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Food and Drug Administration Safety and Innovation Act

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EXECUTIVE SUMMARY

On July 9, 2012, President Obama signed into law the Food and Drug Administration Safety and Innovation Act (“FDASIA”), Pub. L. No. 112-144, 126 Stat. 993 (2012), which primarily amends both the Federal Food, Drug, and Cosmetic Act (“FDC Act”) and Public Health Service Act (“PHS Act”).¹ In addition to reauthorizing and amending several drug and medical device provisions that were scheduled to sunset, the new law establishes new user fee statutes for generic drugs and biosimilars. FDASIA also provides the Food and Drug Administration (“FDA”) with tools intended to expedite the development and review of innovative new medicines that address certain unmet medical needs, and with new authority concerning drug shortages, among other things. The law significantly changes the FDC Act and the PHS Act in several respects that will have considerable short- and long-term effects on the regulated industry.

FDASIA includes 11 titles, the first 5 of which concern drug and medical device user fee and pediatric-related programs. Title VI includes myriad changes to the law styled as medical device regulatory improvements. Title VII makes significant changes to enhance FDA’s inspection authority and the drug supply chain. Title VIII creates incentives to encourage the development of products for antibiotic-resistant infections. Title IX expands the scope of products that qualify for accelerated approval and creates a new “breakthrough therapy” program, among other things. Title X is intended to legislatively address the current drug shortage crisis. Finally, Title XI reauthorizes certain provisions created by the FDA Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) (“FDAAA”), provides for the regulation of medical gases, and includes several miscellaneous provisions, such as provisions on prescription drug abuse, 180-day generic drug marketing exclusivity, citizen petitions, controlled substances, and nanotechnology to name a few.

Among the more controversial provisions that failed to survive the legislative negotiation process were provisions included in an earlier version of S. 3187 concerning Risk Evaluation and Mitigation Strategies (“REMS”) and generic competition, and the creation of so-called “track and trace,” which is a uniform, national traceability framework intended to identify and follow an individual drug through the pharmaceutical supply chain to protect against counterfeit drugs.

¹ A copy of FDASIA (S. 3187) is available at <http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf>. A U.S. Senate and U.S. House of Representatives Conference Report was not published; however, a House Report on H.R. 5651, H.R. Rep. No. 112-495 (2012), a predecessor to S. 3187, was published and is available at <http://www.gpo.gov/fdsys/pkg/CRPT-112hrpt495/pdf/CRPT-112hrpt495.pdf>.

This memorandum summarizes FDASIA, and in particular, the provisions that are of most interest to our clients, and analyzes the new law's potential effects on the FDA-regulated industry. It is organized to summarize each title in the order presented in the new law. In addition to this memorandum, we will periodically report on various FDASIA issues on our firm's blog, The FDA Law Blog (www.FDALawBlog.net). You can register for e-mail updates on the blog.

I. PRESCRIPTION DRUG USER FEE AMENDMENTS OF 2012

A. Significant Changes to PDUFA

FDASIA Title I reauthorizes the Prescription Drug User Fee Act ("PDUFA") through Fiscal Year ("FY") 2017 and, relative to previous reenactments, makes few changes to the law.² PDUFA was first enacted in 1992 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. 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 (the "Performance Goals"). FDA's PDUFA V Reauthorization Performance Goals and Procedures for FYs 2013-2017 ("PDUFA V Performance Goals") also include increasing interaction between drug sponsors and FDA during the review process, improving engagement with patients, including those with rare diseases, improving the transparency of the review process, and undertaking an independent assessment of FDA's performance in reviewing applications for novel drugs.

FDASIA amends FDC Act § 736(b) "Fee Revenue Amounts" to establish user fees (application, establishment, and product fees) for each of FYs 2013-2017 in order to generate annual revenue that is the sum of \$693,099,000, plus a workload adjustment factor and an inflation adjustment factor for FY 2014 that are modified in subsequent FYs. See FDC Act § 736(b), as amended by FDASIA § 103. The manner in which FDA calculates these two adjustment factors has been modified somewhat, but, as before, the fees must be established by FDA 60 days before the start of each FY, see id. § 736, as

² 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 Administration Modernization Act, Pub. L. No. 105-115, 111 Stat. 2296 (1997) ("FDAMA"), by the Prescription Drug User Fee Amendments, Pub. L. No. 107-188, Title V, subtitle A, 116 Stat. 594, 687 (2002) ("PDUFA III"), and by FDAAA, Pub. L. No. 110-85, Title I, 121 Stat. 823, 825 (2007) ("PDUFA IV").

amended by FDASIA § 103, and Performance Reports must be issued by FDA each FY, see id. § 736B(a), as amended by FDASIA § 104.

Establishment and product fees are currently due on or before October 1st of each year. See FDC Act § 736(a)(2) and (a)(3). FDASIA amends these sections to provide that establishment fees are “due on the later of the first business day on or after October 1 of each fiscal year or the first business day after the enactment of an appropriations Act providing for the collection and obligation of fees for such fiscal year under this section.” FDC Act §§ 736(a)(2), (a)(3), as amended by FDASIA §§ 103(1)(C)(ii), (D)(i)(II).

FDASIA also amends the so-called “generic exception” relating to product user fees at FDC Act § 736(a)(3)(B). Previously, the law stated that a prescription drug product is not subject to a fee if such product “is the same product as another product approved under” an NDA or an Abbreviated NDA (“ANDA”). FDC Act § 736(a)(3)(B) (2011). That provision has been amended to state that a prescription drug product is not subject to a fee if such product “is the same product as another product” approved under an NDA or an ANDA and if such other product is not listed in the discontinued section of FDA’s Approved Drug Product With therapeutic Equivalence Evaluations (i.e., the “Orange Book”). FDC Act § 736(a)(3)(B)(ii), as amended by FDASIA § 103(D)(ii). The change legislatively overturns a recent decision by the U.S. District Court for the District of Columbia in which the court found that FDA exceeded its authority in interpreting the generic exception provision to be limited to situations where the generic is not only “approved,” but also in active production. See Stat-Trade Inc. v. Food and Drug Admin., --- F.Supp.2d --- (2012).

B. FDA’s PDUFA V Performance Goals

FDA’s PDUFA V Performance Goals were the result of lengthy negotiations between FDA and industry and include several new provisions, some of which are highlighted below.³

The NME NDA and Original BLA “Program.” Although many of the goals for priority and standard NDA and BLA review, including Class 1 and Class 2 resubmissions, efficacy supplements, and manufacturing supplements remain the same as under PDUFA IV, the PDUFA V Performance Goals establish a new review model that will apply to all New Molecular Entity (“NME”) NDAs and original BLAs received from

³ Copies of FDA’s PDUFA V Performance Goals transmittal letter to Congress and FDA’s PDUFA V Performance Goals will be posted on FDA’s website. The current version of the PDUFA V Performance Goals is available at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm270412.pdf>.

October 1, 2012, through September 30, 2017, including applications that are resubmitted following a Refuse-to-File action.

The new review model, referred to as “the Program” in the PDUFA V Performance Goals, is intended to “promote greater transparency and improve communication between the FDA review team and the applicant” and to “improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics.” PDUFA V Performance Goals at 5-6.⁴

The parameters of the Program include, among other things, a pre-submission meeting that is “strongly encouraged,” a mid-cycle communication “to provide the applicant with an update on the status of the review of their application,” and a late-cycle meeting at which the FDA review team, appropriate team leaders and supervisors, and the applicant will discuss the status of the review of the application. *Id.* at 6-8. A new goal for inspection times is established, as is a quality system approach that implements a tracking system to document review team performance of key milestones for each of the applications reviewed under the Program.

At the pre-submission meeting, “FDA and the applicant will agree on the content of a complete application for the proposed indication(s), including preliminary discussions on the need for [a REMS] or other risk management actions.” *Id.* at 6. In addition, “FDA and the applicant may also reach agreement on submission of a limited number of application components not later than 30 calendar days after the submission of the original application,” such as the submission of updated stability data. *Id.* The agreement cautions that “[i]f the applicant does not have a pre-NDA/BLA meeting with FDA, and no agreement exists between FDA and the applicant on the contents of a complete application or delayed submission of certain components of the application, the applicant’s submission is expected to be complete at the time of original submission.” *Id.* at 7.

As part of the Program, priority and standard NME NDAs and original BLAs will be subject to different review goals as compared to other applications. As shown in the table below, the agreement says that FDA will review and act on 90% of standard NME NDA and original BLA submissions within 10 months of the 60-day **filing** date, and 90% of priority NME NDA and original BLA submissions within 6 months of the 60-day **filing** date. Use of the filing date instead of the submission date essentially means that

⁴ On July 6, 2012, FDA issued a notice seeking public comment on the Agency’s statement of work for an assessment of the Program. *See* 77 Fed. Reg. 40,072 (July 6, 2012).

the reviews are slated to take place within 12 months (standard review) and 8 months (priority review) from application submission.

