manner required.¹⁴² And it deletes the provision in section 502(n) that requires prescription drug advertising regulations to be developed through formal section 701(e) rulemaking procedures, substituting instead “section 701(a).”¹⁴³ Section 906 of the FDAAA also amends section 502(n) by inserting the requirement that print DTC advertisements include conspicuous reference to the 1-800 number and FDA website for reporting “negative side effects of prescription drugs.”¹⁴⁴

Dissemination of a television advertisement without complying with section 503B is a new prohibited act.¹⁴⁵ Section 901 also amends section 303 of the FDCA to create a new civil money penalty provision tied to DTC advertising. Under the new section 303(g), if the holder of an approved NDA for a prescription drug, or the holder of an approved BLA, disseminates or causes another party to disseminate a DTC advertisement that is false or misleading, that person is liable for a civil penalty not to exceed \$250,000 for the first violation in a three-year period and not to exceed \$500,000 for each subsequent violation in any three-year period.¹⁴⁶ The civil penalty is to be assessed by the Secretary in an order on the record, following written notice and an opportunity for a hearing in accordance with 5 U.S.C. § 554.¹⁴⁷ If the application holder requests a hearing, the Secretary may issue subpoenas requiring attendance and testimony of witnesses and production of evidence relating to the matter under investigation.¹⁴⁸ In determining the amount of a penalty under section 303(g), the Secretary must take into account a variety of factors, including whether the person submitted the advertisement for review under the new DTC user fee program, whether the person submitted it (if required) under section 503B, whether the person incorporated the agency’s recommendations regarding the advertisement prior to its dissemination, and whether the person had the advertisement reviewed by qualified medical, regulatory, and legal reviewers prior to its dissemination.¹⁴⁹ Civil money

¹⁴⁰ *Id.* § 503B(e)(2).

¹⁴¹ FDAAA § 901(d)(3)(A), amending FDCA § 502(n).

¹⁴² FDAAA § 901(d)(3)(B).

¹⁴³ *Id.* § 901(d)(6).

¹⁴⁴ *Id.* § 906(a), amending FDCA § 502(n).

¹⁴⁵ *Id.* § 901(d), adding FDCA § 301(kk).

¹⁴⁶ FDCA § 303(g)(1). Repeated dissemination of the same or a similar advertisement prior to receipt of written notice from the Secretary is one violation. Following receipt of notice, all disseminations in a single day are considered one violation. In the case of advertisements that appear in periodicals that are not published daily, each issue date is a single day. *Id.* The Secretary may “compromise, modify, or remit, with or without conditions,” any civil penalty that may be assessed. *Id.* § 303(g)(5).

¹⁴⁷ *Id.* § 303(g)(2).

¹⁴⁸ *Id.* § 303(g)(2).

¹⁴⁹ *Id.* § 303(g)(3).

penalties may not be imposed if the person submitted the advertisement to the Secretary and incorporated every comment from the Secretary, before dissemination.¹⁵⁰ Civil penalties are subject to de novo judicial review by the U.S. Court of Appeals, if the person seeking review requested a hearing at the agency and filed a petition with the court within sixty days following the order assessing the penalty.¹⁵¹

Section 901 also directs the Secretary to submit a report to Congress, within 24 months of enactment of the FDAAA, on DTC advertising and its ability to communicate to subsets of the general population.¹⁵² Section 904 directs the Commissioner to submit a report, within one year of enactment, on how best to communicate to the public the risks and benefits of new drugs and the role of REMS in assessing risks and benefits. The Commissioner may consider including in labeling and DTC advertisements of newly approved drugs a “unique symbol indicating the newly approved status of the drug or indication” for a period of time.¹⁵³ Section 906 requires the Secretary to conduct a study within six months of enactment to determine if the 1-800 and website statement in print DTC advertisements is appropriate for inclusion in DTC television advertisements.¹⁵⁴

6. Active Postmarket Risk Identification and Analysis System

Section 905 of the FDAAA adds paragraphs (3) and (4) to section 505(k) of the FDCA, requiring the Secretary to establish an active postmarket risk identification and analysis system. (Section 921 of the FDAAA, in subtitle B, adds paragraph (5) and is discussed elsewhere in this memorandum.)

