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# **Food and Drug Administration Amendments Act of 2007**

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## **EXECUTIVE SUMMARY**

On September 27, 2007, President Bush signed into law the Food and Drug Administration Amendments Act (“FDAAA”), Pub. L. No. 110-85, \_\_\_ Stat. \_\_\_\_ (2007), which amends both the Federal Food, Drug, and Cosmetic Act (“FDC Act”) and Public Health Service Act (“PHS Act”).<sup>1</sup> In addition to reauthorizing and amending several drug and medical device provisions that were scheduled to sunset, the new law provides the Food and Drug Administration (“FDA”) with new funding and oversight of drug safety. The law significantly changes FDA’s handling of postmarket drug product safety issues and will have considerable short- and long-term effects on drug manufacturers.

FDAAA includes 11 titles, the first 5 of which reauthorize drug and medical device user fee and pediatric-related programs through Fiscal Year (“FY”) 2012. Title III also amends the FDC Act to create new provisions to provide incentives to medical device manufacturers to develop devices for pediatric patients and to provide FDA with new authority to review and regulate such devices. Titles VI-VIII establish a new private-public partnership intended to modernize medical product development and enhance product safety, amend the FDC Act with respect to certain conflict of interest issues among FDA advisory committee members, and establish databases for clinical trial registries and results. Title IX, perhaps the longest reaching FDAAA provision, includes various programs intended to improve the postmarket safety of drugs, including giving FDA the authority to impose Risk Evaluation and Mitigation Strategies (“REMS”). This title also modifies the citizen petition process with respect to petitions having the potential to delay approval of generic drug products. Title X, which concerns food safety, creates a reportable food registry to help track problems in the food supply and to allow for a rapid FDA and industry response. Finally, Title XI includes several miscellaneous provisions intended to, among other things, improve antibiotic access and innovation.

Among the more controversial provisions that failed to survive the legislative negotiation process were the establishment of an abbreviated approval pathway for follow-on versions of approved biological products, and the ability of approved labeling to preempt causes of action for failure to warn under state law.

This memorandum summarizes FDAAA provisions that are of most interest to our clients and analyzes their potential effects on the FDA-regulated industry. It is organized

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<sup>1</sup> A copy of the new law is *available at* [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110\\_cong\\_bills&docid=f:h3580enr.txt.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h3580enr.txt.pdf). A U.S. Senate and House Conference Report was not published; however, a House Report on H. R. 2900, the predecessor to H.R. 3580 (which is the bill that was signed into law), was published and is *available at* [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110\\_cong\\_reports&docid=f:hr225.110.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_reports&docid=f:hr225.110.pdf).

to summarize each title in the order presented in the new law. In addition to this memorandum, we will periodically report on various FDAAA issues on our firm's blog, The FDA Law Blog ([www.FDALawBlog.net](http://www.FDALawBlog.net)). You can register for e-mail updates on the blog.

## **I. PRESCRIPTION DRUG USER FEE AMENDMENTS OF 2007**

FDAAA Title I reauthorizes the Prescription Drug User Fee Act ("PDUFA") through FY 2012 and makes several changes to the law, including the broader use of user fee revenue to fund FDA's drug risk management activities, and the creation of special user fee programs for Positron Emission Tomography ("PET") drugs and Direct-to-Consumer ("DTC") advertisements. PDUFA was first enacted in 1992<sup>2</sup> to generate revenue from user fees paid by drug and biologic manufacturers in exchange for FDA's agreement to expedite the review process for sponsors submitting certain New Drug Applications ("NDAs") under the FDC Act and Biologics License Applications ("BLAs") under the PHS Act.<sup>3</sup> Today, under the new law, user fee revenue will account for approximately 25% of FDA's annual \$1.6 billion budget. Congress appropriates the remaining 75%.

The changes in this fourth iteration of PDUFA ("PDUFA IV") fall into three categories: (1) increased revenue to ensure FDA's financial footing for the Agency's review of human drugs; (2) changes to FDA's premarket review of human drug applications; and (3) modifications to the postmarket drug safety system. In connection with each reenactment of PDUFA, FDA issues a document that, among other things, commits the Agency to certain action timelines on various NDA and BLA review issues

<sup>2</sup> See Prescription Drug User Fee Act, Pub. L. No. 102-571, title I, 106 Stat. 4491 (1992) ("PDUFA I"). PDUFA was reauthorized ("PDUFA II") by the Food and Drug Modernization Act, Pub. L. No. 105-115, 111 Stat. 2296 (1997) ("FDAMA"), and by the Prescription Drug User Fee Amendments, Pub. L. No. 107-188, title V, subtitle A, 116 Stat. 594, 687 (2002) ("PDUFA III").

<sup>3</sup> Under PDUFA, FDA collects three types of user fees for a drug product that is the subject of a human drug application and for a biologic licensed under the PHS Act: (1) a one-time application fee upon submission of the application; (2) an annual establishment fee; and (3) an annual product fee. See FDC Act § 736. FDA recently announced in a notice scheduled to be published in the Federal Register on October 12, 2007 that the FY 2008 application user fee rates will be \$1,178,000 for an application requiring clinical data, and \$589,000 for applications not requiring clinical data and supplements requiring clinical data. FY 2008 product and establishment fee rates will be \$65,030 and \$392,700, respectively. A copy of the pre-publication version of the notice is *available at* <http://www.fda.gov/OHRMS/DOCKETS/98fr/OC2007240-n0000001.pdf>. FDA also recently announced new user fee payment procedures. See FDA, Application Fees for FY08, *available at* [http://www.fda.gov/cder/pdufa/application\\_fees.htm#new](http://www.fda.gov/cder/pdufa/application_fees.htm#new).

(the “Performance Goals”). FDA’s PDUFA IV Performance Goals also include new programs intended to modernize the drug safety system, implement new proprietary name review procedures, and establish new DTC advertisement performance goals.<sup>4</sup>

#### A. Significant Changes to PDUFA

FDAAA amends FDC Act § 736(b) — “Fee Revenue Amounts” — to establish user fees (application, establishment, and product fees) for each of FYs 2008 through 2012 in order to generate annual revenue that is the sum of \$392,783,000 plus a workload adjustment factor for FY 2007 that is modified in subsequent FYs. See FDC Act § 736(b), as amended by FDAAA § 103(b).<sup>5</sup> An additional \$225 million in user fee revenue for drug safety activities is spread across FYs 2008 through 2012 that starts at \$25 million in FY 2008 and increases to \$65 million in FY 2012. See FDC Act § 736(b)(4), as amended by FDAAA § 103(b).

The new law changes several definitions in FDC Act § 735, some of which will have significant effects on NDA and BLA applicants and on how FDA uses fee revenue. In particular, FDAAA amends the definition of “human drug application” at FDC Act § 735(1) and the definition of “process for the review of human drug applications” at FDC Act § 735(6).

Under PDUFA III, the term “human drug application” was defined, in relevant part, to mean: (1) an NDA submitted under FDC Act § 505(b)(1); and (2) a 505(b)(2) application requesting approval of either a new molecular entity or a new “indication for a use” of a previously approved drug. See FDC Act § 735(1)(A)-(B) (2006). Despite this language, FDA broadly interpreted the term “indication for a use” so that almost all 505(b)(2) applications submitted to the Agency were subject to user fees.<sup>6</sup> Under PDUFA IV, the definition of “human drug application” is amended to eliminate the distinction between 505(b)(1) NDAs and 505(b)(2) applications. See FDC Act § 735(1)(A), as amended by FDAAA § 102(2). Under PDUFA IV, all 505(b)(2) applications, regardless of how minimal a change to a listed drug, are subject to user fees to the same extent as 505(b)(1) applications.

<sup>4</sup> A copy of FDA’s PDUFA IV Performance Goals transmittal letter to Congress is *available at* <http://www.fda.gov/oc/pdufa4/pdufa4ltr.pdf>. A copy of FDA’s PDUFA IV Performance Goals is *available at* <http://www.fda.gov/oc/pdufa4/pdufa4goals.html>.

<sup>5</sup> For comparison, the total inflation-adjusted fee revenue under PDUFA III for FY 2007 was \$305,455,400. See Notice, Prescription Drug User Fee Rates for Fiscal Year 2007, 71 Fed. Reg. 43,780, 43,781 (Aug. 2, 2006).

<sup>6</sup> See Robert A. Dormer, Kurt R. Karst, FDA’s Unauthorized User Fee Money Grab, Washington Legal Foundation Legal Backgrounder, Vol. 28, No. 30 (Aug. 12, 2005) *available at* <http://www.wlf.org/upload/081205LBDormer.pdf>.

Since the enactment of PDUFA I, FDA has only been authorized to use user fee revenues “for the process for the review of human drug applications.” FDC Act § 736(g)(1) (2006). PDUFA III first expanded the definition of “process for the review of human drug applications” to include “collecting, developing, and reviewing safety information on [drugs approved after October 1, 2002], including adverse event reports, during a period of time after approval of such applications or supplements, not to exceed three years.” FDC Act § 735(6)(F) (2006). PDUFA IV further expands the range of postmarket activities (without any temporal limitation) for which user fees revenues can be expended by adding the development and use of “improved adverse-event data-collection systems,” and “improved analytical tools to assess potential safety problems,” and enforcement of new provisions of the FDC Act added by FDAAA Title IX into the definition of “process for the review of human drug applications.” FDC Act § 735(6)(F), as amended by FDAAA § 102(5).

FDAAA also amends PDUFA provisions concerning the effect of an applicant’s decision to withdraw an application. First, the law is expanded to provide that FDA may refund 75% of the application fee if a human drug application or a supplement is withdrawn even before a filing decision is made. See id. § 736(a)(1)(D), as amended by FDAAA § 103(a)(2)(A). Under PDUFA III, this provision applied to applications refused for filing. Second, a human drug application or a supplement previously refused for filing or withdrawn before a filing decision is made is subject to a full application fee upon resubmission or a filing over protest (unless such fee is waived or reduced under FDC Act § 736(d)). See id. § 736(a)(1)(E), as amended by FDAAA § 103(a)(2)(C).

While PDUFA II exempted orphan drugs from application fees, FDAAA goes a step further and exempts orphan drugs from annual product and establishment fees. Specifically, an approved drug designated as an orphan drug under is exempt from product and establishment fees if: (1) “[t]he drug meets the public health requirements contained in [FDC Act § 736(d)(1)(A)] as such requirements are applied to requests for waivers for product and establishment fees;” and (2) “[t]he drug is owned or licensed and is marketed by a company that had less than \$50,000,000 in gross worldwide revenue during the previous year,” and provided a certification to this effect is submitted to FDA. FDC Act § 736(k), as amended by FDAAA § 103(f).<sup>7</sup>

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<sup>7</sup> FDC Act § 736(d)(1)(A) provides that user fees may be waived or reduced if FDA finds that “such waiver or reduction is necessary to protect the public health.” The Agency has explained that a public health waiver/reduction may be appropriate when: (1) the product protects the public health; and (2) the person requesting the waiver shows that a waiver is necessary to continue an activity that protects the public health. See FDA, Interim Guidance Document for Waivers of and Reductions in User Fees, at 13 (July 16, 1993). In addition to these criteria, FDA also considers other factors in determining whether a public health waiver/reduction should be granted. These factors include the size and annual gross revenues of a business. See id. at 13-14, 16. FDA interprets the financial test to mean a company with \$10 million in foreign and domestic annual gross revenues

Finally, FDAAA creates special rules for Positron Emission Tomography, (“PET”) drugs. PET drugs have an unusual regulatory status among prescription drugs. Pursuant to FDAMA § 121, there is currently a moratorium on FDA’s regulation of PET products as new drugs until FDA establishes procedures by which PET drugs are to be approved under the FDC Act’s new drug approval process and establishes appropriate PET drug current Good Manufacturing Practices. Therefore, FDA approval of an NDA is not yet required in order to market these drugs, but NDAs will be required once the moratorium has ended.

The unique characteristics and properties of PET drugs require that they be manufactured in close proximity to the point of care and result in the necessity for multiple manufacturing establishments for compounding PET drugs. To the extent that PET drug manufacturers submit NDAs and have multiple manufacturing sites, FDA could assess multiple full establishment user fees for each approved PET drug, thereby resulting in a particular applicant paying FDA a disproportionate amount in establishment fees annually.<sup>8</sup> PDUFA IV, however, includes special PET drug establishment user fee provisions. Specifically, the new law exempts from all annual establishment user fees those PET drug applicants who certify to FDA that they are not-for-profit medical centers with only a single PET drug manufacturing establishment, and provided at least 95% percent of the total number of doses of each PET drug produced by that establishment will be used within the medical center itself. FDC Act § 736(a)(2)(C), as amended by FDAAA § 103(a)(3). In addition, “each person who is named as the applicant in an approved human drug application for a [PET] drug shall be subject . . . to one-sixth of an annual establishment fee with respect to each such establishment identified in the application as producing [PET] drugs under the approved application.” *Id.*

## **B. New DTC Advertisement User Fee Program**

FDAAA creates new FDC Act § 736A – “Fees Relating to Advisory Review of Prescription-Drug Television Advertising” – to establish a new voluntary user fee program authorizing FDA to assess and collect fees for the pre-dissemination review of DTC television ads.<sup>9</sup> The new program could be short-lived, however, unless FDA receives \$11,250,000 in advisory review fees by January 25, 2008. *See* FDC Act § 736A(f)(1), as amended by FDAAA § 104. Under this program, FDA will review and

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and no corporate parent or funding source with annual gross revenues of \$100 million or more. *See id.* at 15-17.