Table 1: Original and Resubmitted Applications and Supplements

SUBMISSION COHORT	STANDARD	PRIORITY
NME NDAs and original BLAs	90% in 10 months of the 60 day filing date	90% in 6 months of the 60 day filing date
Non NME NDAs	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmissions	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmissions	90% in 6 months of the receipt date	90% in 6 months of the receipt date
Original Efficacy Supplements	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmitted Efficacy Supplements	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmitted Efficacy Supplements	90% in 6 months of the receipt date	90% in 6 months of the receipt date
	PRIOR APPROVAL	ALL OTHER
Manufacturing Supplements	90% in 4 months of the receipt date	90% in 6 months of the receipt date

Changes to “Major Amendments.” Another change of note is the treatment of “major amendments” to pending applications. Under PDUFA IV, and FDA’s regulations:

[a] major amendment to an original application, efficacy supplement, or resubmission of any of these applications, ***submitted within three months of a goal date***, may extend the goal date by three months. A major amendment to a manufacturing supplement ***submitted within two months of the goal date*** extends the goal date by two months.

PDUFA IV Performance Goals (emphasis added); see also 21 C.F.R. § 314.60. Under the PDUFA V agreement, however, “[a] major amendment to an original application, efficacy supplement, or resubmission of any of these applications, ***submitted at any time during the review cycle***, may extend the goal date by three months,” and “[a] major amendment

to a manufacturing supplement *submitted at any time during the review cycle* may extend the goal date by two months.” PDUFA V Performance Goals at 32 (emphasis added).

The PDUFA V agreement notes that a major amendment may include, among other things, “submission of a REMS with [Elements To Assure Safe Use (‘ETASU’)] not included in the original application; or significant amendment to a previously submitted REMS with ETASU;” however, “changes to REMS that do not include ETASU and minor changes to REMS with ETASU will not be considered major amendments.” Id.

The PDUFA V Performance Goals eliminates the distinction between solicited and unsolicited major amendments for purposes of determining whether a new review timeline need be provided. Instead, any major amendment that will result in an extension of the PDUFA review clock will require the review division to communicate a new planned review timeline. See id. at 13.

Meeting Management Goals. The PDUFA V Performance Goals add the option for sponsors to request written responses to their questions for pre-Investigational New Drug Application (“IND”) and Type C meeting requests rather than a face-to-face meeting. Additionally, even if the sponsor requests a face-to-face pre-IND or Type C meeting, the Agency may determine that a written response to the sponsor’s questions would be the most appropriate means for responding to the meeting request. See id. at 17.

In addition, meetings regarding REMS or postmarketing requirements that occur outside the context of the review of a marketing application shall be classified as Type B meetings, and post-action meetings requested by the sponsor within three months after an FDA regulatory action other than an approval (i.e., issuance of a complete response letter) shall be classified as a Type A meeting. See id. at 19.

Enhancing Regulatory Science and Expediting Drug Development. The PDUFA V Performance Goals include several items intended to enhance regulatory science and expedite drug development, including: initiatives to enhance FDA-sponsor communications; approaches and methods for the conduct of meta-analyses; advancing the use of biomarkers and pharmacogenomics; advancing the development of patient-reported outcomes and other endpoint assessment tools; and an initiative, styled as “Advancing Development of Drugs for Rare Diseases,” that recognizes the growing importance of orphan drugs. See id. at 2.

II. MEDICAL DEVICE USER FEE AMENDMENTS OF 2012

The Medical Device User Fee Act (“MDUFA”) is intended to supplement FDA’s funding dedicated to device regulation, with a view toward enabling the Agency to increase the speed and efficiency of its new device review, as well as improve its ability to ensure the safety and effectiveness of devices. MDUFA was first enacted in 2002, and was reauthorized in 2007 for FYs 2008-2012.⁵ In addition to modifying the amounts of baseline fees and directing FDA to make specific yearly adjustments to those amounts, MDUFA III broadens the scope of establishments subject to registration fees.

A. Significant Changes to MDUFA

Expansion of Registration Fees. Prior to enactment of FDASIA, three limited categories of establishments were subject to registration fees: (1) manufacturers; (2) single-use device reproducers; and (3) specifications developers. See FDC Act § 737(13)(A)-(C) (2011). Under MDUFA III, any establishment that is “engaged in the manufacture, preparation, propagation, compounding, or processing of a device” is subject to a registration fee. See id. § 737(13), as amended by FDASIA § 202(3). It is estimated that this change will increase the number of fee-paying establishments from 16,000 to 22,000.

Baseline User Fees and Adjustment. FDASIA gradually increases baseline Medical Device Fees for FYs 2013-2017. See id. § 738(b), as amended by FDASIA § 203(b). The fee for a Premarket Approval Application (“PMA”) in FY 2013 will be \$248,000, increasing to \$268,443 by FY 2017. See id. The fee for 510(k) applications will increase apace: MDUFA III sets 510(k) fee amounts at 2% of PMA fees for each FY from 2013 to 2017. See id. § 738(b), as amended by FDASIA § 203(a)(2)(B). Finally, establishment registration fees will increase to \$2,575 in FY 2013, and to \$3,872 by FY 2017. See id. § 738(b), as amended by FDASIA § 203(b). These increased fees are expected to produce an estimated \$595 million in industry payments during MDUFA III.

MDUFA III also includes a provision permitting FDA to waive medical device fees, or reduce applicable fees, if it is in the interest of public health. The sum of all fee waivers and reductions granted in any FY is limited 2% or less of the total fee revenue amounts established by FDASIA § 203(b). See id. § 738(f), as added by FDASIA § 203(d)(2). This waiver and reduction authority expires on October 1, 2017.

⁵ Medical Device User Fee and Modernization Act (“MDUFMA”), Pub. L. No. 107-250, 116 Stat. 1588 (2002); FDAAA, Pub. L. No. 110-85, Title II, 121 Stat. 823, 842 (2007) (“MDUFA II”).

B. FDA's MDUFA III Performance Goals

Industry has long protested that FDA takes too long to complete its pre-market review of medical devices, particularly in comparison with the device regulatory bodies of other developed countries. Under the MDUFA Performance Goals and Procedures (“MDUFA III Performance Goals”), FDA will steadily increase the percentage of medical device submissions that meet the review time goals for FYs 2013-2017.⁶

For original PMAs, panel-track supplements, and premarket report applications, FDA's goals are as follows:

- Within 15 calendar days, communicate with the applicant regarding whether its application has been accepted for filing review.
- Within 45 days of FDA's receipt of the application, communicate with the applicant regarding the application's filing status, including providing specific reasons for any refusal to file.
- Within 90 calendar days of the filing date of the application, communicate with the applicant through a “Substantive Interaction”⁷ for 65% of submissions received in FY 2013, 75% in FY 2014, 85% in FY 2015, and 95% in FYs 2016-2017.
- Within 180 “FDA Days,”⁸ issue a “MDUFA decision”⁹ for submissions that do not require Advisory Committee input for 70% of submissions received in FY 2013, 80% in FYs 2014 and 2015, and 90% in FYs 2016 and 2017;

⁶ Copies of FDA's MDUFA III Performance Goals transmittal letter to Congress and FDA's MDUFA III Performance Goals will be posted on FDA's website. The current version of the MDUFA III Performance Goals is available at <http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/ucm295454.pdf>.

⁷ A “Substantive Interaction” can be any form of communication through which FDA requests additional information, a major deficiency letter that notifies the applicant of substantive deficiencies in its application, or a communication stating that FDA has not identified any deficiencies.

⁸ “FDA Days” are calendar days when a submission is considered to be under review at the agencies (*i.e.*, the submission has been accepted or filed). FDA Days begin on either the date of receipt of the submission, or the date of receipt of the amendment or resubmission that permits the submission to be accepted or filed.

⁹ A “MDUFA decision” is a final decision on the application. For original PMAs, these can be decisions that the application is approved, approvable, approvable pending GMP

- Within 320 FDA Days, issue a MDUFA decision for submissions that require Advisory Committee input for 50% of submissions received in FY 2013, 70% in FY 2014, 80% in FYs 2015 and 2016, and 90% in FY 2017.

MDUFA III Performance Goals at 6-7.