Under paragraph (3), within two years of enactment, the Secretary must develop methods to obtain access to disparate data sources (including data from the Medicare program and private sector health insurance claims data) and develop validated methods for establishment of a system to link and analyze these data, with a goal of including at least 100 million patients by July 2012. Within one year of the development of these methods, the Secretary must establish and maintain actual procedures for, among other things: (a) risk identification and analysis based on electronic health data; (b) active adverse event surveillance using federal health-related electronic data, private sector health-related electronic data, and other data necessary to create a robust system to identify potential drug safety signals; and (c) identification of trends and patterns with respect to data accessed.¹⁵⁵

Paragraph (4) requires “advanced” analysis of drug safety data and will entail, among other things: (a) establishment of a public process to identify priority drug safety questions and consider mechanisms for responding to those questions; and (b) contracting with qualified entities to

¹⁵⁰ *Id.* § 303(g)(4)(A). The Secretary may retract or modify previously made comments on the basis of new information, but he or she must provide written notice of the new views and a reasonable time for the application holder to modify its advertisements, before assessing a civil penalty. *Id.* § 303(g)(4)(B).

¹⁵¹ *Id.* § 303(g)(6). If an applicant ultimately fails to pay an assessed penalty, the Attorney General may bring suit in district court to recover the amount assessed, plus interest. *Id.* § 303(g)(7).

¹⁵² FDAAA § 901(d)(5).

¹⁵³ *Id.* § 904.

¹⁵⁴ *Id.* § 906(b). If the Secretary determines that inclusion of this information is appropriate, he or she must issue regulations requiring the information. *Id.*

¹⁵⁵ FDCA § 505(k)(3).

allow for prompt investigation of those questions, including investigation of safety signals from clinical trials used to support drug approval.¹⁵⁶ Within 18 months of enactment of the FDAAA, the GAO must report to Congress with recommendations regarding the need for any additional legislative or regulatory actions to ensure privacy, confidentiality, and security of the data collected and used in the active surveillance system.¹⁵⁷ And within four years of enactment, the Secretary must report to Congress on the use of the new system to identify specific drug safety signals and to better understand outcomes associated with drugs marketed in the United States.¹⁵⁸

7. Effective Date; Drugs Approved Before Effective Date

Subtitle A takes effect 180 days after enactment of the FDAAA.¹⁵⁹

Certain drugs approved before the effective date of the FDAAA are deemed to have, already, an approved REMS. These are: drugs subject to restrictions on distribution and use under subpart H (drugs) or subpart E (biologics), and drugs with distribution and use restrictions to which the applicant has otherwise agreed.¹⁶⁰ The REMS in question is deemed to consist of the timetable for REMS assessment required under section 505-1(d) of the FDCA, as well as any additional elements under sections 505-1(e) (MedGuide, patient package insert, and communication plan) and 505-1(f) (elements to assure safe use) already in effect for the drug.¹⁶¹ This REMS is subject to enforcement to the same extent as any other REMS strategy, except that the new civil money penalty and misbranding provisions do not apply before the Secretary completes his or her review of (and acts on) the first assessment of the REMS under section 505-1.¹⁶² No later than 180 days after the effective date of the FDAAA, the holder of the approved application for a drug deemed to have a REMS must submit a proposed REMS to the Secretary, and that submission is subject to section 505-1 as if it had been submitted with the application in the first instance.¹⁶³

8. Veterinary Medicine; Appropriations

Section 907 states that nothing in Subtitle A, or the amendments made by Subtitle A, has any effect on the use of drugs approved under section 505 by, or on the order of, a licensed veterinarian. Section 908 authorizes the appropriation of \$25 million for each of fiscal years 2008 through 2012 for carrying out Subtitle A.¹⁶⁴

¹⁵⁶ *Id.* § 505(k)(4).

¹⁵⁷ FDAAA § 905(e).

¹⁵⁸ *Id.* § 905(e).

¹⁵⁹ *Id.* § 909(a).

¹⁶⁰ *Id.* § 909(b)(1). The restrictions in question must have been in effect on the effective date of the FDAAA.

¹⁶¹ *Id.* § 909(b)(2)(A).

¹⁶² *Id.* § 909(b)(2)(B).

¹⁶³ *Id.* § 909(b)(3).

¹⁶⁴ *Id.* § 907.