<sup>8</sup> These issues were first raised in an August 2005 citizen petition (*available at* <http://www.fda.gov/ohrms/dockets/dockets/05p0358/05p-0358-cp00001-01-vol1.pdf>) submitted by the Council on Radionuclides and Radiopharmaceuticals.

<sup>9</sup> FDA’s Division of Drug Marketing, Advertising, and Communications established a website on which it will post information about DTC user fees. The website is *available at* [http://www.fda.gov/cder/ddmac/user\\_fees/default.htm](http://www.fda.gov/cder/ddmac/user_fees/default.htm).

provide comments regarding its view of a submitted DTC advertisement's compliance with the FDC Act, provided that certain fees are paid and that the advertisement has not yet been disseminated. Applicants need not avail themselves of this new system and can instead continue to submit DTC advertisements to FDA in their normal course of business. Any advertisements for which FDA pre-dissemination review is required will not be subject to the user fees authorized by this section.

FDA is authorized to collect a total fixed fee amount for DTC advertisement review in each of FYs 2008 through 2012, subject to certain workload and inflation adjustments. See id. §§ 736A(b), (c), as amended by FDAAA § 104. An applicant that wishes to participate in the new program must predict its DTC needs up to 15 months in advance and pay upfront at the beginning of each FY (except for FY 2008, which will be handled differently). Not later than June 1st each year, FDA must publish a Federal Register notice requesting notification of the number of DTC advertisements that will be submitted for advisory review in the next FY. See id. § 736A(a)(1)(C), (D)(1), as amended by FDAAA § 104. Applicants must respond within 30 days and are bound to pay user fees for the stated number of advertisements. See id. § 736A(a)(1)(D)(ii), as amended by FDAAA § 104. FDA sets the DTC advisory review user fee for a particular FY based on the total number of DTC ads that companies plan for the upcoming FY. The FY 2008 fee is set at a limit of \$83,000 per submission for advisory review. See id. § 736A(c)(3)(B), as amended by FDAAA § 104.

If an applicant submits fewer ads to FDA than planned, then only a single paid advisory review submission carries over to the next FY. See id. § 736A(a)(1)(F)(i), as amended by FDAAA § 104. There are no refunds or exchanges. If, however, an applicant exceeds the number of planned ads, then “the fee [for additional DTC advertisement reviews] shall be equal to 150 percent of the fee that otherwise would have applied.” See id. § 736A(a)(1)(E)(ii), as amended by FDAAA § 104. Therefore, effective use of the new pre-review advisory system necessitates an applicant's accurate predication of upcoming product approvals and commercial activities – a task rendered more difficult for applicants with few approved products.

### **C. FDA's PDUFA IV Performance Goals**

FDA's PDUFA IV Performance Goals make only minor changes to the Agency's PDUFA III Performance Goals (*available at* <http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html>); however, the Agency makes several commitments to issue long-awaited guidance documents, describes a new proprietary name review process, and establishes goals for the DTC advertisement advisory review user fee program established under FDC Act § 736A.

Under PDUFA IV, FDA will maintain the same review performance goals established under PDUFA III for FY 2007 for NDA/BLA submissions and

resubmissions, original efficacy supplements, resubmitted efficacy supplements, and original manufacturing supplements, along with goals for responding to clinical hold complete responses, special protocol assessment and agreement requests and for responding to certain appeals of Agency. See PDUFA IV Performance Goals at §§ IV, V (Section A).

FDA slightly changed other goals. First, FDA increased from 70% to 90% the Agency's goal of providing an applicant notice of substantive review issues identified during the filing review in a 74-day letter for NDA/BLA applications and efficacy supplements. See id. § X.A.5 (Section A). FDA, however, may be slower to respond to meeting requests under PDUFA IV. Under the new goals, "FDA will provide [notification about scheduling a meeting] within 14 days for 90% of Type A meeting requests and within 21 days for 90% of Type B and Type C meeting requests." Id. § III.A.2 (Section A). Under PDUFA III, FDA provided such notification within 14 days for 90% of all types of meeting requests.

New aspects of FDA's PDUFA IV Performance Goals include the development of a 5-year plan to modernize the Agency's drug safety system and pharmacovigilance process. Under this goal, "FDA will adopt new scientific approaches, improve the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events, and continue to enhance and improve communication and coordination between post-market and pre-market review staff." PDUFA IV Performance Goals at § VIII (Section A). FDA will publish a draft 5-year plan by March 31, 2008, and a final plan by December 31, 2008. See id. § VIII.A.2 (Section A).

FDA will also implement various measures with respect to proprietary name review in an attempt to reduce medication errors. These measures include meeting certain proprietary name review performance goals (beginning in FY 2009) during the Investigational New Drug Application ("IND") and NDA/BLA review phases, publishing guidance and policy procedures on proprietary name review and best practices, developing and implementing a pilot program "to enable pharmaceutical firms participating in the pilot to evaluate proposed proprietary names and submit the data generated from those evaluations to the FDA for review," and "exploring the possibility of 'reserving' proprietary names for companies once the names have been tentatively accepted by the Agency." Id. § IX (Section A).

FDA's proprietary name review performance goals state that the Agency will review proprietary names submitted during the IND phase (as early as end-of-phase 2) as follows:

- Review 50% of proprietary name submissions filed during FY 09 within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.

- Review 70% of proprietary name submissions filed during FY 10 within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.
- Review 90% of proprietary name submissions filed during FYs 11 and 12 within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.

Id. § IX.A.1 (Section A). FDA's performance goals for proprietary names submitted with an NDA/BLA are as follows:

- Review 50% of NDA/BLA proprietary name submissions filed during FY 09 within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.
- Review 70% of NDA/BLA proprietary name submissions filed during FY 10 within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.
- Review 90% of NDA/BLA proprietary name submissions filed during FYs 11 and 12 within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.

Id. § IX.A.2 (Section A).

FDA also establishes performance goals and procedures for the Agency's advisory review of DTC television ads. Different performance goals may apply depending on the number of advertisement submissions FDA plans on receiving in a particular FY after FY 2008. See PDUFA IV Performance Goals at § II (Section B). For FY 2008, FDA plans to "[r]eview and provide advisory comments for 75 original submissions within 45 days" (based on 150 anticipated submissions) and to "[r]eview and provide advisory comments for 37 resubmissions of original submissions within 30 days" (based on 75 anticipated resubmissions). Id. § II.A (Section B).

## **II. MEDICAL DEVICE USER FEE AMENDMENTS OF 2007**

FDAAA Title II reauthorizes medical device user fees established under the Medical Device User Fee and Modernization Act ("MDUFMA"), Pub. L. No. 107-250, 116 Stat. 1588 (2002), through FY 2012. The new law substantially reduces all existing Premarket Approval ("PMA") application and 510(k) fees (both standard and small business fees), but creates new types of medical device user fees. Establishment registration reports are now only required annually for device manufacturers instead of semi-annually. FDAAA also creates a new unique identifier system for devices that Congress directs FDA to elaborate on in regulations to be promulgated by the Agency.

## A. Medical Device User Fees

The following changes have been made to medical device user fees established under FDC Act §§ 737 and 738, as amended by FDAAA.<sup>10</sup>

- The PMA application is \$185,000 for FY 2008 (a 34% reduction compared to FY 2007), and increases to \$256,384 by FY 2012, see FDC Act § 738(b), as amended by FDAAA § 212(b);
- Panel track supplements are now assessed 75% of the PMA fee rather than the same amount, or \$138,750 for FY 2008 (a 51% decrease compared to FY 2007); see id. § 738(a)(2)(A)(iii), as amended by FDAAA § 212(a)(1)(A);
- 180-day supplements are now charged 15% of the PMA fee rather than 21.5%, or \$ 27,750 for FY 2008 (a 54% reduction compared to FY 2007), see id. § 738(a)(2)(A)(iv), as amended by FDAAA § 212(a)(1)(B);
- Real-time supplements will be assessed 7% of the PMA fee instead of 7.2%, or \$12,950 for FY 2008 (a 36% decrease compared to FY 2007), see id. § 738(a)(2)(A)(v), as amended by FDAAA § 212(a)(1)(C);
- Premarket notification submissions (*i.e.*, 510(k)s) will be assessed 1.84% of the PMA fee, instead of 1.42%, or \$3,404 for FY 2008 (an 18% reduction from FY 2007), and are no longer subject to adjustment, see FDC Act § 738(a)(2)(A)(viii), as amended by FDAAA § 212(a)(1)(F);
- A new 30-day notice fee will be established at 1.6% of the PMA fee, or \$2,960 for FY 2008, see id. § 738(a)(2)(A)(vi), as amended by FDAAA § 212(a)(1)(D), (E). A 30-day notice is a notice under FDC Act § 515(d)(6) that is limited to a request to make modifications to manufacturing procedures or methods of manufacture affecting the safety and effectiveness of a device;
- A new request for information regarding classification fee is established at 1.35% of the PMA fee, or \$2,498 for FY 2008, see id. § 738(a)(2)(A)(ix), as amended by FDAAA § 212(a)(1)(G). Requests are made under FDC Act § 513(g) for information concerning the class in which a device has been classified or the requirements applicable to a device; and

<sup>10</sup> FDA recently announced that the FY 2008 medical device user fee rates will be published in the Federal Register on October 12, 2007. A copy of the pre-publication version of the notice is *available at* <http://www.fda.gov/OHRMS/DOCKETS/98fr/OC2007242-n000001.pdf>.

- A new fee for periodic reports on Class III medical devices will be subject to an annual fee equal to 3.5% of the PMA fee, or \$6,475 for FY 2008, see id. § 738(a)(2)(A)(x), as amended by FDAAA § 212(a)(1)(G).

FDAAA creates refund specifications particular to “modular PMAs.” If the PMA is withdrawn before any action has been taken on the first module, but before the second module is submitted, then 75% of the fee will be refunded. See FDC Act § 738(a)(2)(D)(iv), as amended by FDAAA § 212(a)(4)(B). If FDA has not taken action on the first module, but a sponsor has submitted a second module, then the amount of the user fee refund will be up to FDA’s discretion (and will depend on the amount of effort FDA expended in reviewing the PMA). See id. § 738(a)(2)(D)(v), as amended by FDAAA § 212(a)(4)(B).

Establishments subject to a registration fee will face an annual fee increasing from \$1,706 in FY 2008 to \$2,364 in FY 2012. See id. § 738(b), as amended by FDAAA § 212(b). The registration fee does not apply to states and exempt Indian reservations unless they commercially distribute a device. See id. § 738(a)(3)(B), as amended by FDAAA § 212(a)(5). If fewer establishments register than expected in a particular FY, then the registration fee may rise, but not by more than 8.5% a year. See id. § 738(b)(2)(A), as amended by FDAAA § 212(b)(2)(B).

Previously, a U.S. income tax return was required to prove a firm’s eligibility for small business user fee exceptions and reductions. This created a problem for foreign firms that did not file U.S. income tax returns. Under FDAAA, a new provision has been added to allow a non-U.S. device firm that did not previously submit a U.S. income tax return to FDA to qualify as a small business eligible for certain user fee reductions. Such firms will be able to follow certain FDA-specified requirements to have the taxing authority of their home country certify that the firm meets the FDC Act requirements in U.S. dollars to be considered a “small business.” See FDC Act § 738(d)(2)(B)(iii), as amended by FDAAA § 212(d)(2)(B)(v). Small businesses pay 25% of the full PMA fee, premarket report fee, supplement fee, and periodic report fee for Class III devices, and 50% of the full fee for a 30-day notice, a request for classification information, and 510(k) submissions. See id. § 738(d)(2)(C), as amended by FDAAA § 212(d)(3).

The tables below summarize the FY 2008 medical devices user fees under the new law.

**FY 2008 Rates for Existing User Fees (FY 2007 Comparison)**

Application Type	FY 2007 Fees		FY 2008 Fees		Percentage Reduction from FY 2007 to FY 2008	
	Standard Fee	Small Business*	Standard Fee	Small Business	Standard Fee	Small Business
Premarket Application	\$ 281,600	\$ 107,008	\$ 185,000	\$ 46,250	-34%	-57%
Panel-track PMA Supplement	\$ 281,600	\$ 107,008	\$ 138,750	\$ 34,688	-51%	-68%
BLA Efficacy Supplement	\$ 281,600	\$ 107,008	\$ 185,000	\$ 46,250	-34%	-57%
180-day PMA Supplement	\$ 60,544	\$ 23,007	\$ 27,750	\$ 6,938	-54%	-70%
Real-time PMA Supplement	\$ 20,275	\$ 7,705	\$ 12,950	\$ 3,238	-36%	-58%
510(k) Premarket Notification	\$ 4,158	\$ 3,326	\$ 3,404	\$ 1,702	-18%	-49%

\* A “small business” is a device firm with \$100 million or less in gross sales and receipts of all affiliates, partners, and parent firms. Small firms with gross sales of \$30 million or less are eligible to have the fee on their first PMA waived.

**New Fee Types**

Application Type	FY 2008	
	Standard Fee	Small Business
30-day Notice	\$ 2,960	\$ 1,480
513(g) Request	\$ 2,498	\$ 1,249
Periodic Reporting on a Class III Device	\$ 6,475	\$ 1,619
Establishment Registration	\$1,706	

FDA has not yet published new medical device performance goals for FYs 2008 through 2012. FDA will post them on the Agency’s website once they are available.