With regard to 180-day PMA supplements, FDA's goal is to communicate with applicants through a Substantive Interaction within 90 calendar days of FDA's receipt of the submission for 65% of submissions received in FY 2013, 75% of those received in FY 2014, 85% in FY 2015, and 95% in FYs 2016 and 2017. See id. at 8. For both 180-day PMA supplements and real-time PMA supplements, FDA will issue a MDUFA decision within 90 FDA Days for 90% of submissions received in FYs 2013 and 2014, and 95% of submissions received in FYs 2015-2017. See id.

FDA has committed to similarly increased percentage compliance with 510(k) MDUFA deadlines. For 510(k)s, FDA's goals are as follows:

- Within 15 calendar days, communicate with the applicant regarding whether the submission has been accepted for review.
- Within 60 calendar days, communicate with the applicant through a Substantive Interaction for 65% of submissions received in FY 2013, 75% of those received in FY 2014, 85% in FY 2015, and 95% in FYs 2016 and 2017.
- Within 90 FDA Days, issue a MDUFA Decision for 91% of submissions received in FY 2013, 93% of submissions received in FY 2014, and 95% of submissions received in FYs 2015-2017.

MDUFA III Performance Goals at 9.

Importantly, the MDUFA III Performance Goals also state that, when FDA first requests more information or issues either a deficiency letter or telephone/email hold, those communications will be based on a review of the entire application or submission,

inspection, not approvable, withdrawn, or denied. For 180-day PMA supplements or real-time PMA supplements, a MDUFA decision can be that the application is approved, approvable, or not approvable. For 510(k)s, which are discussed below, the MDUFA decision can be that the product is substantially equivalent, or not substantially equivalent.

and will include all deficiencies. See id. Any subsequent requests or deficiency communications should be based on information submitted by the applicant in its response to the first communication, unless FDA determines that the initial deficiencies identified are inadequate to address important and materially relevant new issues. See id. When FDA fails to meet its performance goals, the Agency will provide feedback to applicants on outstanding issues with the application or submission, to be discussed in a meeting or teleconference. See id.

III. GENERIC DRUG USER FEE AMENDMENTS OF 2012

After many years of discussing the establishment of a generic drug user fee system – and some failed attempts along the way – FDA and the generic drug industry finally reached an historic agreement that brings ANDA sponsors and manufacturers of generic drugs within the broader user fee system first established for NDA sponsors under PDUFA in 1992. Of the various “UFAs” (User Fee Acts) enacted as part of FDASIA, the Generic Drug User Fee Amendments of 2012 (“GDUFA”) will likely have the most immediate and wide-ranging effects (both on industry and on FDA, and on FDA’s Office of Generic Drugs in particular). The intent of GDUFA, like other user fee statutes, is to provide FDA with funding supplemental to the traditional funds Congress appropriates to FDA each year with the expectation that FDA will significantly enhance the approval process.

A. User Fee Types

GDUFA establishes four types of user fees that together will generate \$299 million in funding for FDA in FY 2013, and adjusted annually thereafter. See FDC Act § 744B(b), as added by FDASIA § 302.

Application fees, which account for 30% of total user fee revenue each FY, include an original ANDA fee and a Prior Approval Supplement (“PAS”) fee, which is one half of the ANDA fee, and a Type II Drug Master File (“DMF”) “first reference fee.” See id. § 744B(a)(2)-(3), as added by FDASIA § 302. Both the original ANDA fee and the PAS fee together account for 24% of the total revenue amount. See id. § 744B(b)(2)(B), as added by FDASIA § 302. The Type II DMF fee accounts for 6% of total revenue amount. See id. § 744B(b)(2)(A), as added by FDASIA § 302.

The Type II DMF fee must be paid by each person that owns a Type II Active Pharmaceutical Ingredient (“API”) DMF “that is referenced on or after October 1, 2012, in a generic drug submission by any initial letter of authorization” See id.

§ 744B(a)(2)(A), as added by FDASIA § 302.¹⁰ The Type II DMF fee is a one-time fee, such that “[i]f a person has paid a [Type II DMF fee], the person shall not be required to pay a subsequent [DMF] fee when that Type II [API DMF] is subsequently referenced in generic drug submissions.” Id. § 744B(a)(2)(B), as added by FDASIA § 302. For FY 2013, FDA must publish notice of the fee amount not later than October 31, 2012. See FDC Act § 744B(a)(2)(C)(i), as added by FDASIA § 302. In subsequent FYs, FDA must publish notice of the fee amount not later than 60 days before the start of the FY. See id. § 744B(a)(2)(C)(ii), as added by FDASIA § 302. Subject to certain limitations, the Type II DMF fee must be paid no later than the date on which the first ANDA is submitted that references the associated Type II DMF. See id. § 744B(a)(2)(E), as added by FDASIA § 302.

In order for an ANDA sponsor to reference a Type II DMF in its application, the DMF must be deemed “available for reference” by FDA. Id. § 744B(a)(2)(D)(i), as added by FDASIA § 302. A Type II DMF is deemed “available for reference” if the fee has been paid within 20 calendar days of the applicable due date and “has not failed an initial completeness assessment” performed by FDA. Id. § 744B(a)(2)(D)(ii), as added by FDASIA § 302. FDA will make publicly available a list of DMFs that have successfully undergone an initial completeness assessment, as well as the criteria for making such an assessment. See id. § 744B(a)(2)(D)(iii), as added by FDASIA § 302. If an ANDA or supplement references a Type II DMF for which the fee has not been paid, FDA will notify the sponsor. See id. § 744B(g)(2)(C)(i), as added by FDASIA § 302. If the fee is not paid within 20 calendar days following such notice, FDA will not receive the ANDA or supplement. See id. § 744B(g)(2)(C)(ii), as added by FDASIA § 302.

Each ANDA or PAS submitted to FDA on or after October 1, 2012 will be subject to an application fee. For FY 2013, FDA must establish the fee by October 31, 2012. See FDC Act § 744B(a)(3)(A), as added by FDASIA § 302. In subsequent FYs, the fee must be established not later than 60 days before the start of the FY. See FDC Act § 744B(a)(3)(B), as added by FDASIA § 302. Except for FY 2013, payment of the fee is due upon submission of the ANDA or PAS. See id. § 744B(a)(3)(C)(i), as added by

¹⁰ The term “generic drug submission” is defined to mean “an [ANDA], an amendment to an [ANDA], or a [PAS] to an [ANDA].” FDC Act § 744A(7), as added by FDASIA § 302. An ANDA is defined to mean “an application submitted under section 505(j), an [ANDA] submitted under section 507 (as in effect on the day before the date of enactment of [FDAMA on November 21, 1997]), or an [ANDA] submitted pursuant to regulations in effect prior to the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984” (i.e., the Hatch-Waxman Amendments). Id. § 744A(1), as added by FDASIA § 302. The term does not include an application for a Positron Emission Tomography (“PET”) drug. See id. PET drugs are exempt from all GDUFA user fees.

FDASIA § 302. For FY 2013, the application fee is due by the *later of* ANDA or PAS submission, 30 calendar days after FDA publishes notice of the FY 2013 fee amount, or 30 calendar days after an appropriations Act is enacted providing for the collection and obligation of GDUFA user fees. See id. § 744B(a)(3)(C)(ii), as added by FDASIA § 302.

FDA must refund 75% of the application or PAS fee if the submission is not received by the Agency within the meaning of FDC Act § 505(j)(5)(A), and if the reason for FDA's refuse-to-file decision is based on something other than failure to pay user fees. See FDC Act § 744B(a)(3)(D), as added by FDASIA § 302. An ANDA or PAS submitted to FDA but not received or withdrawn must pay a new fee upon resubmission. See id. § 744B(a)(3)(E), as added by FDASIA § 302. An application containing information concerning the manufacture of an API at a facility by means other than reference to a Type II DMF, must pay, in addition to an application fee, a special "API fee" to be determined by FDA if "a fee in the amount equal to the [Type II DMF] fee . . . has not been previously paid with respect to such information." See id. § 744B(a)(3)(F), as added by FDASIA § 302.

GDUFA also establishes one-time ANDA backlog fee that will be assessed in FY 2013 for ANDAs pending on October 1, 2012. See id. § 744B(a)(1), as added by FDASIA § 302. An ANDA that is "pending" on October 1, 2012, is an application "that has not received a tentative approval prior to that date." FDC Act § 744B(a)(1)(A), as added by FDASIA § 302. That fee will be calculated by dividing \$50 million by the number of ANDAs in the backlog. See id. § 744B(a)(1)(B), as added by FDASIA § 302. The number of ANDAs in the backlog on October 1, 2012 may increase or decrease from the current backlog number as companies decide whether or not to withdraw pending applications.¹¹ FDA must publish notice of the fee amount not later than October 31, 2012, and payment is due not later than 30 days after such notice is published. See id. § 744B(a)(1)(C)-(D), as added by FDASIA § 302.