B. Subtitle B —Other Provisions to Ensure Drug Safety and Surveillance

1. Antibiotic Drugs

Section 911 of the FDAAA creates a new section 511 of the FDCA, requiring the Secretary to issue guidance for the conduct of clinical trials for antibiotic drugs.¹⁶⁵ This guidance must be issued within one year of enactment of the FDAAA and must indicate “the appropriate models and valid surrogate markers.”¹⁶⁶ No later than five years after enactment, the Secretary must review and update the guidance to reflect developments in scientific and medical information and technology.¹⁶⁷

2. Prohibition Against Foods to Which Drugs or Biological Products Have Been Added

Section 912 of the FDAAA amends section 301 of the FDCA by adding a new subsection (II). Under subsection (II), it is a prohibited act to introduce into interstate commerce any food to which has been added a drug approved under section 505 of the FDCA, a biological product licensed under section 351 of the PHSA, or a drug or biological product for which “substantial clinical investigations” have been instituted and for which the existence of such investigations has been made public.¹⁶⁸ There are four exceptions. First, an exception is provided for any drug or biological product marketed in food before approval under the FDCA or PHSA and before substantial clinical investigations were instituted.¹⁶⁹ Second, an exception is provided where the Secretary has issued a regulation, after notice and comment, approving the use of the drug or biological product in the food.¹⁷⁰ Third, an exception is provided if the drug or biological product is used to enhance the safety of the food and not to have an independent biological or therapeutic effect in humans, provided the use conforms with: (a) a food additive regulation under section 409; (b) a regulation listing or affirming conditions under which the use of the drug or biological product in food is generally recognized as safe (GRAS); (c) the conditions of use identified in a notification to the Secretary claiming exemption from food additive premarket approval requirements based on the notifier’s determination, which has not been questioned by the Secretary, that the use is generally recognized as safe (GRAS); or (d) an effective food contact substance notification; or provided (e) the drug or biological product was marketed for smoking cessation prior to enactment of the FDAAA.¹⁷¹ Finally, an exception is provided if the drug is a new animal drug whose use is not unsafe under section 512.¹⁷² Conforming changes are made to the FDA’s seizure authority under section 304 and its authority to refuse products at the border under section 801(a).¹⁷³

¹⁶⁵ FDCA § 511(a).

¹⁶⁶ *Id.* § 511(a).

¹⁶⁷ *Id.* § 511(b).

¹⁶⁸ *Id.* § 301(II).

¹⁶⁹ *Id.* § 301(II)(1).

¹⁷⁰ *Id.* § 301(II)(2).

¹⁷¹ *Id.* § 301(II)(3).

¹⁷² *Id.* § 303(II)(4).

¹⁷³ FDAAA § 912(b).

3. Assuring Pharmaceutical Safety

Section 913 of the FDAAA creates a new section 505D of the FDCA, which requires the Secretary to develop standards and identify and validate technologies that can be used to secure the drug supply chain against counterfeited, diverted, subpotent, substandard, adulterated, misbranded, and expired prescription drugs.¹⁷⁴ The Secretary must work with the Department of Justice, the Department of Homeland Security, the Department of Commerce, other appropriate federal and state agencies, manufacturers, distributors, pharmacies, and other supply chain stakeholders to prioritize and develop standards for identification, validation, authentication, and tracking and tracing of prescription drugs.¹⁷⁵ No later than 30 months after enactment of the FDAAA, the Secretary must develop a standardized numerical identifier to be applied to every prescription drug at the package or pallet level.¹⁷⁶ The Secretary must also expand and enhance the resources and facilities of FDA components involved with regulatory and criminal enforcement of the FDCA to secure the drug supply chain and must undertake related enhanced and joint enforcement activities with other federal and state agencies.¹⁷⁷

4. Citizen Petitions

Section 914 of the FDAAA adds a new subsection (q) to section 505, regarding petitions and civil actions that relate to approval of applications submitted under section 505(j) or described in section 505(b)(2).¹⁷⁸ The subsection does not apply to a petition relating solely to the timing of approval of an ANDA or to a petition filed by the applicant itself.¹⁷⁹