**B. Medical Device Provision Changes**

FDAAA changes the medical device establishment registration requirements. Although both foreign and domestic drug manufacturers still must register establishments “on or before December 31,” foreign and domestic device manufacturers must now register between October 1st and December 31st each year. FDC Act § 510(i)(1)(B), as amended by FDAAA § 222(b). This change corresponds to the change in the reporting

requirements. Previously, both drug and device manufacturers were required to submit reports semi-annually listing products they had produced or ceased producing. Under the new requirements, while drug manufacturers must still submit this information to FDA semi-annually, device manufacturers must submit it only annually. See id. § 510(j)(2), as amended by FDAAA § 223. In addition, foreign device manufacturers must immediately register upon beginning activity in the U.S., and provide FDA with the name and place of business of the establishment, the name of their U.S. agent, the name of each importer, and the name of each person offering the product for import to the U.S. See id. § 510(i)(1)(A), as amended by FDAAA § 222(b). Once this initial registration is completed, the establishment must continue to submit an annual update. See id. FDC Act § 510(i)(1)(B), as amended by FDAAA § 222(b). In addition, these submissions must now be made electronically unless FDA waives the requirement. See id. § 510(p), as amended by FDAAA § 224.

In what could prove to be one of the most significant of the Government Accountability Office (“GAO”) reports requested in the new law, Congress requests GAO to submit a report on the “appropriate use” of the 510(k) process. See FDAAA § 225(a). Any suggestion in the report that the use of the 510(k) pathway should be restricted could have considerable implications for the device industry.

FDAAA establishes a unique identifier system for all medical devices. Specifically, FDA is directed to promulgate regulations requiring an identifier on the label of each medical device that is specific enough to identify the device through distribution and use. See FDC Act § 519(f), as amended by FDAAA § 226(a)(2). (A similar identifier is required to be developed for prescription drugs. See FDC Act § 505D(b)(2), as amended by FDAAA § 913.)

Importantly, FDAAA now limits the requirement of 5-day and 30-day adverse event reports under the Medical Device Reporting (“MDR”) regulations at 21 C.F.R. Part 803 to Class III devices, Class II devices that are permanently implantable or life sustaining, and other devices after FDA has published a Federal Register notice creating such a requirement. See id. § 519(a)(1)(i), as amended by FDAAA § 227. Summary reports for other devices must be submitted quarterly. See id. § 519(a)(1)(ii), as amended by FDAAA § 227. Under prior law, the quarterly MDR reporting option was only available on a case-by-case basis.

FDAAA makes minor “housekeeping” changes with respect to accredited inspectors for devices marketed both in the U.S. and in a foreign country. Specifically, FDA is allowed to accredit more than 15 inspectors who may handle the requirements for the new quality system standards. See FDC Act § 704(g), as amended by FDAAA § 228. To obtain an inspection by an accredited person, the owner of the establishment must submit a notice with certain information and a certification that at least one of the devices manufactured at the facility is marketed in the U.S. and in a foreign country that accepts

the results of an inspection by the requested inspector. See id. § 704(g)(6)(A)(ii), as amended by FDAAA § 228(4). Provided these requirements are met and the firm does not receive a response from FDA within 30 days of submission, the establishment is considered to have received approval. See FDC Act § 704(g)(6)(B)(i), as amended by FDAAA § 228(4). FDA may deny clearance to participate upon the belief that the information is false or that the establishment is not in compliance with the requirements. See id. § 704(g)(6)(C), as amended by FDAAA § 228(4). If this occurs, then the device establishment can submit a second request. See id. FDC Act §§ 704(g)(6)(C)(iii)(II) and 704(g)(6)(C)(iv), as amended by FDAAA § 228(4).

In order to help develop “risk-based inspectional priorities,” FDA must accept voluntary submissions of audit reports assessing compliance with International Organization for Standardization (“ISO”) quality systems. See FDC Act § 704(g)(6)(F), as amended by FDAAA § 228(5). If a company decides to submit this information, then the company should do so for the prior 2-year period. See id.

FDAAA directs the GAO to submit a report by September 27, 2008 on the cause of nosocomial infections relating to medical devices. See FDAAA § 229(a). FDAAA defines a “nosocomial infection” to mean “an infection that is acquired while an individual is a patient at a hospital and was neither present nor incubating in the patient prior to receiving services in the hospital.” Id. § 229(b). GAO’s report must discuss the number of such infections, as well as the causes, including from reprocessed single-use devices, handling already sterilized devices, in-hospital sterilization of devices, the practices of healthcare practitioners, hospital infection prevention policies, and hospital practices for handling medical waste. See id. § 229(a).

Finally, Title II directs FDA to determine and report (by September 27, 2008) whether the labeling requirements for tanning beds adequately warn against the dangers of permanent skin and eye damage. See id. FDAAA § 230.

### **III. PEDIATRIC MEDICAL DEVICE SAFETY AND IMPROVEMENT ACT OF 2007**

FDAAA Title III amends the FDC Act to provide incentives to medical device manufacturers to create devices for children and to set forth the procedures for the approval and monitoring of those devices. The provision is largely viewed as companion legislation to the pediatric drug-related provisions reauthorized under FDAAA (see Titles IV and V below).

FDAAA § 302 creates new FDC Act § 515A, which requires that an application or protocol submitted for a device, such as a Humanitarian Device Exemption (“HDE”) or

PMA application, include a description of any “pediatric subpopulation”<sup>11</sup> that suffers from the disease or condition that the device is intended to treat and the number of affected “pediatric patients.”<sup>12</sup> New FDC Act § 515A also requires FDA to provide annual reports with sufficient information to track the number and types of devices approved for children, the number of devices approved that are labeled for use in pediatric patients, the number of pediatric devices approved that are exempt from a user fee, and the review time for each. See FDC Act § 515A(a)(3), as amended by FDAAA § 302. Finally, the new law gives FDA the authority to accept unique data to support pediatric device applications. For example, adult data may be used to support an effectiveness determination in pediatric populations, if “the course of the disease or condition and the effects of the device are sufficiently similar in adults and pediatric patients.” Id. § 515A(b)(1) as amended by FDAAA § 302. Data from one pediatric subpopulation may also be extrapolated to another subpopulation. See id. § 515A(b)(2), as amended by FDAAA § 302.

FDAAA § 303 also amends the FDC Act’s HDE provisions to permit manufacturers to make a profit from the sale of Humanitarian Use Devices (“HUDs”). See FDC Act § 520(m)(3), as amended by FDAAA § 303. Specifically, FDAAA § 303 allows a manufacturer to make a profit from devices that: (1) are intended for the treatment of a disease or condition that occurs in pediatric patients or pediatric subpopulations and are labeled for such use; and (2) were not approved prior to September 27, 2007. See id. § 520(m)(6)(A)(i), as amended by FDAAA § 303. The profit, however, is limited to the number of devices estimated to be needed for the approved condition and must not exceed 4,000. See id. § 520(m)(6)(A)(ii), as amended by FDAAA § 303.

In addition, to increase oversight of pediatric HUDs, FDAAA requires that FDA refer all adverse events involving pediatric HUDs to FDA’s Office of Pediatric Therapeutics. See FDC Act § 520(m)(7), as amended by FDAAA § 303. The Pediatric Advisory Committee must conduct an annual review of all pediatric HUDs to ensure continued compliance with HDE requirements. See id. § 520(m)(8), as amended by FDAAA § 303. Furthermore, FDAAA grants FDA’s Pediatric Advisory Committee the authority to monitor pediatric devices and to make recommendations for improving their availability and safety. See 42 U.S.C. § 284m, as amended by FDAAA § 306.

FDAAA requires the GAO to submit a report on the effects of the pediatric HDE profit exemption by January 1, 2012, including whether it has increased the availability

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<sup>11</sup> The term “pediatric subpopulation” is defined as neonates, infants, children, or adolescents. FDC Act § 520(m)(6)(E)(ii), as amended by FDAAA § 303.

<sup>12</sup> The term “pediatric patients” is defined as “patients who are 21 years of age or younger at the time of the diagnosis or treatment.” FDC Act § 520(m)(6)(E)(i), as amended by FDAAA § 303.

of pediatric devices, and any increase or decrease in the costs of pediatric devices and the profits made by pediatric HUD manufacturers. See FDAAA § 303. The new law also directs FDA to issue guidance for institutional review committees on how to evaluate HDE requests. See id.

FDAAA § 304 requires the National Institutes of Health (“NIH”) to designate a “contact point” to help innovators access existing funding for pediatric medical device development. In addition, FDAAA § 305 requires FDA to issue grant requests to nonprofit consortia for demonstration projects that promote pediatric device development and authorizes \$6,000,000 for such grants for FYs 2008 through 2012. See id. § 305.

FDAAA § 307 amends FDC Act § 522 concerning postmarket surveillance. Specifically, the new law adds an additional category of devices — those “expected to have significant use in pediatric populations” — to devices for which FDA may require postmarket surveillance. FDC Act § 522(a), as amended by FDAAA § 307. Pre-existing law allowed FDA to require such studies for Class II and Class III devices “the failure of which would be reasonably likely to have serious adverse health consequences” or that are intended to be “implanted in the human body for more than one year,” or are “a life sustaining or life supporting used outside a device user facility.” FDC Act § 522(a) (2006). The wording of this new pediatric category (*i.e.*, devices “expected to have significant use in pediatric populations”) was intended to ensure that FDA could require postmarket studies for devices 510(k) cleared without a pediatric indication but that are expected to be used in pediatric patients (in addition to those devices cleared specifically for pediatric uses). See H.R. Rep. No. 110-225, at 35 (2007).

FDAAA § 307 also allows FDA to order a pediatric device manufacturer to conduct long-term postmarket surveillance. See FDC Act § 522(b)(2), as amended by FDAAA § 307. Pre-existing law only allowed FDA to require more than 36 months of surveillance if it was mutually agreed on by FDA and the manufacturer. See FDC Act § 522(b) (2006). Now, FDA may by order require more than 36 months of surveillance for a pediatric device if the device is expected to have significant use in pediatric populations and more than 36 months are necessary to further assess safety and efficacy. See FDC Act § 522(b)(2), as amended by FDAAA § 307.

Finally, Title III adds a dispute resolution provision to FDC Act § 522 that allows a manufacturer to request review under FDC Act § 562 (the general FDC Act dispute resolution provision) of any “order or condition” requiring postmarket surveillance. FDC Act § 522(c), as amended by FDAAA § 307.

#### IV. PEDIATRIC RESEARCH EQUITY ACT OF 2007

Title IV reauthorizes and amends the Pediatric Research Equity Act (“PREA”), Pub. L. No. 108-155, 117 Stat. 1936 (2003), through FY 2012. In 2003, PREA amended the FDC Act to require that most applications for drugs and biologics submitted under FDC Act § 505 and PHS Act § 351, respectively, include a pediatric assessment (unless waived or deferred), and that applicants of marketed drugs and biologics<sup>13</sup> conduct such an assessment by a specified date (unless waived) under certain circumstances. See FDC Act § 505B. Such pediatric assessment must contain:

data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate — (i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective.

FDC Act § 505B(a)(2)(A).

FDAAA makes several changes to PREA, which are, for the most part, intended to improve FDA and applicant accountability for the agreed upon pediatric assessments. FDAAA adds the provision that “[a] brief documentation of the scientific data supporting the conclusion [that pediatric effectiveness may (or may not) be extrapolated from adequate and well-controlled studies in adults or extrapolated between pediatric age groups] shall be included in any pertinent reviews for the [NDA or BLA].” Id. at § 505B(a)(2)(B)(iii), as amended by FDAAA § 402.

FDAAA also amends the FDC Act to include several accountability provisions for deferred pediatric assessments. Although the pre-FDAAA version of the law provided that pediatric assessments may be deferred “until a specified date after approval,” FDC Act § 505B(a)(3) (2006), FDAAA requires that pediatric assessments can only be deferred provided there is “a timeline for the completion of such studies.” FDC Act § 505B(a)(3)(A)(ii)(IV), as amended by FDAAA § 402. In addition, the new law requires applicants to annually update FDA on the status of deferred pediatric assessments by providing “[i]nformation detailing the progress made in conducting pediatric studies” and, if no progress has been made, “evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time.” Id. § 505B(a)(3)(B)(i)(I), (II), as amended by FDAAA § 402. Information submitted in such

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<sup>13</sup> That is, those NDA/BLA applicants that submit an application (or supplement to an application) requesting FDA approval “for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.” FDC Act § 505B(a)(1)(A), (B), as amended by FDAAA § 402.

annual reports will be made publicly available on FDA's website. See id. § 505B(a)(3)(B)(ii), as amended by FDAAA § 402.

Consistent with the pre-FDAAA version of PREA, FDA may waive (partially or fully) the PREA pediatric assessment requirement for several reasons, including if “the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.” Id. § 505B(a)(4)(B)(iv). Under the new law, if FDA waives the PREA pediatric assessment on this basis, then the applicant “shall submit to [FDA] documentation detailing why a pediatric formulation cannot be developed and, if the waiver is granted, the applicant's submission shall promptly be made available to the public in an easily accessible manner, including through posting on [FDA's website].” Id. § 505B(a)(4)(C), as amended by FDAAA § 402. The same provision applies to applicants with approved NDAs/BLAs for whom the pediatric assessment is waived. See id. § 505B(b)(2)(C), as amended by FDAAA § 402.