An annual facility fee, which accounts for 70% of total fee revenue each FY, must be paid by both Finished Dosage Form ("FDF") and API manufacturers. Specifically, the fee must be paid by each person that owns a facility "identified, or intended to be identified, in at least one generic drug submission that is pending or approved to produce a [FDF] of a human generic drug or an [API] contained in a human generic drug." FDC Act § 744B(a)(4)(A), as added by FDASIA § 302. FDF facility fees account for 80% of facility fee revenue (56% of the total revenue amount), and API facilities account for

¹¹ FDA has already begun the process of determining what ANDAs will be included in the backlog. In a June 2012 notice, FDA announced the Agency's intention to deem to be withdrawn certain incomplete ANDAs as to which the applicant has not communicated with FDA since July 8, 1991. See 77 Fed. Reg. 35,691 (June 14, 2012).

20% of facility fee revenue (14% of the total revenue amount). See id. § 744B(b)(2)(C)-(D), as added by FDASIA § 302. There is a fee differential of not less than \$15,000 and not more than \$30,000 for foreign FDF and API facilities, which is intended to reflect the added costs of foreign inspections conducted by FDA. See id. Facilities that produce both FDF and API must pay two annual facility fees – one with respect to FDF manufacturing and another with respect to API manufacturing. See FDC Act § 744B(a)(4)(A)(iii), as added by FDASIA § 302.

For purposes of determining the annual facility fee amounts, FDA must, not later than October 1, 2012, publish notice requiring the submission of certain information by certain facilities, sites, and organizations. See FDC Act § 744B(f)(1), as added by FDASIA § 302. For FY 2013, such information must be submitted to FDA not later than 60 days after publication of the aforementioned notice. See id. § 744B(f)(2)(A), as added by FDASIA § 302. In subsequent FYs, such information must “be submitted, updated, or reconfirmed on or before June 1 of the previous year.” Id. § 744B(f)(2)(B), as added by FDASIA § 302. FDA must set and publish notice of the FY 2013 facility fee amounts not later than 45 days after receiving facility information. See id. § 744B(f)(2)(B), as added by FDASIA § 302. In subsequent FYs, FDA must establish the facility fee amounts not more than 60 days before the start of the FY. See id. § 744B(d)(2), as added by FDASIA § 302. Payment of the facility fee for FY 2013 is due on the *later of*: (1) not later than 45 days after FDA announces the user fee amounts; or (2) 30 days after the date on which an appropriations Act is enacted providing for the collection and obligation of GDUFA user fees. See id. § 744B(a)(4)(D)(i), as added by FDASIA § 302. In subsequent FYs, payment of the facility fee is due on the *later of* the beginning of the FY (*i.e.*, the first business day on or after October 1st) or the first business day after the date on which an appropriations Act is enacted providing for the collection and obligation of GDUFA user fees. See id. § 744B(a)(4)(D)(ii), as added by FDASIA § 302.

If a company or manufacturer believes it paid a fee to FDA in error, it must submit “a written request justifying such return within 180 calendar days after such fee was paid.” See id. § 744B(m), as added by FDASIA § 302. Unlike PDUFA, GDUFA does not provide FDA with the authority to waive user fees. The only class-wide statutory exemption from GDUFA user fees is for PET drugs. See supra note 10.

B. Failure to Pay User Fees

Failure to pay the ANDA backlog fee will result in placing the ANDA sponsor on an arrears list, “such that no new [ANDAs] or supplement submitted on or after October 1, 2012, from that person, or any affiliate of that person, will be received within the meaning of [FDC Act § 505(j)(5)(A)] until such outstanding fee is paid.” FDC Act § 744B(g)(1), as added by FDASIA § 302.

Failure to pay the Type II DMF fee within 20 calendar days of the due date will “result in the Type II [API DMF] not being deemed available for reference.” An affected ANDA “shall not be received within the meaning of [FDC Act § 505(j)(5)(A)]” unless the fee “has been paid within 20 calendar days of the Secretary providing the notification to the sponsor of the [ANDA] or supplement of the failure of the owner of the Type II [API DMF] to pay the [DMF] fee” Id. § 744B(g)(2), as added by FDASIA § 302.

Failure to pay the required application fee within 20 calendar days of the due date will result in the application not being received by FDA until the fee is paid. See id. § 744B(g)(3), as added by FDASIA § 302.

ANDA receipt date is particularly important when 180-day generic drug exclusivity is at stake. This fact is recognized in the new statute, which states:

An [ANDA] that is not considered to be received within the meaning of [FDC Act § 505(j)(5)(A)] because of failure to pay an applicable fee under this provision within the time period specified in [FDC Act § 744B(g)] shall be deemed not to have been “substantially complete” on the date of its submission within the meaning of section 505(j)(5)(B)(iv)(II)(cc). An [ANDA] that is not substantially complete on the date of its submission solely because of failure to pay an applicable fee under the preceding sentence shall be deemed substantially complete and received within the meaning of section 505(j)(5)(A) as of the date such applicable fee is received.

FDC Act § 744B(n), as added by FDASIA § 302.

Failure to pay a facility fee within 20 calendar days of the due date will result in the following consequences:

- (1) identification of the facility on a “publicly available arrears list, such that no new [ANDA] or supplement submitted on or after October 1, 2012, from [that] person that is responsible for paying such fee, or any affiliate of that person, will be received within the meaning of [FDC Act § 505(j)(5)(A)];”
- (2) “[a]ny new generic drug submission submitted on or after October 1, 2012, that references such a facility shall not be received, within the meaning of section [FDC Act § 505(j)(5)(A)] if the outstanding facility fee is not paid within 20 calendar days of the Secretary providing the notification to the

sponsor of the failure of the owner of the facility to pay the facility fee under [FDC Act § 744B(a)(4)(C);” and

(3) “[a]ll drugs or [APIs] manufactured in such a facility or containing an ingredient manufactured in such a facility being deemed misbranded under [FDC Act § 502(aa)].”

FDC Act § 744B(g)(4)(A), as added by FDASIA § 302.¹² Moreover, “[t]he penalties under [FDC Act § 744B(g)(4)] shall apply until the [facility] fee . . . is paid or the facility is removed from all generic drug submissions that refer to the facility.” *Id.* at § FDC Act § 744B(g)(4)(B), as added by FDASIA § 302. The misbranding provision, which was a point of controversy during GDUFA negotiations, appears to be intended to add some teeth to the user fee statute.

C. FDA’s GDUFA Performance Goals

The GDUFA Program Performance Goals and Procedures (“GDUFA Performance Goals”),¹³ which are based on certain assumptions and aspirations, contain detailed information on the ANDA review and action goals FDA agreed to meet, as well as a host of new FDA procedures and processes. Below are some of the highlights.

Application Metrics. GDUFA is structured based on five cohorts of submission dates for original electronic ANDAs, which correspond to the five FYs covered under GDUFA. For ANDAs in the year 1 and 2 cohorts (*i.e.*, FYs 2013 and 2014), FDA did not agree to any specific metrics; however, FDA agreed to “expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted” so as to avoid the possible forfeiture of 180-day exclusivity for failure to obtain timely tentative approval. GDUFA Performance Goals at

¹² New FDC Act § 502(aa) states that a drug shall be deemed to be misbranded:

[i] If it is a drug, or an [API], and it was manufactured, prepared, propagated, compounded, or processed in a facility for which fees have not been paid as required by [FDC Act § 744A(a)(4)] or for which identifying information required by [FDC Act § 744B(f)] has not been submitted, or it contains an [API] that was manufactured, prepared, propagated, compounded, or processed in such a facility.

FDC Act § 502(aa), as added by FDASIA § 306.

¹³ Copies of FDA’s GDUFA Performance Goals transmittal letter to Congress and FDA’s GDUFA Performance Goals will be posted on FDA’s website. The current version of the GDUFA Performance Goals is available at <http://www.fda.gov/downloads/ForIndustry/Userfees/GenericDrugUserFees/ucm282505.pdf>.

6. For ANDAs in the year 3 cohort (i.e., FY 2015), FDA will review and act on 60% of submissions within 15 months from the date of submission. See id. At 9. For ANDAs in the year 4 (i.e., FY 2016) and year 5 (i.e., FY 2017) cohorts, FDA will review and act on 75% of submissions within 15 months from the date of submission, and 90% of submissions within 10 months from the date of submission, respectively. See id. Amendments to pending original ANDAs adjust the goal date for an original ANDA. See id. Amendments, which are grouped as Tier 1, Tier 2, or Tier 3 amendments depending on number and their status as solicited or unsolicited and major or minor, have their own complex action goal calculus. See id. At 10-12.