The Secretary may not delay approval of such an application because of any request to take action regarding that application, unless: (1) the petition is submitted in writing pursuant to 21 C.F.R. § 10.30 (citizen petition) or § 10.35 (administrative stay of action), or their successor regulations; and (2) the Secretary has determined that a delay is necessary to protect the public health.¹⁸⁰ If the Secretary makes this determination, he or she must notify the applicant within 30 days and summarize the substantive issues raised in the petition.¹⁸¹ If the Secretary determines that the petition or a supplement to the petition was submitted with the “primary purpose” of delaying approval of the application and that the petition does not on its face raise “valid” scientific or regulatory issues, he or she may deny the petition at any point.¹⁸²

The Secretary must take “final agency action” on a petition no later than 180 days after it was submitted, and he or she may not extend this deadline for any reason.¹⁸³ If the generic

¹⁷⁴ FDCA § 505D(a).

¹⁷⁵ *Id.* § 505D(b)(1).

¹⁷⁶ *Id.* § 505D(b)(2).

¹⁷⁷ *Id.* § 505D(c).

¹⁷⁸ *Id.* § 505(q)(1)(A).

¹⁷⁹ *Id.* § 505(q)(4).

¹⁸⁰ *Id.* § 505(q)(1)(A).

¹⁸¹ *Id.* § 505(q)(1)(B).

¹⁸² *Id.* § 505(q)(1)(E).

¹⁸³ *Id.* § 505(q)(1)(F). The Secretary will be deemed to have taken final agency action if he or she makes a final decision within the first 180 days or otherwise at the expiry of the 180-day period. If a civil action is filed against the Secretary with (continued...)

drug application in question received first-filer status for purposes of 180-day exclusivity and approval of the application was delayed because of the petition, the 30-month deadline for tentative approval (which triggers forfeiture of exclusivity) is extended by the number of days the petition is pending.¹⁸⁴ Finally, the Secretary may not consider a petition unless it is signed and contains a certification (or, in the case of a supplement or comments on a petition, a verification) regarding, among other things, sources of remuneration and the date on which the underlying information was first learned.¹⁸⁵

The Secretary must report annually to Congress on the number of applications under sections 505(j) and 505(b)(2) that were approved during the preceding twelve months, the number whose effective dates were delayed by petitions, the length of those delays, and the number of petitions filed.¹⁸⁶ No later than one year after enactment of the FDAAA, the Secretary must submit a report to Congress on ways to encourage the early submission of petitions.¹⁸⁷

5. Postmarket Drug Safety Information for Patients and Providers

Section 915 of the FDAAA adds a new subsection (r) to section 505 of the FDCA, which requires the Secretary to improve the “transparency” of information about drugs and to allow patients and providers better access through the Internet to information about drugs. Within one year after enactment, the Secretary must establish a website that contains links to the following for each prescription drug approved under section 505 or licensed under section 351 of the PHSA: (1) drug safety information found on the National Library of Medicine’s Daily Med and Medline Plus Web sites; (2) patient labeling and patient package inserts; (3) information about whether a Med Guide is required; (4) a link to the clinical trial registry and results database entries for the drug; (5) safety information and alerts issued by FDA including product recalls, warning letters, and import alerts; (6) publicly available information about any applicable RiskMAP or REMS; (7) guidance documents and regulations relating to drug safety; and (8) other materials determined appropriate by the Secretary.¹⁸⁸ The website should also provide: (1) access to summaries of the data collected using the active surveillance system required under section 505(k)(3); and (2) eighteen months after approval, or following use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug.¹⁸⁹ Within 21 days after approval or licensure of a drug, the Secretary must also post the approved package insert and any required patient labeling.¹⁹⁰

6. Action Package for Approval

Section 916 of the FDAAA amends section 505(l) of the FDCA by adding a new paragraph requiring publication on the FDA website of an “action package for approval” of each

respect to an issue raised in the petition, prior to final agency action, the court must dismiss the action without prejudice for failure to exhaust administrative remedies. *Id.* § 505(q)(2).

¹⁸⁴ *Id.* § 505(q)(1)(G).

¹⁸⁵ *Id.* § 505(q)(1)(H) and (I).

¹⁸⁶ *Id.* § 505(q)(3).

¹⁸⁷ FDAAA § 914(b).

¹⁸⁸ FDCA § 505(r)(1) and (2).

¹⁸⁹ *Id.* § 505(r)(2).