FDAAA removes a provision under prior law that prohibited FDA from requiring a PREA pediatric assessment for an approved application unless: (1) the Agency issued a pediatric written request for a related pediatric study under FDC Act § 505A(c) or PHS Act § 409I; (2) the recipient of the request did not agree to it (or failed to timely respond to the request); and (3) there was a determination that the government could not fund the studies. See FDC Act § 505B(b)(3)(A) (2006). Given the absence of this provision in FDAAA, FDA appears to have broader authority to request a pediatric assessment for an approved product.

FDAAA creates new FDC Act § 505C, which requires FDA to establish an internal committee with pediatric expertise to carry out certain activities under PREA (FDC Act § 505B) and the Best Pharmaceuticals for Children Act (“BPCA”) (FDC Act § 505A, which is discussed below in Section V). See FDC Act § 505C, as amended by FDAAA § 403. Under PREA, the committee is required to provide consultation to FDA review divisions on all pediatric plans and assessments and on all deferral and waiver requests. See FDC Act § 505B(f)(1), as amended by FDAAA § 402. By September 27, 2008 the committee is required to:

conduct a retrospective review and analysis of a representative sample of assessments submitted and deferrals and waivers approved under [FDC Act § 505B] since the enactment of [PREA in] 2003. Such review shall include an analysis of the quality and consistency of pediatric information in pediatric assessments and the appropriateness of waivers and deferrals granted.

FDC Act § 505B(f)(5), as amended by FDAAA § 402. Based on the committee's review and analysis, “[FDA] shall issue recommendations to the review divisions for improvements and initiate guidance to industry related to the scope of pediatric studies

required under this section.” Id. In addition, the committee must track and publish information on the number of pediatric assessments issued, the number of waivers and deferrals, and information on the drugs and labeling changes made under PREA. Id. § 505B(f)(6), as amended by FDAAA § 402. Presumably this information will be posted on FDA’s pediatric website at <http://www.fda.gov/cder/pediatric/>.

FDAAA also clarifies the types of labeling changes that should be made pursuant to an applicant’s pediatric assessment. Specifically, if FDA:

makes a determination that a pediatric assessment conducted under [FDC Act § 505B] does or does not demonstrate that the drug that is the subject of such assessment is safe and effective in pediatric populations or subpopulations, including whether such assessment results are inconclusive, [FDA] shall order the label of such product to include information about the results of the assessment and a statement of [FDA’s] determination.

FDC Act § 505B(g)(2), as amended by FDAAA § 402. As under the BPCA, if an applicant does not make required labeling changes, then FDA can deem the product misbranded. See id. § 505B(g)(1)(D), as amended by FDAAA § 402.

The new law also creates special adverse event reporting requirements for products whose labeling has changed as the result of a pediatric assessment. Specifically, during the 1-year period after such a labeling change is made, all adverse event reports for the drug are to be referred to FDA’s Office of Pediatric Therapeutics. See FDC Act § 505B(i)(1), as amended by FDAAA § 402. The Office of Pediatric Therapeutics must request the Pediatric Advisory Committee to review any adverse events reports and obtain the committee’s recommendation as to whether any action should be taken to respond to them. See id. FDA may continue this process in subsequent years. See id. § 505B(i)(2), as amended by FDAAA § 402.

Finally, FDAAA requires the publication of reports assessing PREA and the BPCA. New FDC Act § 505B(l) requires FDA to contract with the Institute of Medicine (“IOM”) to conduct a study that reviews and assesses the effects of PREA, as well as its precursor regulation.<sup>14</sup> See FDC Act § 505B(l), as amended by FDAAA § 402. The report must be provided to Congress not later than September 27, 2010. See id. In addition, FDA, in consultation with the GAO, must submit a report to Congress (not later

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<sup>14</sup> In PREA, Congress codified many of the elements of a 1998 FDA final rule. See Final Rule, Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (Dec. 2, 1998) (the “Pediatric Rule”). The Pediatric Rule was suspended on October 17, 2002 by a court order finding that FDA lacked the authority to promulgate the rule. See Association of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D.D.C. 2002).

than January 1, 2011) that addresses the effectiveness of PREA and the BPCA “in ensuring that medicines used by children are tested and properly labeled,” and that recommends modifications to these laws. FDAAA § 404.

## V. BEST PHARMACEUTICALS FOR CHILDREN ACT OF 2007

Title V reauthorizes and amends the Best Pharmaceuticals for Children Act (“BPCA”), Pub. L. No. 107-109, 115 Stat. 1408 (2002), through FY 2012. The precursor law to BPCA, FDAMA § 111, amended the FDC Act to add § 505A, which provides an additional 6 months of patent protection (*i.e.*, Orange Book-listed patents) and non-patent market exclusivity (*i.e.*, 3-year and 5-year Hatch-Waxman exclusivity, and 7-year orphan drug exclusivity) to NDA applicants that conduct acceptable pediatric studies of new and currently-marketed drug products for which pediatric information would be beneficial that have been identified by FDA in a Pediatric Written Request (“PWR”). FDAAA makes several changes to the BPCA, some of which, like the changes made to PREA, are intended to improve FDA and applicant accountability for the agreed-upon pediatric studies. FDAAA broadens the definition of “pediatric studies” to include preclinical studies, and narrows the timeframe for sponsors to qualify for pediatric exclusivity.

FDAAA amends the definition of “pediatric studies” in FDC Act § 505A(a), the effect of which is to permit FDA to request preclinical studies in addition to one or more clinical investigations in a PWR. Specifically, amended FDC Act § 505A(a) now defines the term “pediatric studies” to mean “at least one clinical investigation (that, at [FDA’s] discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of [FDA], may include preclinical studies.” FDC Act § 505A(a), as amended by FDAAA § 502(a) (emphasis added). This change allows FDA to request animal data in addition to clinical and pharmacokinetic data – an authority which the Agency claimed to already have under the pre-FDAAA FDC Act.

Amended FDC Act § 505A also narrows the timeframe for NDA sponsors to qualify for pediatric exclusivity. Under the new law, FDA “shall not extend the period referred to in [either § 505A(b)(1)(A) or (1)(B), or § 505A(c)(1)(A) or (1)(B), concerning patent protection and non-patent market exclusivity] if the determination made under [§ 505A(d)(3) by FDA concerning whether the terms of the PWR have been met] is made later than 9 months prior to the expiration of such period.” FDC Act § 505A(b)(2), 505A(c)(2), as amended by FDAAA § 502(a). This provision effectively replaces former § 505A(e), which permitted FDA to delay the acceptance or approval of a 505(b)(2) application or an Abbreviated NDA (“ANDA”) by up to 90 days if an NDA sponsor submitted study results in response to a PWR immediately prior to the expiration of any applicable period of patent or non-patent market exclusivity. Former § 505A(e) allowed sponsors to obtain a period of *de facto* pediatric exclusivity while FDA reviewed study

results even if the Agency ultimately determined that the studies did not meet the terms of the PWR.

FDAAA also makes several amendments to the BPCA concerning the conduct of pediatric studies, and codifies current FDA policies. For example, FDAAA requires that an applicant respond to a PWR indicating whether or not it will comply with the PWR, provides FDA with 180 days (as opposed to 60 days in the old law) to determine whether a sponsor's submitted studies meet the terms of the PWR, and codifies FDA's policy that a single PWR "may relate to more than one use of a drug." FDC Act § 505A(d)(1)(B)(i), (d)(3), as amended by FDAAA § 502(a). The new law also requires applicants that do not agree to a PWR because it is not possible to develop an appropriate pediatric formulation to provide FDA with the reasons for such a determination. See id. § 505A(d)(2)(A)(ii), as amended by FDAAA § 502(a). An applicant that agrees to a PWR must provide FDA with information on all postmarket adverse event reports at the same time as the submission of the sponsor's pediatric study reports. See id. § 505A(d)(2)(B), as amended by FDAAA § 502(a). In addition, FDAAA amends FDC Act § 505A to give FDA the authority to issue a PWR that "may include both approved and unapproved uses." See id. FDC Act § 505A(d)(1)(B)(ii), (d)(3), as amended by FDAAA § 502(a). Previously, FDA would "not combine requests for studies on unapproved and approved indications in one [PWR]." FDA, Guidance for Industry, Qualifying for Pediatric Exclusivity Under FDC Act § 505A, at 7 (Sept. 1999).

Once FDA determines that the terms of a PWR have been met and grants pediatric exclusivity, FDAAA requires the Agency to publish the previously required Federal Register notice 30 days after such determination and include a copy of the PWR. See FDC Act § 505A(e)(1), as amended by FDAAA § 502(a). In addition, FDAAA requires FDA to make a public disclosure with respect to any pediatric formulation developed, studied, and found to be safe and effective but that is not marketed within 1 year after FDA's publication of the Federal Register notice described in FDC Act § 505A(e)(1). See id. § 505A(e)(2), as amended by FDAAA § 502(a).

The pediatric committee established under FDC Act § 505C is required by FDAAA § 403 to review all PWRs prior to issuance, and "may review studies conducted pursuant to [BPCA] to make a recommendation to [FDA] whether to accept or reject such reports." FDC Act § 505A(f), as amended by FDAAA § 502(a). In addition, the committee is required to track and report on, among other things, the number of pediatric studies conducted under FDC Act § 505A. See id. § 505A(f)(6), as amended by FDAAA § 502(a).

PWRs issued after FDAAA's enactment will include a new requirement. Specifically, sponsors whose pediatric studies result in labeling changes will be required to distribute information to physicians and healthcare providers about pediatric labeling changes. See FDC Act § 505A(k)(2), as amended by FDAAA § 502(a). Finally,

FDAAA requires FDA to enter into a contract with IOM to “conduct a study and report to Congress regarding the [PWRs] made and the studies conducted pursuant to [FDC Act § 505A].” FDC Act § 505A(p), as amended by FDAAA § 502(a).

## VI. REAGAN-UDALL FOUNDATION

FDAAA Title VI amends the FDC Act to establish a non-profit corporation whose purpose is to advance FDA’s Critical Path Initiative<sup>15</sup> to “modernize medical, veterinary, food, food ingredient, and cosmetic product development, accelerate innovation, and enhance product safety.” FDC Act § 770(a)-(b), as amended by FDAAA § 601. This corporation, known as the Reagan-Udall Foundation for FDA (the “Foundation”) allows FDA to collaborate with other researchers to foster newer methods of testing that are needed to assess newer technologies. See H.R. Rep. No. 110-225, at 12 (2007).

FDAAA § 601 sets forth the duties of the Foundation, which primarily include identifying unmet needs in the sciences of developing, manufacturing, and evaluating the safety and effectiveness of diagnostics, devices, biologics, and drugs. Other duties include establishing goals and priorities to meet such unmet needs; assessing Federal intramural and extramural research and development programs, and facilitating interagency coordination of such programs; awarding grants to advance the goals and priorities identified; recruiting meeting participants and sponsor meetings to further such goals and priorities; releasing, publishing, licensing, and distributing material, reagents, and techniques to meet such goals and priorities; ensuring the necessary actions are taken to patent and license inventions developed by the Foundation; providing objective clinical and scientific information to FDA and other Federal agencies; and conducting annual assessments of the unmet needs identified. See FDC Act § 770(c)(1)-(8), as amended by FDAAA § 601.

The Foundation’s Board of Directors will initially include four ex-officio members — the FDA Commissioner, and the Directors of the National Institutes of Health, Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Policy — who appoint the remaining 14 members from industry, academia, patient/consumer groups and health care providers. See FDC Act § 770(d)(1)(A), (B), as amended by FDAAA § 601. All appointed members of the Board shall be voting members. Id.<sup>16</sup> The

<sup>15</sup> The Critical Path Initiative is FDA’s effort to modernize the scientific process through which a potential drug, biologic, or medical device is transformed from discovery into a medical product. Additional information on FDA’s Critical Path Initiative is *available at* <http://www.fda.gov/oc/initiatives/criticalpath/>.

<sup>16</sup> On October 3, 2007, FDA issued a Federal Register notice seeking nominations for the Foundation. See Nominations for Membership on the Board of Directors of the Reagan-Udall Foundation From Consumer Advocacy Groups, Professional Scientific and Medical Societies, and Industry Trade Organizations, 72 Fed. Reg. 56,362 (Oct. 3, 2007).

Board of Directors is tasked with establishing bylaws and policies and for providing the Foundation's overall direction. See id. § 770(d)(2)(A)-(D), as amended by FDAAA § 601.

FDAAA requires that any recipient of a Foundation grant, contract, fellowship, memorandum of understanding, or cooperative agreement submit an annual report to the Foundation that describes their activities. See id. § 770(l)(1), as amended by FDAAA § 601. Beginning in FY 2009, the Foundation must provide FDA and Congress an annual report describing the Foundation's activities, financial accounting of its funds, and recommendations for incorporating results of the Foundation's activities into FDA's "regulatory and product review activities." Id. § 770(l)(2), as amended by FDAAA § 601.

FDAAA requires FDA to transfer between \$500,000 and \$1,250,000 in funding to the Foundation annually, and sets forth FDA's activities in conjunction with the Foundation. See FDC Act § 770(n), as amended by FDAAA § 601. FDAAA also adds FDC Act § 910, which establishes the Office of the Chief Scientist within the Office of the FDA Commissioner. See id. § 910(a), as amended by FDAAA § 602. The Office of Chief Scientist is required to, among other things, oversee and coordinate intramural research programs and develop and advocate for a budget to support intramural research. See id. § 910(b), as amended by FDAAA § 602.

Finally, FDAAA adds FDC Act § 566, which establishes certain partnerships between FDA and eligible non-profit and higher education institutions to advance FDA's Critical Path Initiative. These partnerships are to be carried out by "developing innovative, collaborative projects in research, education, and outreach for the purpose of fostering medical product innovation, enabling the acceleration of medical product development, manufacturing, and translational therapeutics, and enhancing medical product safety." FDC Act § 566(a), as amended by FDAAA § 603.