Backlog Metrics. FDA agreed to review and act on 90% of all ANDAs, ANDA amendments and ANDA PASs by the end of FY 2017, regardless of current review status (whether electronic, paper, or hybrid) pending on October 1, 2012. GDUFA Performance Goals at 5.

Current Good Manufacturing Practice (“CGMP”) Inspection Metrics. FDA agreed to conduct “risk-adjusted biennial CGMP surveillance inspections of generic API and generic [FDF] manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017.” Id. Domestic and foreign facility parity was an important concept during GDUFA negotiations. As noted in GDUFA meeting minutes, “[t]he program’s goals of ensuring FDA has necessary resources to conduct needed inspections as part of the complete review framework and achieve parity of GMP inspections for foreign and domestic facilities by the 5th year of the user fee program will [] provide significant value to industry participants given that outstanding inspections can result in delays of ANDA approvals.” GDUFA Negotiations Meeting Minutes at 3 (Aug. 31, 2011).

Efficiency Enhancements. FDA agreed to implement various efficiency enhancements including: (1) use of complete review/response letters for ANDAs and DMFs; (2) a DMF completeness assessment (at least for DMFs intending to be referenced by ANDA sponsors); (3) division level deficiency review for ANDAs and DMFs; (4) rolling review of ANDAs and DMFs; and (5) first cycle deficiency meetings for ANDAs and DMF. GDUFA Performance Goals at 6-9.

Regulatory Science. FDA also agreed to “undertake various initiatives designed to enhance post-market safety, to develop guidance to industry, and to mitigate regulatory science gaps in select generic regulatory pathways.” GDUFA Negotiations Meeting Minutes at 4 (Aug. 31, 2011). The initiatives cover myriad topics, including bioequivalence of local acting orally inhaled drug products, pharmacokinetic studies and evaluation of anti-epileptic drugs, and evaluation of drug product physical attributes on

patient acceptability (e.g., tablet size, shape, coating, and scoring configuration). See GDUFA Performance Goals at 18-19.

IV. BIOSIMILAR USER FEE ACT OF 2012

The Biosimilar User Fee Act of 2012 (“BsUFA”) is the second new UFA included in FDASIA, and like the other UFAs, is in effect from FYs 2013 through 2017. See FDASIA § 404(a). BsUFA brings to fruition the development of a user fee system envisioned by the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”), which was enacted on March 23, 2010 as Title VII, Subtitle A of the Patient Protection and Affordable Care Act, Pub. L. No. 111-148 §§ 7001-03, 124 Stat. 119 (2010). Among other things, the BPCIA amended the PHS Act to create a new pathway under § 351(k) for the licensure of applications for biological products shown to be “biosimilar” to or “interchangeable” with a “reference product” licensed under PHS Act § 351(a).¹⁴ BPCIA § 7002(f) required FDA to “develop recommendations to present to Congress with respect to the goals, and plans for meeting the goals, for the process for the review of biosimilar biological product applications submitted under [PHS Act § 351(k)] for the first 5 fiscal years” beginning in FY 2013, and expressed the sense of the U.S. Senate that based on those recommendations, “Congress should authorize a program, effective on October 1, 2012, for the collection of user fees” for biosimilar applications. BPCIA § 7002(f)(A), (C).

A. User Fee Types

BsUFA establishes four general types of biosimilars user fees. Three of the fees – the one-time application fee, and the annual product and establishment fees – are familiar to the regulated industry and would be set equal to the rates established under PDUFA for a particular FY. See FDC Act § 744H(b)(1)(D)-(F), as added by FDASIA § 402. The new user fee that sets BsUFA apart from PDUFA is the Biosimilar Biological Product Development (“BPD”) fee for products in development. As discussed below, the BPD fee is structured in such a manner as to generate user fee revenue to FDA in the near-term

¹⁴ Under the PHS Act, a biosimilar product is defined to mean a biological product that is both “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and for which “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” PHS Act § 351(i)(2). An interchangeable product is defined to mean a biological product that “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.” Id. § 351(i)(3).

and to enable § 351(k) sponsors to have meetings with FDA early in the development of biosimilar product candidates.

Biosimilar Biological Product Development Fee. BsUFA states that each person that submits to FDA either a request for a “biosimilar biological product development meeting”¹⁵ for a product, or a “clinical protocol” consistent FDC Act § 505(i) and FDA’s IND regulations describing an investigation that FDA determines is intended to support a “biosimilar biological product application”¹⁶ for a product, must pay an initial BPD fee. *Id.* § 744H(a)(1)(A), as added by FDASIA § 402. The amount of that fee is equal to 10% of the application fee FDA establishes under PDUFA for the FY in which the biosimilar submission is made to FDA. *Id.* § 744H(b)(1)(A), as added by FDASIA § 402. The initial BDP fee is due upon the *earlier of* the date of submission of an IND “describing an investigation that [FDA] determines is intended to support a biosimilar biological product application,” or not later than 5 days after FDA grants a request for a “biosimilar biological product development meeting.” *Id.* § 744H(a)(1)(A)(iv), as added by FDASIA § 402.

BsUFA also includes a “transition rule” for companies that submitted an IND to FDA prior to the July 9, 2012 enactment of FDASIA. For pre-BsUFA INDs, the initial BBPD fee must be paid by the *earlier of* the following: (1) not later than September 7,

¹⁵ The term “biosimilar biological product development meeting” is defined to mean “any meeting, other than a biosimilar initial advisory meeting, regarding the content of a development program, including a proposed design for, or data from, a study intended to support a biosimilar biological product application.” FDC Act § 744G(5), as added by FDASIA § 402. A “biosimilar initial advisory meeting” is defined as a meeting that is limited to: “(i) a general discussion regarding whether licensure under [PHS Act § 351(k)] may be feasible for a particular product; and (ii) if so, general advice on the expected content of the development program.” FDC Act § 744G(8), as added by FDASIA § 402. Such a meeting “does not include any meeting that involves substantive review of summary data or full study reports.” *Id.*

¹⁶ The term “biosimilar biological product application” is defined to mean “an application for licensure of a biological product under [PHS Act § 351(k)].” FDC Act § 744G(4)(A), as added by FDASIA § 402. The terms does not include “a supplement to such an application,” “an application filed under [PHS Act § 351(k)] that cites as the reference product a bovine blood product for topical application licensed before September 1, 1992, or a large volume parenteral drug product approved before such date,” “an application filed under [PHS Act § 351(k)] with respect to – (I) whole blood or a blood component for transfusion; (II) an allergenic extract product; (III) an in vitro diagnostic biological product; or (IV) a biological product for further manufacturing use only,” or “an application for licensure under [PHS Act § 351(k)] that is submitted by a State or Federal Government entity for a product that is not distributed commercially.” FDC Act § 744G(4)(B), as added by FDASIA § 402.

2012, if FDA determines that the IND “describes an investigation that is intended to support a biosimilar biological product application;” or (2) not later than 5 days after FDA grants a request for a “biosimilar biological product development meeting.” FDC Act § 744H(a)(1)(A)(v), as added by FDASIA § 402.

After paying the initial BDP fee, sponsors must pay an annual BPD fee “beginning in the fiscal year following the fiscal year in which the initial biosimilar [BPD] fee was paid.” Id. § 744H(a)(1)(B)(i), as added by FDASIA § 402. The amount of the annual BDP fee is equal to 10% of the application fee FDA establishes under PDUFA for that particular FY. Id. § 744H(b)(1)(B), as added by FDASIA § 402. Payment of the annual BPD fee is due on the later of: (1) the first business day on or after October 1st of each year; or (2) “the first business day after the enactment of an appropriations Act providing for the collection and obligation of fees for such year under [PHS Act § 744H].” Id. § 744H(a)(1)(B)(ii), as added by FDASIA § 402. The user fee payment obligation would continue until the sponsor submits a § 351(k) application that is accepted for filing, or until the sponsor discontinues participation in the BPD program for the product either by providing FDA with a timely written declaration, or by withdrawing the relevant IND. See id. §§ 744H(a)(1)(B)(iii), 744H(a)(1)(C), as added by FDASIA § 402.