¹⁹⁰ *Id.* § 505(r)(3).

application under section 505(b) of the FDCA or section 351 of the PHSA.¹⁹¹ Within 48 hours after approval of the application, except where redaction is required, the Secretary must publish a summary review that documents conclusions about the drug from all reviewing disciplines, noting any critical issues and disagreements with the applicant and within the review team and how they were resolved, recommendations for action, and an explanation of any non-concurrence with review conclusions.¹⁹² The remaining pieces of the action package must be posted within 30 days of approval, if the application relates to a drug no active ingredient (including any ester or salt of the active ingredient) of which has been previously approved in an application under section 505 of the FDCA or section 351 of the PHSA, or within 30 days of the third request under FOIA for any other drug.¹⁹³ Those pieces are: (1) documents generated by FDA related to review of the application; (2) documents pertaining to the format and content of the application generated during drug development; (3) labeling submitted by the applicant; (4) the Division Director and Office Director's decision document, including a brief statement of concurrence with the summary review, a separate review or addendum to the review if disagreeing with the summary review, and a separate review or addendum to the review to add further analysis; (5) the name of each officer or employee of FDA who participated in the decision to approve the application and consented to have his or her name included.¹⁹⁴ Subparagraph (e) states that the new paragraph does not authorize the disclosure of any trade secret, confidential commercial or financial information, or other matter protected from disclosure under FOIA.¹⁹⁵ Section 505(l)(2) adds that a scientific review of an application is "considered the work of the reviewer" and may not be "altered" by management or the reviewer "once final."¹⁹⁶

7. Database for Authorized Generic Drugs

Section 920 of the FDAAA amends section 505 of the FDCA by adding a new subsection (t), which requires the Secretary to establish a database of authorized generic drugs.¹⁹⁷ No later than nine months after enactment of the FDAAA, the Commissioner must publish a complete list on the FDA website of all authorized generic drugs, including drug trade name, brand company manufacturer, and the date the authorized generic entered the market.¹⁹⁸ This list must include each authorized generic drug included in annual reports submitted to the Secretary by the sponsor of the listed drug after January 1, 1999.¹⁹⁹ The list must be updated quarterly, to include each authorized generic drug included in annual reports submitted in the prior three months.²⁰⁰

¹⁹¹ *Id.* § 505(l)(2)(A).

¹⁹² *Id.* § 505(l)(2)(B) and (C)(iv).

¹⁹³ *Id.* § 505(l)(2)(A).

¹⁹⁴ *Id.* § 505(l)(2)(C).

¹⁹⁵ *Id.* § 505(l)(2)(E).

¹⁹⁶ *Id.* § 505(l)(2)(D).

¹⁹⁷ *Id.* § 505(t).

¹⁹⁸ *Id.* § 505(t)(1). An "authorized generic drug" is defined to mean a listed drug that has been approved under section 505(c) of the FDCA and is marketed, sold, or distributed directly, or indirectly, to retail class of trade under labeling, packaging (other than repackaging as the listed drug), product code, labeler code, trade name, or trade mark different from the listed drug. *Id.* § 505(t)(3).

¹⁹⁹ *Id.* § 505(t)(2).

²⁰⁰ *Id.* § 505(t)(1).

8. Risk Communication

Section 917 of the FDAAA adds section 567 to the FDCA. This section requires the Secretary to establish an Advisory Committee on Risk Communication, which will advise the Commissioner on methods to communicate effectively the risks associated with products regulated by FDA.²⁰¹

9. Referral to Advisory Committee

Section 918 of the FDAAA adds a new subsection (s) to section 505 of the FDCA. Under this subsection, if an application relates to a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under section 505 or section 351 of the PHSA, the Secretary must either refer the drug to an advisory committee or state in the action letter on the application the reasons the Secretary did not refer the drug.²⁰²

10. Response to Institute of Medicine

Section 919 requires the Secretary to respond, within one year of the date of enactment of Title IX, to the Institute of Medicine's 2006 report entitled *The Future of Drug Safety — Promoting and Protecting the Health of the Public*.²⁰³