## **VII. ADVISORY COMMITTEE CONFLICTS OF INTEREST**

FDAAA Title VII creates FDC Act § 712, which continues the requirement that all individuals under consideration for appointment to serve on an FDA advisory committee disclose to the Agency all financial interests that would be affected by the committee's actions. Earlier this year, FDA issued a guidance document that discusses the procedures for determining conflicts of interest and advisory committee member eligibility. See FDA, Draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees, (Mar. 2007) *available at* <http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0101-gdl0001.pdf>.

FDAAA § 701 requires FDA to, among other things, develop and implement strategies to recruit potential advisory committee members, particularly for those advisory committees “with the greatest number of vacancies.” FDC Act § 712(b)(1)(A), as amended by FDAAA § 701. FDA may grant a conflict waiver if it is necessary to afford the panel essential expertise. See id. § 712(c)(2)(B), as amended by FDAAA § 701. The waiver may allow the advisory committee member to participate as either a non-voting member or a voting member with respect to a particular matter. See id. § 712(c)(2)(B)(i)-(ii), as amended by FDAAA § 701. FDA’s ability to grant waivers is not limitless, however. FDA is required to determine how many advisory committee members needed waivers for financial conflicts of interest in FY 2007, and must reduce the number of waivers by 5% in each of FYs 2008 through 2012 for a total 25% reduction in the aggregate number of waivers issued over the next 5 years. See id. § 712(c)(2)(C), as amended by FDAAA § 701.

Disclosure of the waiver must be made no later than 15 days prior to a scheduled advisory committee meeting. See FDC Act § 712(c)(3), as amended by FDAAA § 701. The disclosure must be posted on FDA’s website and must specify the type, nature, and magnitude of the financial interest to which the waiver applies. See id. § 712(c)(3)(A), as amended by FDAAA § 701. In addition, FDA must disclose the reasons for granting the waiver. See id. § 712(c)(3)(A)(ii), as amended by FDAAA § 701. Disclosure of the waiver must be included in the public record and transcript of each advisory committee meeting. See id. § 712(d), as amended by FDAAA § 701.

FDAAA requires FDA to submit an annual report to Congress describing the number of vacancies on each advisory committee, the number of nominees received for each committee, and the number of nominees willing to serve. See FDC Act § 712(e), as amended by FDAAA § 701. The annual report must also include, among other things, the aggregate number of disclosures required for each meeting, the percentage of individuals for which a disclosure was not required, and strategies on how to reduce the number of advisory committee vacancies. See id. § 712(e), as amended by FDAAA § 701. Finally, FDA must review and update Agency guidance documents on conflict of interest waiver determinations at least once every 5 years. See id. § 712(f), as amended by FDAAA § 701.

## **VIII. CLINICAL TRIAL DATABASES**

One of the more significant changes FDAAA makes is a dramatic expansion of the current clinical trial registry database, and the creation of a new clinical trial results database. Previously, statutory requirements for listing information in the clinical trials database (*i.e.*, ClinicalTrials.gov) only included information on clinical trials of drugs and biologics conducted under FDA’s IND regulations that were intended to treat serious or life-threatening diseases or conditions. The new clinical trials database includes trials for

all diseases and conditions, expands the information available on the trial, and adds clinical trials of medical devices. The second database — the results database — will include results (including adverse events) on all trials that form the primary basis of an efficacy claim or that are conducted after a drug or a device is approved.<sup>17</sup>

### A. Clinical Trial Registry Database

FDAAA requires the “responsible party” for each applicable clinical drug or device trial to submit information on the trial to NIH for inclusion in an expanded database. See PHS Act § 402(j)(2)(A)(ii), as amended by FDAAA § 801(a)(2). The term “responsible party” is defined as: (1) “the sponsor of the clinical trial,” as defined in 21 C.F.R. § 50.3; or (2) “the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under this subsection for the submission of clinical trial information.” See id. PHS Act § 402(j)(1)(A)(ix), as amended by FDAAA § 801(a)(2). The term “applicable device clinical trial” is defined as: (1) “a prospective clinical study of health outcomes comparing an intervention with a device subject to [FDC Act §§ 510(k), 515, or 520(m)] against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes);” and (2) “a pediatric postmarket surveillance as required under [FDC Act § 522].” PHS Act § 402(j)(1)(A)(ii), as amended by FDAAA § 801(a)(2). The term “applicable drug clinical trial” is defined as “a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to [FDC Act § 505] or to [PHS Act § 351].” Id. § 402(j)(1)(A)(iii), as amended by FDAAA § 801(a)(2).

The information that must be submitted to NIH includes information describing the study, recruitment requirements, location and contacts, and administrative data. See PHS Act § 402(j)(2)(A)(ii), as amended by FDAAA § 801(a)(2). In addition to stating clinical study inclusion requirements, the submission must indicate whether expanded access to the drug is available under FDC Act § 561 and explain how to obtain information about such access. See id. § 402(j)(2)(A)(ii)(II)(gg), as amended by FDAAA § 801(a)(2).

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<sup>17</sup> While FDAAA only requires adverse event results for drugs, a technical correction to FDAAA, introduced as a concurrent resolution in Congress, would add device adverse events as well. See H. Con. Res. 217, *available at* [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110\\_cong\\_bills&docid=f:hc217rfs.txt.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:hc217rfs.txt.pdf). The U.S. House of Representatives passed the resolution in late September 2007, but it is pending in the U.S. Senate.

NIH must ensure that the clinical trial database is searchable by keywords and at least one of the following parameters: the disease or condition, name of the drug or device, location, age group, study phase, sponsor, recruitment status, or identification number. See id. § 402(j)(2)(B), as amended by FDAAA § 801(a)(2). In addition, the database must be searchable by the safety issue, if any, being studied in the clinical trial by March 27, 2009. See id. § 402(j)(2)(B)(ii), as amended by FDAAA § 801(a)(2). The responsible party of a clinical trial that is initiated after September 27, 2007, or that is ongoing on December 25, 2007, must submit the required information by December 25, 2007 or 21 days after the first patient is enrolled in the clinical trial, whichever is later, unless the clinical trial is ongoing on September 27, 2007 and is not for a serious or life-threatening disease or condition, in which case the information must be submitted by September 27, 2008. See id. § 402(j)(2)(C), as amended by FDAAA § 801(a)(2). The information on most drug and device clinical trials will be posted to the database within 30 days of submission, except that for devices not previously cleared or approved, no information will be posted until clearance or approval is obtained. See id. § 402(j)(2)(D), as amended by FDAAA § 801(a)(2).

## **B. Clinical Trial Results Database**

One major change to the clinical trial database is that not later than December 25, 2007, the database must include links to information on clinical trial results. The term “results” is used fairly broadly in FDAAA to include summary information FDA has posted from an advisory committee meeting that considered a particular study, FDA public health advisories, FDA’s application review documents, Medline citations to any publications focused on the results of the trial, and the drug entry in the National Library of Medicine database of structured product labels (if available). See PHS Act § 402(j)(3)(A)(ii), as amended by FDAAA § 801(a)(2). By September 27, 2008, the results database must include the demographic and baseline characteristics of the subjects who participated in the study, primary and secondary outcomes (including statistical results), a point of contact for scientific information about the study, and whether there exists an agreement restricting the ability of the principal investigator to discuss or publish the results of the study. See id. § 402(j)(3)(C), as amended by FDAAA § 801(a)(2). The database may also include information on studies completed prior to September 27, 2007. See id. § 402(j)(3)(A)(iii), as amended by FDAAA § 801(a)(2). Study results that provide the basis for approval or studies that are conducted after a drug or device is approved must be posted to the database not earlier than 30 days after approval and not later than 30 days after the information becomes public. See id. § 402(j)(3)(A)(i), as amended by FDAAA § 801(a)(2).

By September 27, 2010, regulations must be promulgated that expand the results database to include drugs approved under FDC Act § 505 or licensed under PHS Act § 351, and devices cleared under FDC Act § 510(k) or approved under FDC Act §§ 515 or 520(m). See PHS Act § 402(j)(3)(D), as amended by FDAAA § 801(a)(2). The

regulations must also determine whether unapproved drugs or devices should be included in the database. See id. § 402(j)(3)(D)(ii)(II), as amended by FDAAA § 801(a)(2). The regulations may, among other things, clarify administrative requirements and expand the basic results to include a plain language summary of the trial and results and a technical summary, the full protocol, and other categories of information deemed appropriate. See id. § 402(j)(3)(D)(iii), as amended by FDAAA § 801(a)(2).

Under the new law, the party responsible for the study has one year to submit information from the earlier of either the estimated completion date of the trial, or the date the trial is completed. See PHS Act § 402(j)(3)(E), as amended by FDAAA § 801(a)(2). This information must be submitted within 30 days of approval for drugs or devices that were not yet approved when the trial was conducted. See id. § 402(j)(3)(E)(iv), as amended by FDAAA § 801(a)(2). If the trial was for a new use of an approved drug or device, then the information is due 30 days after the drug or device is approved, after FDA issues an action letter not approving or clearing the submission, or if the marketing application or notification was withdrawn and has not been resubmitted within the last 210 days. See id. § 402(j)(3)(E)(v), as amended by FDAAA § 801(a)(2). This means that results of most clinical trials conducted after a drug or device has been approved will be made publicly available, regardless of whether the trials result in FDA approval of new uses of the drug or device.

### **C. Other Database Information, Procedures, and Penalties**

By March 27, 2009, regulations must be promulgated to include serious adverse event and frequent adverse event information in the two clinical trial databases. See PHS Act § 402(j)(3)(I)(i), as amended by FDAAA § 801(a)(2). If such regulations are not issued by September 27, 2009, then tables showing serious adverse events and tables showing adverse events occurring in more than 5% of any arm in the trial must be included in the two databases. Both sets of tables must show both anticipated and unanticipated adverse events, grouped by organ system, showing number and frequency of the events. See id. § 402(j)(3)(I)(iii)(I), as amended by FDAAA § 801(a)(2).

The party responsible for the clinical trial is obligated to update any information contained in the database, which must occur at least once every 12 months, unless the information did not change. See PHS Act § 402(j)(4)(C), as amended by FDAAA § 801(a)(2). If the recruitment status changes, or if the study is completed, then this information must be submitted within 30 days of the event. Most updates will be added to the database and will not replace prior database information. See id. § 402(j)(4)(C)(ii), as amended by FDAAA § 801(a)(2).

For studies funded in part by any agency within the Department of Health and Human Services (“DHHS”), all grant and progress report forms must include a certification that the responsible party has made all required clinical trial database

submissions. See PHS Act § 402(j)(5)(A)(i), as amended by FDAAA § 801(a)(2). Before releasing funds, the head of the agency must verify that the clinical information has been submitted. See id. § 402(j)(5)(A)(ii), as amended by FDAAA § 801(a)(2). If not, then the responsible party will be provided 30 days to submit the required information. See id. § 402(j)(5)(A)(iii), as amended by FDAAA § 801(a)(2). The DHHS Secretary will also consult with other agencies not falling under DHHS that conduct research involving humans to determine whether those studies should also qualify as reportable clinical trials. See id. § 402(j)(5)(A)(iv)(I), as amended by FDAAA § 801(a)(2).

Drug, biological, and device applications or notifications for marketing must include a certification that the clinical trial registry and results provisions have been satisfied. A responsible party that fails to submit the required certification or clinical trial information, or that submits false or misleading clinical trial information, is subject to a civil fine of not more than \$10,000 for all violations adjudged in a single proceeding. See FDC Act § 303(f)(3)(A), as amended by FDAAA § 801(b)(2). If the violation is not corrected within 30 days, an additional \$10,000 will be assessed per day until the violation is corrected. See id. § 303(3)(B), as amended by FDAAA § 801(b)(2).

#### **D. Preemption and Prohibition Against Using Clinical Trial Information to Establish Intended Use**

FDAAA § 801(d) includes a preemption rule applicable to the registry and results databases, which provides that “no State or political subdivision of a State 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.” FDAAA § 801(d)(1).

In a rule of construction, FDAAA explains that if information is submitted in compliance with the new law:

[t]he fact of submission of clinical trial information . . . that relates to a use of a drug or device not included in the official labeling of the approved drug or device shall not be construed by [DHHS] or in any administrative or judicial proceeding, as evidence of a new intended use of the drug or device that is different from the intended use of the drug or device set forth in the official labeling of the drug or device. The availability of clinical trial information through the registry and results data bank . . . shall not be considered as labeling, adulteration, or misbranding of the drug or device under the [FDC Act].

Id. § 801(d)(2).

FDA's "intended use" regulations at 21 C.F.R. § 201.128 (drugs) and § 801.4 (devices) define to term broadly to mean, in relevant part, the "objective intent of the persons legally responsible for the labeling of [drugs/devices]." *Id.* Such intent may be shown "if a manufacturer knows, or has knowledge of facts that would give him notice, that a [drug/device] introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it." *Id.* This provision thus serves to shield drug and device firms from liability for information submitted to the databases that might otherwise be used by FDA as evidence of "intended use" in an administrative or judicial proceeding.