A biosimilar sponsor who has discontinued participation in the BPD program for a particular product, but who decides to reengage FDA on the product, must pay a “reactivation fee” equal to 20% of the application fee FDA establishes under PDUFA for that particular FY. See FDC Act §§ 744H(a)(1)(D)(i), 744H(b)(1)(C), as added by FDASIA § 402. Payment of the reactivation fee is due by the *earlier of* the following: (1) not later than 5 days after FDA “grants a request for a biosimilar biological product development meeting for the product (after the date on which such participation was discontinued),” or (2) on the date of submission of an IND “(after the date on which such participation was discontinued)” describing an investigation for that product that FDA determines is intended to support a biosimilar biological product application. Id. § 744H(a)(1)(D)(i)(I)-(II), as added by FDASIA § 402. For purposes of strategically timing any reactivation, sponsors should be aware that “[a] person that pays a reactivation fee for a product shall pay for such product, beginning in the next fiscal year, the annual [BPD] fee” Id. § 744H(a)(1)(D)(ii), as added by FDASIA § 402.

Failure to pay the any of the BPD fees (*i.e.*, initial, annual, or reactivation) has several consequences. First, FDA must refuse to grant a biosimilar biological product development meeting relating to the biosimilar biological product for which the fees are owed. See FDC Act § 744H(a)(1)(E)(i), as added by FDASIA § 402. Second, if a sponsor that owes a BPD fee submits an IND to FDA that the Agency determines is intended to support a biosimilar biological product application, FDA cannot, except in extraordinary circumstances, consider the sponsor’s IND to have been received under

FDC Act § 505(i)(2). See id. § 744H(a)(1)(E)(ii), as added by FDASIA § 402. Third, for a sponsor with an existing IND, FDA must, except in extraordinary circumstances, impose a “financial hold” prohibiting the sponsor from continuing the investigation. See id. § 744H(a)(1)(E)(iii), as added by FDASIA § 402. Fourth, if a sponsor has failed to pay any required BPD fee, then “any biosimilar biological product application or supplement submitted by that person shall be considered incomplete and shall not be accepted for filing by the Secretary until all such fees owed by such person have been paid.” Id. § 744H(a)(1)(E)(iv), as added by FDASIA § 402.

Application, Supplement, Establishment, and Product Fees. Each person that submits a § 351(k) application or “supplement”¹⁷ for a biosimilar product on or after October 1, 2012 is subject to a one-time application fee. A full fee equal to the application fee FDA establishes under PDUFA for that particular FY, minus the cumulative BBPD fees previously paid by the sponsor, is due upon the submission of “a biosimilar biological product application for which clinical data (other than comparative bioavailability studies) with respect to safety or effectiveness are required for approval.” FDC Act §§ 744H(a)(2)(A)(i), 744H(b)(1)(D), as added by FDASIA § 402. A fee that is one half of the application fee FDA establishes under PDUFA for that particular FY, minus the cumulative BBPD fees previously paid by the sponsor, is due upon the submission of “a biosimilar biological product application for which clinical data (other than comparative bioavailability studies) with respect to safety or effectiveness are not required.” Id. § 744H(a)(2)(A)(ii), as added by FDASIA § 402. A half fee is also due upon the submission of “a supplement for which clinical data (other than comparative bioavailability studies) with respect to safety or effectiveness are required.” Id. § 744H(a)(2)(A)(iii), as added by FDASIA § 402. As opposed to the full and half fees applicable to biosimilar biological product applications, the supplement fee does not take into consideration previously paid BPD fees.

Similar to PDUFA, BsUFA includes provisions concerning previously filed applications and supplements and withdrawn applications. Specifically, if a biological product application or supplement was submitted by a person that paid the applicable fee, and the application or supplement was accepted for filing but was not approved or was withdrawn (without a waiver), then “the submission of a biosimilar biological product application or a supplement for the same product by the same person (or the person’s licensee, assignee, or successor) shall not be subject to” an application or supplement fee. FDC Act § 744H(a)(2)(D), as added by FDASIA § 402. In addition, FDA must refund

¹⁷ The term “supplement” is defined to mean a request to FDA “to approve a change in a biosimilar biological product application which has been approved, including a supplement requesting that the Secretary determine that the biosimilar biological product meets the standards for interchangeability described in [PHS Act § 351(k)(4)].” FDC Act § 744G(14), as added by FDASIA § 402.

75% of the application or supplement fee paid “for any application or supplement which is refused for filing or withdrawn without a waiver before filing.” Id. § 744H(a)(2)(E), as added by FDASIA § 402. Finally, “[a] biosimilar biological product application or supplement that was submitted but was refused for filing, or was withdrawn before being accepted or refused for filing” is subject to a full application or supplement fee upon resubmission or filing over protest, unless the fee is otherwise waived. Id. § 744H(a)(2)(F), as added by FDASIA § 402.

An establishment fee equal to the establishment fee FDA sets under PDUFA for that particular FY is due by the later of the first business day after October 1st of each FY, or the first business day after an applicable appropriations Act is enacted, “for each biosimilar biological product establishment that is listed in the approved biosimilar biological product application as an establishment that manufactures the biosimilar biological product named in such application.” FDC Act §§ 744H(a)(3)(A), (C), 744H(b)(1)(E), as added by FDASIA § 402. The annual establishment fee is assessed in each FY for which the biosimilar biological product named in the § 351(k) application is assessed a biosimilar product fee, “unless the biosimilar biological product establishment listed in the application does not engage in the manufacture of the biosimilar biological product during such fiscal year.” FDC Act § 744H(a)(3)(B), as added by FDASIA § 402.

A single establishment fee is assessed per “biosimilar biological product establishment,” which is defined in the law to mean “a foreign or domestic place of business – (i) that is at one general physical location consisting of one or more buildings, all of which are within 5 miles of each other; and (ii) at which one or more biosimilar biological products are manufactured in final dosage form.” Id. § 744G(7), as added by FDASIA § 402. If an establishment is listed in a § 351(k) application by more than one applicant, then the single establishment fee is “divided equally and assessed among the applicants whose biosimilar biological products are manufactured by the establishment during the fiscal year and assessed biosimilar biological product fees” Id. § 744H(a)(3)(D), as added by FDASIA § 402. The establishment fee is not reapportioned based on events that occur during a FY after the fee has been paid. See id. § 744H(a)(3)(E), as added by FDASIA § 402.

A product fee equal to the product fee FDA establishes under PDUFA for that particular FY must be paid for each “biosimilar biological product” (*i.e.*, a product for which a § 351(k) application has been approved). See FDC Act §§ 744H(a)(4)(A), (b)(1)(F), as added by FDASIA § 402. The fee is due by the later of the first business day after October 1st of each FY, or the first business day after an applicable appropriations Act is enacted. See id. § 744H(a)(4)(B), as added by FDASIA § 402.

BsUFA provides for only a single basis on which to seek a user fee waiver. Specifically, FDA must waive the application fee “for the first biosimilar biological product application that a small business or its affiliate submits to the Secretary for review.” FDC Act § 744H(c)(1), as added by FDASIA § 402.¹⁸ In determining whether or not to grant a small business application fee waiver, FDA “shall consider only the circumstances and assets of the applicant involved and any affiliate of the applicant.” *Id.* § 744H(c)(2), as added by FDASIA § 402.

Small business waiver requests (and any application fee refund requests) must be submitted to FDA in writing not later than 180 days after the fee is due. *See id.* § 744H(g), as added by FDASIA § 402. In addition, failure to pay any BsUFA user fees will result in FDA determining that a § 351(k) application or supplement is “considered incomplete and shall not be accepted for filing by [FDA] until all fees owed by such person have been paid.” *Id.* § 744H(d), as added by FDASIA § 402.

B. FDA’s BsUFA Performance Goals

The Biosimilar Biological Product Authorization Performance Goals and Procedures FYs 2013-2017 (“BsUFA Performance Goals”) FDA and industry agreed to cover a number of items, including § 351(k) application and supplement review performance goals, first cycle performance goals, proprietary name review, major dispute resolution, clinical holds, special protocol assessments, and meeting management goals. We highlight a few of those items below.¹⁹

FDA’s BsUFA Performance Goals include goals for biosimilar biological product application submissions and resubmissions, supplements with clinical data, and original manufacturing supplements. As with the initial iteration of PDUFA, FDA takes a step-wise approach over the first few FYs to reach a goal of 90% for original and resubmitted § 351(k) applications. This is depicted in the table below.

¹⁸ A “small business” is defined in the law to mean “an entity that has fewer than 500 employees, including employees of affiliates, and does not have a drug product that has been approved under a human drug application (as defined in section 735) or a biosimilar biological product application (as defined in section 744G(4)) and introduced or delivered for introduction into interstate commerce.” *Id.* § 744H(c)(3), as added by FDASIA § 402.

¹⁹ Copies of FDA’s BsUFA Performance Goals transmittal letter to Congress and FDA’s BsUFA Performance Goals will be posted on FDA’s website. The current version of the BsUFA Performance Goals is available at <http://www.fda.gov/downloads/DevelopmentApprovalProcess/HowDrugsAreDeveloped/Approved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm281991.pdf>.