11. Adverse Drug Reaction Reports and Postmarket Safety

Section 921 of the FDAAA adds a paragraph (5) to section 505(k). This paragraph requires the Secretary to conduct regular screening of the Adverse Event Reporting System database and to post quarterly reports on the Adverse Event Reporting System website of any new safety information or potential signals of serious risk.²⁰⁴ It also requires the Secretary to report to Congress no later than two years after enactment of the FDAAA on agency procedures and processes for addressing postmarket safety issues identified by the Office of Surveillance and Epidemiology.²⁰⁵ And it requires annual review of the backlog of postmarket safety commitments to determine which should be revised or eliminated, with reporting to Congress on those determinations.²⁰⁶

TITLE XI — OTHER PROVISIONS

A. Subtitle A — In General

1. Scientific Articles Published by FDA Employees

Section 1101 of the FDAAA adds a new section 713 to the FDCA, requiring clear and publicly available written policies on the review and clearance of scientific articles (including papers, posters, abstracts, books, book chapters, and other published writing) published or presented by FDA

²⁰¹ *Id.* § 567.

²⁰² *Id.* § 505(s).

²⁰³ FDAAA § 919.

²⁰⁴ FDCA § 505(k)(5)(A).

²⁰⁵ *Id.* § 505(k)(5)(B).

²⁰⁶ *Id.* § 505(k)(5)(C).

employees.²⁰⁷ These policies must govern the timely submission, review, and clearance of articles, as well as the disclaimer requirements that apply.²⁰⁸ If the policies require submission to a supervisor or other official for review and clearance, each employee must submit his or her article for that review no fewer than 30 days before submitting it for publication or presentation.²⁰⁹ The supervisor or reviewing official must review and provide written clearance (or clearance with conditions) within 30 days.²¹⁰ If the supervisor or reviewing official does not do so, on the 31st day the employee may consider the article cleared and may submit it for publication or presentation.²¹¹

2. Treatments for Tropical Diseases

Section 1102 of the FDAAA adds a new section 524 to the FDCA, which authorizes the use of priority review vouchers to encourage the development of treatments for tropical diseases.²¹² Under section 524(b), the Secretary must award a priority review voucher to the sponsor of a tropical disease product application, upon approval of that application.²¹³ The voucher entitles its holder to priority review of one NDA submitted under section 505(b)(1) or one BLA submitted under the PHSA.²¹⁴ The recipient of the voucher may transfer or sell the voucher.²¹⁵ Vouchers are not available for tropical disease product applications submitted prior to enactment of section 524 and, in fact, may not be awarded for the first year after enactment of the FDAAA.²¹⁶

The sponsor of an application to which the voucher will be applied must notify the Secretary no later than 365 days prior to submission of the application in question.²¹⁷ This notification constitutes a legally binding commitment to pay a special user fee under section 524.²¹⁸ Ordinary application user fees also apply.²¹⁹ Section 524(c) authorizes the Secretary to establish the user fee program in question and directs the Secretary to base the fee each fiscal year on the average cost

²⁰⁷ *Id.* § 713(a) and (b).

²⁰⁸ *Id.* § 713(b).

²⁰⁹ *Id.* § 713(c).

²¹⁰ *Id.* § 713(d).

²¹¹ *Id.* § 713(e).

²¹² Tropical diseases are listed in section 524(a)(3).

²¹³ *Id.* § 524(b)(1). A “tropical disease product application” is an application under section 505(b)(1) of the FDCA, an application under section 505(b)(2) for an active ingredient or indication that has not been previously approved, or an application under section 351 of the PHSA, for prevention or treatment of a tropical disease, if the Secretary found the application itself eligible for priority review. *Id.* § 524(a)(4). It must be approved after enactment of the FDAAA for use in the prevention, detection, or treatment of a tropical disease. *Id.* And no active ingredient (including any ester or salt of the active ingredient) in the drug may have been approved in any other application under section 505(b)(1) of the FDCA or section 351 of the PHSA. *Id.*

²¹⁴ *Id.* § 524(a)(2).

²¹⁵ *Id.* § 524(b)(2).

²¹⁶ *Id.* § 524(b)(3).

²¹⁷ *Id.* § 524(b)(4).

²¹⁸ *Id.* § 524(b)(4).