## **IX. EXPANDED FDA AUTHORITY FOR POSTMARKET SAFETY OF DRUGS**

FDAAA Title IX is the longest reaching provision of the new law and the reason it has been referred to as the "drug safety law." Subtitle A amends the FDC Act to give FDA the authority to require postapproval studies or clinical trials, to request that safety information be provided in labeling, or to require an applicant to submit and execute a Risk Evaluation and Mitigation Strategy, or REMS. Subtitle B is a potpourri of provisions amending the FDC Act to address various issues ranging from the dissemination of postmarket drug safety information, to citizen petition modification, to foods added to drugs or biologics, and authorized generics.

The primary catalyst for Title IX occurred on September 30, 2004 when Merck withdrew the non-steroidal anti-inflammatory drug VIOXX (rofecoxib) from the market after a long-term postmarket study of the drug product was halted because of an increased risk of serious cardiovascular events (including heart attack and stroke) among study subjects taking the drug product compared to subjects administered a placebo. Following that action, allegations surfaced about FDA's handling of certain postmarket data. In the ensuing years, postmarket safety issues on other products surfaced, Congress held hearings to investigate these issues (which included testimony from dissatisfied staff members within FDA's Office of Drug Safety), and in September 2006, the IOM issued a report, titled The Future of Drug Safety: Promoting and Protecting the Health of the Public, which included various recommendations on how FDA could improve its drug safety efforts. Although FDA immediately began making some internal changes, Congress viewed the IOM report as an opportunity to implement broader drug safety reform and various members began drafting what was eventually enacted as part of FDAAA.

## A. Subtitle A – Postmarket Studies and Surveillance

### 1. Postmarket Studies and Clinical Trials

FDAAA creates new FDC Act § 505(o), which gives FDA the authority to require postapproval studies and clinical trials from a “responsible person” for a “covered application.” FDC Act §§ 505(o)(1), (2), as amended by FDAAA § 901(a). A “responsible person” means a person who “(i) has submitted to [FDA] a covered application that is pending; or (ii) is the holder of an approved covered application.” Id. at § 505(o)(2)(A), as amended by FDAAA § 901(a). A “covered application” is an NDA for a prescription drug or a BLA. See id. § 505(o)(2)(B), as amended by FDAAA § 901(a).

FDA can require postmarket studies or clinical trials “on the basis of scientific data deemed appropriate by [the Agency], including information regarding chemically-related or pharmacologically-related drugs” to assess a known serious risk or signals of a serious risk related to the drug, or to “identify an unexpected serious risk when available data indicates the potential for a serious risk.” FDC Act § 505(o)(3), as amended by FDAAA § 901(a). FDA can apply FDC Act § 505(o) to previously approved “covered applications” if such a determination is based on postapproval safety information. See FDC Act § 505(o)(3)(C), as amended by FDAAA § 901(a). In order for FDA to require a “responsible person” to conduct a postmarket study, however, the Agency must first determine that currently required postmarket reports will be insufficient to assess or identify the risk. See id. § 505(o)(3)(D)(i), as amended by FDAAA § 901(a). FDA must notify the “responsible person” of the need for a postapproval study or clinical trial by the deadlines established in the Agency’s PDUFA IV Performance Goals, and the “responsible person” must submit a timetable for its completion and periodic status reports. See id. § 505(o)(3)(E), as amended by FDAAA § 901(a). A “responsible person” may appeal an FDA determination for a postmarket study or clinical trial by following the Agency’s dispute resolution procedures. See id. § 505(o)(3)(F), as amended by FDAAA § 901(a).

If FDA becomes aware of new safety information that should be included in product labeling, then the Agency must “promptly notify the responsible person or, if the same drug approved under section 505(b) is not currently marketed, the holder of an [ANDA].” FDC Act § 505(o)(4)(A), as amended by FDAAA § 901(a). Following receipt of such notification, the “responsible person” or ANDA holder has 30 days to respond by either submitting a labeling supplement, or by submitting a statement explaining why such a labeling change is not needed. See id. § 505(o)(4)(B), as amended by FDAAA § 901(a). FDA must promptly approve any labeling supplement, or, if the Agency does not agree with either the proposed labeling changes or the reasons provided for not making labeling changes, then FDA will discuss the issue with the “responsible person” or ANDA holder and attempt to reach an agreement within the next 30 days. See

id. §§ 505(o)(4)(C), (D), as amended by FDAAA § 901(a). Within 15 days of the end of this discussion period FDA can order compliance with the Agency’s demands, at which point the “responsible person” or ANDA holder has 15 days to comply or 5 days to appeal using the Agency’s dispute resolution procedures. See id. § 505(o)(4)(E), (F), as amended by FDAAA § 901(a). After the 15 days (if there is no appeal), or 15 days from the conclusion of a dispute resolution proceeding, if FDA’s request has not been met, then the “responsible person” or ANDA holder is considered to be in violation of the FDC Act. See FDC Act § 505(o)(4)(G), as amended by FDAAA § 901(a). The timelines discussed above may be shortened if FDA determines there is a public health threat. See FDC Act § 505(o)(4)(H), as amended by FDAAA § 901(a).

## 2. REMS

FDAAA provides a new statutory framework for integrating REMS into drug and biologic reviews and postmarket activities. The REMS provisions are an outgrowth of actions FDA took pursuant to PDUFA III, under which FDA issued several risk management guidance documents, including the Agency’s “Development and Use of Risk Minimization Action Plans” (“RiskMAP Guidance”). A REMS incorporates many of the existing risk minimization tools in the RiskMAP Guidance, as well as those in FDA’s accelerated approval regulations at 21 C.F.R. §§ 314.500-314.560 and 601.40-601.46.

The initial REMS provision provides that “[a] person may not introduce or deliver for introduction into interstate commerce a new drug if:” (1) the product is covered under an approved NDA, ANDA, or BLA; and (2) “a [REMS] is required under [FDC Act § 505-1] with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under [FDC Act § 505-1], including requirements regarding assessments of approved strategies.” FDC Act § 505(p)(1), as amended by FDAAA § 901(a). In addition, an applicant’s failure to conduct a required postmarket study under FDC Act § 506 (Fast Track) or FDA’s accelerated approval regulations is deemed to be a violation of new FDC Act § 505(p)(1). See id. § 505(p)(2), as amended by FDAAA § 901(a).

New FDC Act § 505-1 provides FDA with the authority to require the person submitting a marketing application to also submit a proposed REMS if the Agency determines that such a strategy “is necessary to ensure that the benefits of the drug outweigh the risks of the drug.” FDC Act § 505-1(a)(1), as amended by FDAAA § 901(b). FDA may also require a REMS for a previously approved covered application if the Agency “becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug.” Id. § 505-1(a)(2), as amended by FDAAA § 901(b). In determining whether or not to impose a REMS, FDA must consider several factors, including: (1) “[t]he estimated size of the population likely to use the drug involved;” (2) “[t]he seriousness of

the disease or condition that is to be treated with the drug;” (3) “[t]he expected benefit of the drug with respect to such disease or condition;” (4) “[t]he expected or actual duration of treatment with the drug;” (5) “[t]he seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;” and (6) “[w]hether the drug is a new molecular entity.” Id. § 505-1(a)(1), as amended by FDAAA § 901(b). For approved drugs, applicants have 120 days after FDA notification to submit a proposed REMS. See id. § 505-1(a)(2)(B), as amended by FDAAA § 901(b).

At a minimum, a REMS must include assessments 18 months, 3 years, and 7 years after strategy approval. See id. FDC Act § 505-1(d), as amended by FDAAA § 901(b). FDA may also require a MedGuide or patient package insert for distribution with the drug, communication with healthcare providers about risks of the drug, and procedures to assure safe use or components of the safety protocol that the provider should implement (such as periodic monitoring or tests). See id. § 505-1(e), as amended by FDAAA § 901(b).<sup>18</sup>

For drugs that are effective but also have serious risks, FDA can establish a REMS to mitigate those risks. See FDC Act § 505-1(f)(1), as amended by FDAAA § 901(b). FDA must post a statement on the Agency’s website within 30 days of imposing a REMS explaining how the strategy will mitigate the risk. See id. § 505-1(f)(2)(B), as amended by FDAAA § 901(b). When imposing a REMS under this provision, FDA must ensure that the strategy is commensurate with the risks involved. See id. § 505-1(f)(2)(A), as amended by FDAAA § 901(b). This includes considering whether the strategy will be unduly burdensome on patient access to the drug, particularly for patients with life-threatening diseases or patients with reduced access to healthcare. See id. § 505-1(f)(2)(C), as amended by FDAAA § 901(b). FDA must also issue regulations explaining how a physician may provide a REMS drug under the FDC Act’s expanded access provisions at § 561. See id. § 505-1(f)(6), as amended by FDAAA § 901(b).

A responsible person may submit an assessment of and modification to a REMS at any time. See FDC Act § 505-1(g)(1), as amended by FDAAA § 901(b). Assessments are required when submitting an application for a new indication of the drug, when required based on the agreed plan, when requested by FDA based on new information, or within 15 days of notification by FDA that withdrawal of approval may be appropriate under FDC Act § 505(e). See id. § 505-1(g)(2), as amended by FDAAA § 901(b).

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<sup>18</sup> A drug approved under an ANDA is subject to fewer potential REMS components than a drug under a “covered application.” Specifically, REMS generic drugs may require a MedGuide or patient package insert (if required for the reference listed drug) and elements to assure safe use (if required for the reference listed drug). See FDC Act § 505-1(i)(1), as amended by FDAAA § 901(a).

Disputes arising from a REMS upon the initial approval of a drug will be handled under FDA's dispute resolution procedures. See FDC Act § 505-1(h)(4), as amended by FDAAA § 901(b). Disputes arising in all other cases will be handled by a Drug Safety Oversight Board created under FDC Act § 505-1(h). See id. § 505-1(h)(5), as amended by FDAAA § 901(b). While the elements of a strategy can be reviewed, FDA's decision to require a REMS is not reviewable. See id. § 505-1(h)(5)(A)(i), as amended by FDAAA § 901(b).

Drugs approved prior to September 27, 2007 are considered to have a REMS in effect if an agreement has been reached with FDA regarding elements to assure safe use of the drug or if there are elements in effect required by FDA's "accelerated approval" regulations. See FDAAA § 909(b)(1). Such applicants are required to submit a proposed strategy to FDA by March 24, 2008. See id. FDAAA § 909(b)(3).

### **3. Penalties for Violations of FDC Act §§ 505(o), 505(p), and 505-1**

A responsible person can be held liable for violations of FDC Act §§ 505(o), 505(p), and 505-1 concerning the new postmarket requirements. Specifically, failure to follow the requirements deems a drug misbranded under FDC Act § 502. See FDC Act § 502(y), (z), as amended by FDAAA § 902(a). The civil penalties are capped at \$250,000 per violation, up to a maximum of \$1,000,000 for all violations in a single proceeding. See id. § 303(f)(4)(A)(i), as amended by FDAAA § 902(b). Additional penalties can be assessed if the violation does not cease immediately upon notice. See id. § 303(f)(4)(A)(ii), as amended by FDAAA § 902(b). If such activity continues, then a responsible person is subject to an additional \$250,000 for the next 30-day period (or any part thereof). See id. This amount increases to \$500,000 for the next 30-day period, and \$1 million for each period thereafter, and is capped at \$10 million in any single proceeding. See id.

### **4. Prereview of DTC Advertisements**

FDAAA amends the FDC Act to create new § 503B — "Prereview of Television Advertisements" — which gives FDA the authority to require prereview of television advertisements. See FDC Act § 503B(a), as amended by FDAAA § 901(d)(2). FDA's authority is generally limited, however, to providing recommendations after reviewing an ad. See id. § 503B(b), as amended by FDAAA § 901(d)(2). FDA may require a change if it addresses a serious risk with the drug, or if the Agency requires the inclusion of the approval date in the ad (which may occur for up to 2 years after approval). See id. §§ 503B(c), (e) as amended by FDAAA § 901(d)(2).

Although an applicant need not submit an ad or make certain recommended changes, doing so protects the applicant from civil violations for the advertisement. See

FDC Act § 503B(g)(4)(A), as amended by FDAAA § 901(d)(2). A false or misleading DTC ad is punishable by penalties capped at \$250,000 for the first violation in any 3-year period, and capped at \$500,000 for each subsequent violation during that 3-year period. See id. § 303(g)(1), as amended by FDAAA § 901(d)(3). FDA can assess the civil penalty after opportunity for a hearing. If a hearing is requested, FDA is given subpoena power. See id. § 303(g)(2), as amended by FDAAA § 901(d)(3). When determining the penalty, FDA must take into account several factors, including, for example, “[w]hether the person incorporated any comments made by [FDA] with regard to the advertisement into the advertisement prior to its dissemination,” whether the advertisement was “reviewed by qualified medical, regulatory, and legal reviewers” before it was disseminated, and “[w]hether the violations were material.” Id. § 303(g)(3), as amended by FDAAA § 901(d)(3).

FDAAA also requires the statement “You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088” to be included in all published DTC ads for human drugs, and requires FDA to undertake a study to determine whether it is necessary to require the same statement in television ads (or whether doing so would detract from the ad’s safety messages). FDC Act § 502(n), as amended by FDAAA § 906.

## **B. Subtitle B – Other Provisions to Ensure Drug Safety and Surveillance**

FDAAA Title IX, Subtitle B, contains myriad provisions intended to ensure drug safety and surveillance. Some of the provisions are very clearly connected to drug safety and surveillance as they relate to the new provisions enacted as part of Title IX, Subtitle A, and some of the provision are connected to drug safety and surveillance only in the very broadest sense.