Table 2: Performance Goals for Original and Resubmitted Applications and Supplements

SUBMISSION COHORT	PERFORMANCE GOAL				
	2013	2014	2015	2016	2017
Original Biosimilar Biological Product Application Submissions	70% in 10 months of the receipt date	70% in 10 months of the receipt date	80% in 10 months of the receipt date	85% in 10 months of the receipt date	90% in 10 months of the receipt date
Resubmitted Original Biosimilar Biological Product Applications	70% in 6 months of the receipt date	70% in 6 months of the receipt date	80% in 6 months of the receipt date	85% in 6 months of the receipt date	90% in 6 months of the receipt date

Original Supplements with Clinical Data	90% in 10 months of the receipt date
Resubmitted Supplements with Clinical Data	90% in 6 months of the receipt date
Manufacturing Supplements	90% in 6 months of the receipt date

With respect to first-cycle review performance goals, FDA agreed to report, within 74 calendar days from the date of the Agency’s receipt of original biosimilar biological product applications and supplements with clinical data, substantive review issues identified during the initial filing review to the applicant for 90% of applications. See BsUFA Performance Goals at 5. FDA will also inform the applicant of the planned timeline for review of the application or supplement with clinical data. See id.

Added to FDA’s meeting lexicon are 5 types of meetings related to a sponsor’s biosimilar biological product development program:

- (1) Biosimilar Initial Advisory Meeting – This is an initial assessment meeting limited to a general discussion regarding the feasibility of licensure under PHS Act § 351(k), and general advice on the expected content of the development program if the § 351(k) route is feasible.

- (2) BPD Type 1 Meeting – Similar to a Type A meeting under PDUFA, this is “a meeting which is necessary for an otherwise stalled drug development program to proceed (e.g. meeting to discuss clinical holds, dispute resolution meeting), a special protocol assessment meeting, or a meeting to address an important safety issue.” Id. at 14.
- (3) BPD Type 2 Meeting – This is a meeting for the sponsor and FDA to discuss a specific issue, such as a proposed study design or endpoints, or to discuss questions seeking targeted advice from FDA regarding an ongoing development program.
- (4) BPD Type 3 Meeting – This is an in-depth data review and advice meeting that may include “substantive review of full study reports, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding additional studies, including design and analysis.” Id.
- (5) BPD Type 4 Meeting – This is a meeting to discuss the format and content of a § 351(k) application or supplement.

For 90% of meeting requests, FDA will notify the requestor in writing of the date, time, place, and format for the meeting within 14 calendar days of the Agency’s receipt of a request and meeting package for a BPD Type 1 Meeting, or within 21 calendar days of the Agency’s receipt of a request and meeting package from industry for a Biosimilar Initial Advisory Meeting or a BPD Type 2, 3, or 4 Meeting. See id. at 10. FDA’s performance goal for holding each meeting type begins with 70% in FY 2013 and progress to 90% by FY 2017. See id. at 11. “FDA will provide meeting minutes within 30 days of the date of the meeting for 90 percent of Biosimilar Initial Advisory Meetings and BPD Type 1-4 Meetings.” Id.

With respect to proprietary name review, for proprietary names submitted during the BPD phase, FDA agreed to review 90% of proprietary name submissions filed within 180 days of receipt and to notify sponsor of tentative acceptance or non-acceptance of the name. BsUFA Performance Goals at 7. For proprietary names submitted to FDA with a biosimilar biological product application, the Agency agreed to review 90% of submissions filed within 90 days of receipt and to notify sponsor of tentative acceptance or non-acceptance of the name. See id.

“For procedural or scientific matters involving the review of biosimilar biological product applications and supplements . . . that cannot be resolved at the signatory authority level (including a request for reconsideration by the signatory authority after

reviewing any materials that are planned to be forwarded with an appeal to the next level),” FDA agreed to answer 90% of such major dispute resolution requests within 30 calendar days of the Center’s receipt of the written appeal. See id.

With respect to special protocol assessments and agreement requests, FDA agreed to respond to such requests within 45 days with a 70% goal in FY 2013 and that improves to 90% by FY2017. See id. at 9-10. Finally, with respect to a sponsor’s complete response to a clinical hold, FDA agreed to respond to 90% of complete responses within 30 days of the Agency’s receipt of the submission of such sponsor’s response. See id. at 8-9.

V. PEDIATRIC DRUGS AND DEVICES

FDASIA § 501 makes permanent both the Best Pharmaceuticals for Children Act (“BPCA”) and Pediatric Research Equity Act (“PREA”) – the so-called “carrot and stick” approach to pediatric testing – by eliminating the “sunset” provision of the BPCA and a related PREA provision. See FDASIA §§ 501(a)-(b).

Enacted in 1997 as part of FDAMA, the BPCA provides marketing incentives for the conduct of studies of drugs in children. This law provides 6 months of marketing exclusivity in return for conducting pediatric studies, provided that certain conditions are met. When enacted in 1997, the BPCA was originally set to “sunset” after 5 years but it was reauthorized, with some modifications in 2002 (Pub. L. No. 107-109 (115 Stat. 1408) (2002)), and was reauthorized again in 2007 as part of FDAAA.

PREA was originally signed into law on December 3, 2003 (Pub. L. No. 108-155 (117 Stat. 1936) (2003)), and was also reauthorized in 2007 as part of FDAAA. Under PREA, a sponsor is required to conduct pediatric studies for most drug and biological products. Under this law, original NDAs and BLAs (or supplements to such applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration) must contain a “pediatric assessment” unless the applicant has obtained a waiver or deferral. A pediatric assessment is data and information required “to assess the safety and efficacy of the drug or biologic for the claimed indications in all relevant pediatric subpopulations; and 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). PREA also authorized FDA to require holders of applications for previously approved marketed drugs and biological products to submit a pediatric assessment under certain circumstances.

To qualify for pediatric exclusivity under the BPCA, an applicant must have received a “Written Request” for pediatric studies from FDA. See FDC Act § 505A(d). A Written Request describes in detail the pediatric studies needed to qualify for exclusivity and the time frame for their completion. The Written Request may include studies for indications that are not currently in the labeling for the product if FDA determines that such information will benefit the public health. The study reports described in the Written Request must be submitted to FDA after the Agency has issued the request. FDA then reviews the studies to ensure that the studies submitted meet the terms of the Written Request. FDASIA § 502 clarifies that studies conducted under PREA may also be used, at least in part, to qualify for exclusivity pursuant to the BPCA so long as those studies are also described and requested in the Written Request. See FDC Act § 505A(h), as amended by FDASIA § 502(a).

If a Written Request does not include studies in neonates, the BPCA now requires FDA to include in the Written Request “a statement describing the rationale for not requesting studies in neonates.” FDC Act § 505A(d)(1), as amended by FDASIA § 502(b). FDA’s rationale will be subject to public review in most cases because Written Requests are publicly available on FDA’s web site after FDA has made a determination regarding exclusivity. See FDC Act § 505A(e)(1).

The Pediatric Review Committee (“PeRC”) is an internal FDA committee that was established by FDAAA. The PeRC is currently charged with reviewing Written Requests and studies submitted pursuant to a Written Request under the BPCA, as well as pediatric assessments and deferral and waiver requests under the PREA. This internal committee consists of FDA employees “with expertise in pediatrics (including representation from the Office of Pediatric Therapeutics), biopharmacology, statistics, chemistry, legal issues, pediatric ethics, and the appropriate expertise pertaining to the pediatric product under review, such as expertise in child and adolescent psychiatry, and other individuals designated by the Secretary.” FDC Act § 505C. Under FDASIA, the Secretary is required to issue “internal standard operating procedures” providing for PeRC review of any significant modifications made to the PREA pediatric study plans, or to Written Requests issued under the BPCA. These procedures must be issued by July 9, 2013, and be made publicly available on FDA’s web site. See FDASIA § 503.

When PREA and BPCA were reauthorized in 2007 as part of FDAAA, Congress required FDA to make available certain information submitted under these statutes that resulted in labeling changes regarding the use of the product in pediatric populations. This information included the number of studies or assessments conducted, the drugs and the uses studied, the types of studies conducted, and the labeling changes made as a result of such studies. See FDC Act §§ 505A(f)(6), 505B(f)(6). In partial satisfaction of these requirements, FDA has been posting on its web site the medical, statistical, and clinical

pharmacology reviews of Written Requests made since 2007. FDASIA gives FDA 3 years to make public the medical, statistical, and clinical pharmacology reviews of Written Requests made between 2002 and 2007 for which exclusivity was granted and which resulted in a labeling change. See FDASIA § 504.