²¹⁹ *Id.* § 524(c)(1).

incurred by the agency in the review of human drug applications subject to priority review in the prior fiscal year.²²⁰

3. Genetic Testing; NIH Amendments

Section 1103 of the FDAAA states that if the Secretary's Advisory Committee on Genetics, Health, and Society does not complete and submit the Regulatory Oversight of Genetic/Genomic Testing Report & Action Recommendations to the Secretary by July of 2008, the Secretary must enter into a contract with the Institute of Medicine to study the overall safety and quality of genetic tests and make recommendations regarding federal oversight and regulation of those tests.²²¹ Section 1104 makes a variety of technical changes to provisions of the PHSA governing the National Institutes of Health.²²²

4. Severability

Section 1105 of the FDAAA states that if any provision of the Act, or an amendment made by the Act, or the application of a provision or amendment to a person or situation, is held unconstitutional, the remainder will not be affected.²²³

B. Subtitle B — Antibiotic Access and Innovation

1. Identification of Clinically Susceptible Concentrations of Antimicrobials

Section 1111 of the FDAAA requires the Commissioner to identify, periodically update, and post on the Internet "clinically susceptible concentrations," meaning specific values that characterize bacteria as clinically susceptible, intermediate, or resistant to a drug or drugs being tested.²²⁴

2. Orphan Antibiotic Drugs

Section 1112 of the FDAAA requires the Commissioner to convene a public meeting regarding which serious and life-threatening infectious diseases, such as diseases due to gram-negative bacteria and other diseases due to antibiotic-resistant bacteria, potentially qualify for grants and contracts under the Orphan Drug Act.²²⁵ It also revises section 5(c) of the Orphan Drug Act, which is not codified as part of the FDCA, by authorizing appropriation of \$30 million dollars for each of fiscal years 2008 through 2012 for these grants and contracts.²²⁶

²²⁰ *Id.* § 524(c)(4).

²²¹ FDAAA § 1103.

²²² *Id.* § 1104.

²²³ *Id.* § 1105.

²²⁴ *Id.* § 1111.

²²⁵ *Id.* § 1112(a).

²²⁶ *Id.* § 1112(b).

3. Exclusivity of Certain Drugs Containing Single Enantiomers

Section 1113 of the FDAAA revises section 505 of the FDCA by adding a new subsection (u). Under section 505(u), the sponsor of an application under section 505(b) for a non-racemic drug containing as an active ingredient (including any ester or salt of the active ingredient) a single enantiomer of a previously approved racemic drug may elect to have the single enantiomer not considered the “same active ingredient” as that contained in the previously approved racemic drug.²²⁷ This election may be made if: (1) the single enantiomer has not previously been approved except in the approved racemic drug; (2) the application submitted under section 505(b) contains full reports of new clinical investigations necessary for its approval and conducted or sponsored by the applicant; (3) the application does not rely on any investigations that are part of an application submitted under subsection (b) for approval of the approved racemic drug; and (4) the application for the non-racemic drug is not submitted for approval of a condition of use in a therapeutic category in which the approved racemic drug has been approved or a condition of use for which any other enantiomer of the racemic drug has been approved.²²⁸

If an applicant elects to be considered not the same active ingredient under subsection 505(u), then until ten years after approval of the non-racemic drug, the Secretary may not approve the non-racemic drug for any condition of use in the therapeutic category in which the racemic drug has been approved.²²⁹ The non-racemic drug’s labeling must include, if applicable, a statement that it has not been approved for, and has not been shown safe and effective for, any condition of use for which the racemic drug has been approved.²³⁰

Section 505(u) expires in 2012. Specifically, the election can be made only with respect to an application submitted after the date of enactment of section 505(u) and before October 1, 2012.²³¹

4. Report

No later than January 1, 2012, the Comptroller General must submit a report to the relevant Congressional committees that examines whether and how this subtitle has: (1) encouraged the development of new antibiotics and other drugs, and (2) prevented or delayed timely generic drug entry.²³²

²²⁷ FDCA § 505(u)(1).

²²⁸ *Id.* § 505(u)(1). “Therapeutic category” means a therapeutic category identified by the United States Pharmacopeia in its implementation of Medicare Part D. *Id.* § 505(u)(3)(A).

²²⁹ *Id.* § 505(u)(2)(A).

²³⁰ *Id.* § 505(u)(2)(B).

²³¹ *Id.* § 505(u)(4).

²³² FDAAA § 1114.

* * *

This information is not intended as legal advice, which may often turn on specific facts. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein.

If you have any questions about this memorandum, please contact any of the attorneys listed below.

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