### **1. Antibiotic Clinical Trial Guidance**

FDAAA § 911 amends the FDC Act to create § 511 – “Clinical Trial Guidance for Antibiotic Drugs.” It requires FDA to issue guidance not later than September 27, 2008 enactment concerning “the conduct of clinical trials with respect to antibiotic drugs, including antimicrobials to treat acute bacterial sinusitis [(‘ABS’)], acute bacterial otitis media, and acute bacterial exacerbation of chronic bronchitis [(‘ABECB’)].” FDC Act § 511(a), as amended by FDAAA § 911. Such guidance must “indicate the appropriate models and valid surrogate markers” and must be updated by FDA by September 27, 2012 “to reflect developments in scientific and medical information and technology.” Id. § 511(a), (b), as amended by FDAAA § 911.

New FDC Act § 511 stems from recent concern over a shifting approval standard for certain antibiotic drugs for conditions like ABS and ABECB. In the past, FDA

approved antibiotic drugs for these indications based on the results from clinical trials designed to show non-inferiority (*i.e.*, clinical studies designed to show that a new drug is no worse than an approved drug at treating an illness). Recent discussions, however, have raised questions about the interpretability of a finding of non-inferiority in some less serious infectious diseases, such as ABS and mild to moderate ABECB, as opposed to findings in placebo-controlled studies. In December 2006, during a joint meeting of the Anti-Infective Drugs and Drug Safety and Risk Management Advisory Committees convened to discuss the continued approval of KETEK (telithromycin), there was significant discussion about the appropriate clinical study design for antibiotics for ABS and ABECB and the lack of FDA guidelines. The intent of FDAAA § 911 is to expedite the publication of such guidance.

## **2. Prohibition Against Foods to Which Drugs or Biological Products are Added**

Hidden in Title IX, FDAAA § 912 is of potential significance to the development of functional food ingredients by the food and dietary supplement industries. Section 912 creates new FDC Act § 301(ll) — “Prohibition Against Food to Which Drugs or Biological Products Have Been Added.” FDC Act § 301(ll), as amended by FDAAA § 912(a). The prohibition is patterned after the exclusionary clause found in the definition of “dietary supplement” at FDC Act § 201(ff)(3)(B).

New FDC Act § 301(ll) prohibits foods containing an approved drug, an approved biological product, 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.” FDC Act § 301(ll), as amended by FDAAA § 912(a). There are 4 (narrow) exceptions to this prohibition. The addition of a drug or biologic to a food is not prohibited if: (1) the drug or biological product “was marketed in food before” it was approved as a drug or licensed as a biologic and “before any substantial clinical investigations involving the drug or [biologic product] have been instituted;” (2) FDA has “issued a regulation” allowing “use of [the] drug or [biological product] in the food;” (3) the drug or biological product is added to food “to enhance the safety of the food” and not for “independent biological or therapeutic effect on humans;” or (4) the drug is an approved animal drug. *Id.* § 301(ll)(1)-(4), as amended by FDAAA § 912(a). The third exception, allowing the addition of a drug or biological product only to enhance food safety, is further limited by the requirement that the drug or biological product must also be an approved food additive; listed or affirmed as generally recognized as safe (“GRAS”); the subject of a GRAS notification that FDA did not question or the subject of an effective food contact substance notification; or it must have been marketed as a smoking cessation product. *See id.* § 301(ll)(3)(A)-(E), as amended by FDAAA § 912(a). Absent from this exception are self-affirmations of GRAS status and new dietary ingredient notifications.

FDC Act § 301(ll) is difficult to interpret. At first glance, the prohibition appears similar to the exclusionary clause for dietary supplements, which provides that a dietary supplement does not include “an article that is approved as a new drug[,] licensed as a [biologic,] or an article authorized for investigation as a new drug . . . or [biologic] for which substantial clinical investigations have been instituted and . . . made public.” FDC Act § 201(ff)(3)(B) (the “dietary supplement exclusionary clause”) (emphasis added). There are, however, significant differences between the two. New FDC Act § 301(ll) speaks in terms of a “drug” and “biological product” rather than an article. Under the FDC Act, whether a substance is a “food” or a “drug” generally depends on its “intended use,” and not on an inherent characteristic or the chemical identity of the substance. See FDC Act § 201(g). Indeed, a substance may be a “drug” for one use and a “food” for another use. FDC Act § 301(ll) refers to a drug and a biologic as if it is the chemical identity of the substance or article that controls, independent of the intended use.

Another notable difference between new FDC Act § 301(ll) and the exclusionary clause for dietary supplements can be found in the nature of clinical investigations that trigger the prohibition. FDC Act § 301(ll) applies when “substantial clinical investigations have been instituted” and made public for a drug or biological product, whereas the supplement exclusion at FDC Act § 201(ff)(3)(B)(ii) applies when “substantial clinical investigations have been instituted” and made public for “an article authorized for investigation as a new drug . . . or [biologic].” FDC Act § 201(ff)(3)(B)(ii) (emphasis added). Clinical investigations for use of a substance as a new drug or biologic require INDs, and this is reflected in the supplement exclusionary clause. FDC Act § 301(ll), however, does not on its face require the public clinical investigations to be for new drug use.

In addition, the grandfather provision in new FDC Act § 301(ll)(1) allows food use of a drug or biologic that “was marketed in food” before any drug approval or biologic license was issued, and “before any substantial clinical investigations involving the drug or biological product” were instituted. FDC Act § 301(ll)(1) (emphasis added), as amended by FDAAA § 912(a). The corresponding dietary supplement provision allows supplement use of articles that were first “marketed as a dietary supplement or as a food.” FDC Act § 201(ff)(3)(A) (emphasis added).

Finally, FDAAA § 912 does not amend the provision that “dietary supplement[s] shall be deemed to be a food within [the FDC Act].” FDC Act § 201(ff). Therefore, new FDC Act § 301(ll) applies to all foods including dietary supplements. Consequently, in addition to creating a new prohibition for foods other than dietary supplements, new FDC Act § 301(ll) potentially expands the existing dietary supplement exclusionary clause.

### 3. Assuring Pharmaceutical Security

FDAAA § 913 amends the FDC Act to create new § 505D – “Pharmaceutical Security.” This new section of law requires FDA to “develop standards and identify and validate effective technologies for the purpose of securing the drug supply chain against counterfeit, diverted, subpotent, substandard, adulterated, misbranded, or expired drugs.” FDC Act § 505D(a), as amended by FDAAA § 913. FDA must consult with a broad array of public (both state and federal) and private entities on the development of such standards, including the Departments of Justice, Homeland Security and Commerce, and prescription drug manufacturers, distributors and pharmacies. *See id.* §§ 505D(b)(1), (4), as amended by FDAAA § 913. “Promising technologies” for the development of such standards identified in the new law include Radio Frequency Identification (“RFID”), nanotechnology, encryption technologies, and “other track-and-trace or authentication technologies.” *Id.* § 505D(b)(3), as amended by FDAAA § 913.

Not later than March 2010, FDA must develop a “standardized numerical identifier” that is to be applied to a prescription drug “at the point of manufacturing and repackaging . . . at the package or pallet level, sufficient to facilitate the identification, validation, authentication, and tracking and tracing of the prescription drug.” FDC Act § 505D(b)(2), as amended by FDAAA § 913. In order to secure the drug supply against violative drug products, FDA is required to “expand and enhance the resources and facilities” of its components involved with regulatory and criminal enforcement and to “undertake enhanced and joint enforcement activities with other Federal and State agencies, and establish regional capacities for the validation of prescription drugs and the inspection of the prescription drug supply chain.” *Id.* § 505D(c), as amended by FDAAA § 913.

FDAAA § 913 complements FDA’s current counterfeit drug efforts. In February 2004, FDA issued a report, titled “Combating Counterfeit Drugs: A Report of the Food and Drug Administration” (*available at* [http://www.fda.gov/oc/initiatives/counterfeit/report02\\_04.html](http://www.fda.gov/oc/initiatives/counterfeit/report02_04.html)), in which the Agency outlined a specific approach to protecting U.S. consumers from counterfeit drugs, including the use of innovative technologies like RFID. FDA has also assembled a Counterfeit Drug Task Force (information *available at* <http://www.fda.gov/oc/initiatives/counterfeit/>).

### 4. Citizen Petition Modification

FDAAA § 914 is one of the few provisions that could have a significant effect on generic drug applicants — that is, those companies that submit ANDAs and certain 505(b)(2) applications. It amends the FDC Act to create new § 505(q) — “Petitions and Civil Actions Regarding Approval of Certain Applications” — to provide that FDA will not delay the approval of a pending ANDA or a pending 505(b)(2) application as a result

of a citizen petition submitted pursuant to 21 C.F.R. §10.30 or § 10.35, unless the Agency determines that “a delay is necessary to protect the public health.” FDC Act § 505(q)(1)(A), as amended by FDAAA § 914(a).

The submission and timing of submission of citizen petitions requesting that the FDA impose specific additional requirements for approval on ANDAs for a particular drug product have long been criticized as a lifecycle management strategy intended only to delay generic competition. In 1999, FDA stated that “[q]uestions have . . . arisen whether a citizen petition can be used for improper purposes, such as delaying competition . . . or delaying agency action,” and proposed several options intended to, among other things, avoid frivolous petitions. Proposed Rule, Citizen Petitions; Actions That Can be Requested by Petition; Denials, Withdrawals, and Referrals for Other Administrative Action, 64 Fed. Reg. 66,822 (Nov. 30, 1999). FDA withdrew the proposal in April 2003, but once again noted in September 2005 that “[t]he citizen petition process is in some cases being abused.” Remarks of Mr. Sheldon Bradshaw, Chief Counsel, FDA, at the Generic Pharmaceutical Association’s first annual Policy Conference, Sept. 19, 2005.

Under the new law, if FDA determines that delaying the approval of a generic application is necessary to protect the public health, then FDA must provide to the generic applicant (within 30 days of making such a determination): (1) notice of such determination; (2) clarification of the information that such applicant should submit to the public docket established for the petition to allow FDA to promptly review the petition; and (3) a brief summary of the substantive issues raised in the petition that led to FDA’s determination. See FDC Act § 505(q)(1)(B), as amended by FDAAA § 914(a). FDA may deny a petition at any point if the Agency determines that the petition (or a supplement to the petition) “was submitted with the primary purpose of delaying the approval of an application and the petition does not on its face raise valid scientific or regulatory issues.” Id. § 505(q)(1)(E), as amended by FDAAA § 914(a). In all cases, FDA is required to take final agency action on a petition not later than 180 days after it is submitted to the Agency. Id. § 505(q)(1)(F), as amended by FDAAA § 914(a).

Petitions submitted to FDA must include a specific certification identified in the statute. This certification, which also applies to petition supplements and petition comments, requires, among other things, identification of the date upon which the petitioner first became aware of the information that forms the basis of the request, and the persons or organizations from whom a payment or other form of consideration was (or will be) received with respect to the petition or comment. FDC Act §§ 505(q)(1)(H), (I), as amended by FDAAA § 914(a).

An ANDA applicant that is a “first applicant” under FDC Act § 505(j)(5)(B)(iv)(II)(bb) eligible for a period of 180-day exclusivity, and whose application approval is delayed as the result of a petition covered under new FDC Act

§ 505(q), is entitled to an extension of the 30-month period under FDC Act § 505(j)(5)(D)(i)(IV) (concerning forfeiture of 180-day exclusivity because of failure to obtain ANDA tentative approval) “equal to the period beginning on the date on which [FDA] received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether [FDA] grants, in whole or in part, or denies, in whole or in part, the petition.” FDC Act § 505(q)(1)(G), as amended by FDAAA § 914(a). Thus, a “first applicant” whose ANDA is delayed as a result of a petition will not automatically forfeit 180-day exclusivity eligibility if tentative approval is not obtained “within 30 months after the date on which the application is filed.” FDC Act § 505(j)(5)(D)(i)(IV).

## **5. Dissemination of Postmarket Drug Safety Information**

FDAAA § 915 amends the FDC Act to create new § 505(r) — “Postmarket Drug Safety Information for Patients and Providers” — in an effort to improve the transparency of drug information and to allow patients and healthcare providers better access to drug information. Not later than September 27, 2008, FDA is required to develop and maintain a consolidated and easily searchable website that provides, among other things, patient and professional labeling, recent safety information, publicly available information about implemented RiskMAPs and REMS, drug safety guidance documents and regulations, and drug-specific summary analyses of adverse drug reaction reports. See FDC Act § 505(r)(2), as amended by FDAAA § 915. FDA’s new Advisory Committee on Risk Communications will regularly review the information made available on FDA’s website to “facilitate the efficient flow of information to patients and providers” and will make recommendations to improve the dissemination of such information. Id. § 505(r)(6), as amended by FDAAA § 915.

## **6. Summary Basis of Approval Reform**

FDAAA § 916 amends FDC Act § 505(l) to require FDA to make “action packages” — sometimes referred to as Summary Basis of Approvals (“SBAs”) — for approved drugs and licensed biologics publicly available more promptly. SBAs often only become available many months (or years) after product approval, and sometimes only after interested parties have submitted a Freedom of information Act (“FOIA”) request. Under FDAAA, however, FDA is required to post SBAs on its website for new chemical entities not later than 30 days after approval, and not later than 30 days after the third FOIA request for an SBA for any other drug. See FDC Act § 505(l)(2)(A), as amended by FDAAA § 916.

In addition, FDA is required to post on its website, within 48 hours after approval of an application, a “summary review that documents conclusions from all reviewing disciplines about the drug, 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 nonconcurrency with review conclusions,” except when such documents require redaction. See FDC Act §§ 505(l)(2)(B), (C)(iv), as amended by FDAAA § 916.

## 7. Advisory Committees

FDAAA § 917 amends the FDC Act to require FDA to establish a permanent advisory committee known as the Advisory Committee on Risk Communication to advise the FDA Commissioner “on methods to effectively communicate risks associated with” FDA-regulated products. FDC Act § 567(a), as amended by FDAAA § 917. FDAAA § 918 amends the FDC Act to create new § 505(s) to require advisory committee referral of any new chemical entity, unless FDA determines otherwise. See FDC Act § 505(s), as amended by FDAAA § 918. If FDA decides not to seek advisory committee review, then the Agency must “provide in the action letter on the application for the drug a summary of the reasons why the [Agency] did not refer the drug to an advisory committee prior to approval.” Id. § 505(s)(2), as amended by FDAAA § 918.

## 8. Miscellaneous Issues

FDAAA § 919 requires FDA to respond to the IOM’s September 2006 drug safety report not later than September 27, 2008, and prescribes the content of FDA’s report, which includes an assessment of the execution of new FDC Act § 505-1(c)(2) with respect to the cooperation of FDA’s preapproval and postapproval safety components in implementing new FDC Act § 505-1. See FDAAA § 919.

FDAAA § 920 amends the FDC Act to create new § 505(t) – “Database for Authorized Generic Drugs” – that requires FDA to compile and publish (by June 27, 2008) a complete list of all authorized generic drugs identified in annual reports submitted to the Agency since January 1, 1999. FDC Act § 505(t)(1)(A), as amended by FDAAA § 920. The new law defines an “authorized generic” as a drug listed in FDA’s Orange Book that was approved under FDC Act § 505(c) (*i.e.*, a “full” 505(b)(1) NDA or 505(b)(2) application) and that “is marketed, sold, or distributed directly or indirectly to retail class of trade under a different labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark than the listed drug.” Id. § 505(t)(3), as amended by FDAAA § 920. The list must be updated on a quarterly basis. See id. § 505(t)(1)(A)(ii), as amended by FDAAA § 920. Among other uses, this list will assist the Federal Trade Commission as that agency moves ahead with its study of the competitive effects of authorized generics.

Finally, FDAAA § 921 amends FDC Act § 505(k) to require FDA to (1) “conduct regular, bi-weekly screening of the Adverse Event Reporting System database and post a quarterly report on the Adverse Event Reporting System Web site of any new safety

information or potential signal of a serious risk identified by Adverse Event Reporting System within the last quarter;” (2) report to Congress by September 27, 2009 “on procedures and processes of the [FDA] for addressing ongoing post market safety issues identified by the Office of Surveillance and Epidemiology and how recommendations of the Office of Surveillance and Epidemiology are handled within the agency,” and (3) annually “review the entire backlog of postmarket safety commitments to determine which commitments require revision or should be eliminated, report to the Congress on these determinations, and assign start dates and estimated completion dates for such commitments.” FDC Act § 505(k)(5), as amended by FDAAA § 921.

## **X. FOOD SAFETY**

FDAAA Title X is dedicated to human and pet food safety issues and includes several new provisions of law. The most significant provision in FDAAA Title X is the creation of a Reportable Food Registry under FDC Act § 417 for foods “for which there is a reasonable probability that the use of, or exposure to, such article of food will cause serious adverse health consequences or death to humans or animals.” FDC Act § 417(a)(2), as amended by FDAAA § 1005(b). (This definition is the standard FDA uses for Class I recalls. See 21 C.F.R. § 7.3(m)(1).) The purpose of the registry is to facilitate tracking of problems in the food supply and to allow a more rapid response by FDA and the food industry to such problems.

Via an electronic portal created under FDAAA for this purpose, a “responsible party” (defined as the owner operator or agent in charge of the facility registered pursuant to FDC Act § 415(a)) must report incidents in which a food may be adulterated and pose a significant or potentially significant risk to human or animal health. See FDC Act § 417(a)(1), as amended by FDAAA § 1005(b). The reporting duty is not limited to the party that is responsible for the adulteration but applies to anyone who is registered pursuant to FDC Act § 415(a) and discovers the adulteration.

A report must be submitted to FDA within 24 hours after a determination is made that such a risk exists. The required elements of the report are specified in new FDC Act § 417(e) and include, among other things, product and contact information and a description of the adulteration. See id. § 417(e), as amended by FDAAA § 1005(b). A responsible party’s failure to submit a report, or the falsification of such a report, is a prohibited act under the FDC Act. See id. § 301(nn), as amended by FDAAA § 1005(d). Upon FDA’s receipt of a report, the Agency reviews the information and determines whether to issue an alert or notification. See id. § 417(d)(5)-(6), as amended by FDAAA § 1005(b). The food registry must be in effect by September 27, 2008, and FDA must issue guidance concerning the registry not later than June 27, 2008. See FDAAA §§ 1005(e), (f). Public availability of records from the Reportable Food Registry is subject to FOIA.

New FDC Act § 417 does not apply to dietary supplements, which are subject to separate and more burdensome mandatory adverse event reporting requirements under the recently-enacted Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006, Pub. L. No. 109-462.

Title X also requires that FDA develop a more efficient and effective system for communicating information during a food recall. Specifically, FDA must create and maintain a searchable and accessible website for posting information on human and pet food recalls. FDAAA § 1003. Congress did not establish a deadline for FDA's creation of the website.

In response to several high-profile pet food safety issues earlier this year, FDAAA includes several provisions intended to strengthen FDA's oversight of pet food safety. Specifically, by September 27, 2009, FDA must establish ingredient and processing standards and definitions for pet food, and update standards for the labeling of pet food. *Id.* § 1002(a). In addition, FDA must establish (September 27, 2008) early warning surveillance and notification systems "to identify adulteration of the pet food supply and outbreaks of illness associated with pet food." *Id.* § 1002(b). Currently, the FDC Act and FDA's regulations do not differentiate between pet and animal food.

Finally, Title X includes several provisions encouraging FDA to cooperate with States and other federal agencies on food safety issues, such as produce safety. *See, e.g.*, FDAAA § 1004. In addition, FDA must report to Congress by March 24, 2008 on the current aquaculture and seafood inspection system, a risk assessment of contaminants in aquaculture and seafood, and the feasibility of developing a traceability system for catfish and seafood products. *See id.* § 1006(c). FDA must also prepare annual reports concerning food imports and resources dedicated to their inspection, as well as annual reports concerning the pesticide residue program. *See id.* §§ 1009, 1010(a).

## **XI. MISCELLANEOUS PROVISIONS**

Title XI includes various miscellaneous provisions concerning a range of topics from antibiotic access and innovation, to transferable priority review, to enantiomer exclusivity.

### **A. FDA Review and Clearance of Employee Scientific Articles**

FDAAA adds FDC Act § 713 – "Policy on the Review and Clearance of Scientific Articles Published by FDA Employees." The new law requires FDA to "establish and make publicly available clear written policies" that "govern the timely submission, review, clearance, and disclaimer requirements for articles," which includes a "paper,

poster, abstract, book, book chapter, or other published writing.” FDC Act § 713, as amended by FDAAA § 1101.

## **B. Transferable Priority Review**

FDAAA creates a new transferable priority review program in which applicants for certain new drugs and biologics for “tropical diseases” that have received priority review receive a “priority review voucher” entitling the holder to a 6-month FDA review of another application that would otherwise be reviewed under FDA’s standard 10-month review clock. The priority review voucher may be used or sold by the company granted the voucher for an application “submitted after the date of the approval of the tropical disease product application.” FDC Act § 524(b)(2), as amended by FDAAA § 1102. The tropical diseases that can qualify an applicant are enumerated in new FDC Act § 524(a)(3), and include “infectious disease[s] for which there is no significant market in developed nations and that disproportionately [affect] poor and marginalized populations, designated by regulation by [FDA].” FDC Act § 524(a)(3)(Q), as amended by FDAAA § 1102.

Applicants that use a priority review voucher are required to pay FDA a priority review user fee in addition to other required user fees, and no such fee may be waived, reduced, or refunded. See FDC Act §§ 524(c)(1) and 524(c)(4)(C), as amended by FDAAA § 1102. FDA will establish the amount of the priority review user fee before the beginning of each FY. See id. § 524(c)(3), as amended by FDAAA § 1102.

## **C. Genetic Test Safety and Quality**

FDAAA § 1103 provides that if the DHHS Secretary’s Advisory Committee on Genetics, Health, and Society (“SACGHS”) fails to complete and submit to the DHHS Secretary its “Regulatory Oversight of Genetic/Genomic Testing Report & Action Recommendations” by July 2008, then DHHS may enter into a contract with IOM to “conduct a study to assess the overall safety and quality of genetic tests and prepare a report that includes recommendations to improve Federal oversight and regulation of genetic tests.” FDAAA § 1103. SACGHS was established in September 2002 (re-chartered in 2004) to serve as a public forum for deliberations on a range of issues raised by the development and use of generic technologies and is reportedly actively working on its regulatory oversight report and recommendations. Additional information about the SACGHS is available at <http://www4.od.nih.gov/oba/SACGHS.HTM>.

## **D. Antibiotic Access and Innovation**

In addition to other FDAAA provisions requiring FDA to issue guidance on antibiotic drug development (*i.e.*, FDAAA § 911), FDAAA § 1111 requires FDA to identify, periodically update, and make publicly available information on “clinically susceptible concentrations” of antimicrobials — that is, the “specific values which

characterize bacteria as clinically susceptible, intermediate, or resistant to the drug (or drugs) tested.” FDAAA § 1111. The new law also requires FDA to convene a public meeting concerning “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 available grants and contracts under section 5(a) of the Orphan Drug Act (21 U.S.C. 360ee(a)) or other incentives for development,” and makes \$30 million for each of FYs 2008 through 2012 available under the Orphan Drug Act for such purposes. FDAAA § 1112.

### **E. Enantiomer Exclusivity**

Enantiomers are stereoisomers of a chiral compound that are non-superimposable mirror images of one another. Enantiomers may be either right-handed (dextro-rotary) S(+)-isomers, or left-handed (levo-rotary) R(-)-isomers. A racemic mixture is one that has equal amounts of left- and right-handed enantiomers of a particular chiral molecule. For example, omeprazole (PRIOSEC) is a racemic mixture; esomeprazole, the S-isomer (enantiomer) of the racemate, is approved under the brand name NEXIUM.

FDA has for decades treated single enantiomers of approved racemates as previously approved active moieties not eligible for 5-year new chemical entity exclusivity (but eligible for 3-year exclusivity). In the preamble to FDA’s July 1989 proposed regulations implementing the Hatch-Waxman Act, the Agency stated this position: “FDA will consider whether a drug contains a previously approved active moiety on a case-by-case basis. FDA notes that a single enantiomer of a previously approved racemate contains a previously approved active moiety and is therefore not considered a new chemical entity.” Proposed Rule, ANDA Regulations, 54 Fed. Reg. 28,872, 28,898 (July 10, 1989). In 1997, FDA issued a Federal Register notice requesting comment on whether granting a 5-year period of exclusivity to enantiomers of previously approved racemates would encourage medically significant innovation. See Notice, Policy on Period of Marketing Exclusivity for Newly Approved Drug Products With Enantiomer Active Ingredients; Request for Comments, 62 Fed. Reg. 2167 (Jan. 15, 1997). FDA never completed the rulemaking.

FDAAA amends the FDC Act to permit the applicant of a 505(b)(1) NDA for an enantiomer (that is contained in an approved racemic mixture) containing full reports of clinical investigations conducted or sponsored by the applicant (and that does not rely on information in another NDA) to “elect to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug.” FDC Act § 505(u)(1), as amended by FDAAA § 1113. There are, however, certain limitations. The enantiomer NDA must not be for a condition of use “(i) in a therapeutic category in which the approved racemic drug has been approved; or (ii) for which any other enantiomer of the racemic drug has been approved.” Id. § 505(u)(1)(B), as amended by FDAAA § 1113. In addition, if the enantiomer NDA applicant elects to receive

exclusivity, then FDA may not approve the enantiomer drug for any condition of use in the “therapeutic category” in which the racemic drug is approved until 10 years after approving the enantiomer. See id. § 505(u)(2)(A), as amended by FDAAA § 1113. The term “therapeutic category” is defined in FDC Act § 505(u) to mean “a therapeutic category identified in the list developed by the United States Pharmacopeia pursuant to section 1860D-4(b)(3)(C)(ii) of the Social Security Act and as in effect on [September 27, 2007],” which FDA must publish and that may be amended by regulation. Id. § 505(u)(3), as amended by FDAAA § 1113.<sup>19</sup> FDC Act § 505(u) sunsets on September 30, 2012, unless reauthorized (presumably under PDUFA V). See id. § 505(u)(4), as amended by FDAAA § 1113.

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The information in this memorandum is not intended as legal advice. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein. For more information about this memorandum or about FDAAA, please contact Robert A. Dormer (202.737.4282; rdormer@hpm.com) or Kurt R. Karst (202.737.7544; kkarst@hpm.com).

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<sup>19</sup> This provision of the Social Security Act states:

The Secretary shall request the United States Pharmacopeia to develop, in consultation with pharmaceutical benefit managers and other interested parties, a list of categories and classes that may be used by prescription drug plans under this paragraph and to revise such classification from time to time to reflect changes in therapeutic uses of covered part D drugs and the additions of new covered part D drugs.

42 U.S.C. § 1395w-104(b)(3)(C)(ii).