Under PREA, either FDA or the sponsor can request a deferral of pediatric studies for some or all of the pediatric subpopulations. A deferral is appropriate if FDA finds that the drug or biological product is ready for approval for use in adults before pediatric studies are complete; pediatric studies should be delayed until additional safety or effectiveness data have been collected; or there is another appropriate reason for deferral. See FDC Act § 505B(a)(3)(A)(i). The applicant must submit a certification of the grounds for deferring the assessments; a description of the planned or ongoing studies; evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and a timeline for the completion of such studies. See id. § 505B(a)(3)(A)(ii). FDASIA would allow FDA to extend the pediatric study deadlines under certain circumstances. The applicant would be required to submit an extension request proposing a new deadline at least 90 days before the current deadline expires. FDA would have 45 days to respond to the request. If the current deferral expires prior to July 9, 2012 or by April 5, 2013, the applicant may submit the extension request by January 5, 2013 and FDA would have up to one year to respond. See FDC Act § 505B(a)(3)(B), as amended by FDASIA § 505(a). Current tracking requirements would be expanded to collect certain information about deferral extensions, including the new timeline to completion of the required assessments. See id. § 505B(f)(6)(D), as amended by FDASIA § 505(b).

FDASIA would also amend PREA to require FDA to issue a “non-compliance letter” to any person that fails to submit the required assessment, keep a deferral current, or “fails to submit a request for approval of a pediatric formulation.” FDC Act § 505B(d), as amended by FDASIA § 505(c). Beginning April 5, 2013, if a required pediatric study was not completed or deferred, the Secretary must issue a letter and require a response within 45 days, both of which would be made publicly available. See id.

Under PREA, for new drugs and biologics, pediatric assessments must be submitted with the application or with most supplements, as appropriate. According to a draft FDA guidance document on the PREA requirements, “[f]or products that are not intended for treatment of life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss the pediatric plan no later than the end-of-phase 2 meeting.” FDA, Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act, at 7 (Sept. 2005). FDASIA amends the law to require applicants to submit an initial pediatric plan to FDA no later than 60 days after such a meeting with

FDA unless the applicant and the Secretary agree to an alternate date. See FDC Act § 505B(e)(2)(a), as amended by FDASIA § 506(a). The initial pediatric plan must contain an outline of the pediatric studies the applicant plans to conduct as well as any request for deferral or waiver. See id. § 505B(e)(2)(B), as amended by FDASIA § 506(a). Within 90 calendar days, the Secretary and the applicant must either meet to discuss the initial pediatric plan or respond to the applicant in writing. See id. § 505B(e)(2)(C), as amended by FDASIA § 506(a). Ninety days after that, the applicant must then document agreement on the initial pediatric plan in a submission marked “Agreed Initial Pediatric Study Plan.” See id. § 505B(e)(3), as amended by FDASIA § 506(a). The Secretary has 30 days to confirm the agreement, including a recommendation as to whether a deferral or waiver is appropriate. See id. §§ 505B(e)(3)-(4), as amended by FDASIA § 506(a). Either the Secretary or the applicant could seek to amend the agreed initial pediatric plan. See id. § 505B(e)(5), as amended by FDASIA § 506(a).

The Secretary would be required to consult with the PeRC for the review of the initial pediatric plan, the agreed initial pediatric plan, and all “significant amendments” to such plans. See FDC Act § 505B(e)(6), as amended by FDASIA § 506(a). FDA is required to issue regulations further defining this process by July 9, 2013, but the law becomes effective on January 5, 2013 even if final regulations have not been promulgated. See id. § 505B(e)(7), as amended by FDASIA § 506(a).

VI. MEDICAL DEVICE REGULATORY IMPROVEMENTS

A. Investigational Device Exemptions

FDASIA § 601 amends FDC Act § 520(g), which authorizes the Investigational Device Exemption (“IDE”) approval process for investigational devices. Pursuant to § 520(g) and FDA’s implementing regulations (21 C.F.R. Part 812), an IDE approval is needed to initiate a clinical study of significant risk devices. It has been a concern in industry that a recent FDA draft guidance might result in IDE disapprovals for studies not viewed by FDA as likely to support ultimate 510(k) clearance or premarket approval. Some in industry feel this approach would be overly restrictive and prevent the initiation of important developmental studies that pose little or no risk to patients. FDA officials denied this interpretation of the draft guidance, but officials did note that in the past studies have been permitted to go forward that would not support approval, only to have the sponsor futilely seek approval based upon such studies. The House Report accompanying H.R. 5651 took the position that industry should be permitted to assume this risk, because some studies may have developmental value even if they do not support clearance or approval. See H.R. Rep. No. 112-495, at 26.

B. Clarification of Least Burdensome Standard

FDASIA § 602 attempts to strengthen the least burdensome provisions added to the FDC Act by FDAMA. The existing “least burdensome” provisions limit FDA to requesting only “necessary” clinical data for clearance or approval. See FDC Act §§ 513(a)(3)(D)(ii), 513(i)(1)(D). The term “necessary” was left undefined. FDASIA now defines “necessary” as “the minimum required information” that would support a clearance or approval. FDC Act § 513(a)(3)(D)(iii), as amended by FDASIA § 602(a). At the same time, the provision specifically states that this definition does not alter the standard for granting clearance or approval. See id. § 513(a)(3)(D)(iv), as amended by FDASIA § 602(a).

The changes made by FDASIA § 602 are intended to prevent FDA reviewers from requesting information that is scientifically or medically interesting but not essential to clearance or approval. See H.R. Rep. No. 112-495, at 26-27. The problem is that “minimum required” is no less subjective than “necessary.” There is much room for disagreement and no good way to enforce a distinction between nice-to-have and essential data requests. Indeed, this provision merely codifies concepts that FDA had already voluntarily adopted in a guidance document issued in 2002. See FDA, *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry* (Oct. 2002). Just as that guidance document has not prevented industry unhappiness with data requests that are not “necessary,” this provision is unlikely to prevent requests that industry perceives as exceeding the “minimum required information.”

C. Agency Documentation and Review of Decisions

FDASIA § 603 requires FDA reviewers to provide a substantive summary of the scientific or regulatory rationale for significant decisions, and it would establish an expedited appellate process for challenging those decisions.

Section 603 adds § 517A to the FDC Act. It requires FDA to document the scientific and regulatory rationale for “significant decisions” (a term left undefined) regarding IDE applications, 510(k) submissions and PMA applications. FDC Act § 517A(a), as added by FDASIA § 603. The documentation must note “significant controversies or differences of opinion” and their resolution. Id. Applicants are to be given a copy of the documentation upon request (no time frame is provided). Applicants have 30 days to appeal such decisions, and have a right to a telephone or in-person meeting with FDA. FDA must decide the appeal within 45 days, or within 30 days of the

telephone or in-person meeting if one was held. See id. § 517A(b), as added by FDASIA § 603.

This provision could be helpful in improving FDA's regulatory processes. First, it will provide greater transparency and clarity to FDA's decisions. Many times, FDA's reasons for a decision are difficult to discern and represent something of a moving target. Second, this provision appears to require FDA to provide an appeal decision in a commercially reasonable time frame. In the recent past, many appeals have taken longer than the original decision.

There is some vagueness as to exactly what point the appeal clock starts ticking, how quickly FDA must hand over the documentation, interaction with Freedom of Information Act ("FOIA") regulations, and interaction with the existing supervisory review regulation (21 C.F.R. § 10.75). These logistical issues, however, are manageable and will no doubt be resolved with time.

D. Device Modifications Requiring Premarket Notification

Under existing law, a modification to a cleared device requires a new 510(k) if the change "could significantly affect safety or effectiveness" or "constitute a major change or modification in intended use." 21 C.F.R. § 807.81(a)(3). FDA has a longstanding guidance document to assist industry in making this determination. See FDA, Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1) (Jan. 1997). In 2011, FDA issued a draft guidance intended to update and supersede the 1997 guidance. It received a great deal of criticism, and FDA had already announced its intent to re-issue a revised draft in light of the comments.

FDASIA § 604 trumps FDA's plan. It requires FDA to withdraw the draft guidance, and within 18 months report directly to Congress on the approach that should be taken as to when a device modification will require new clearance. See FDC Act § 510(n)(2), as amended by FDASIA § 604. FDA may not issue any new guidance on this subject until at least 12 months after the report has been submitted to Congress. The upshot is that the 1997 guidance will likely remain in force for at least the next couple of years.

E. Program to Improve the Device Recall System

FDASIA § 605 adds § 518A to the FDC Act. This new section requires FDA to create a program to assess information submitted or reported pursuant to device recalls, removals, and corrections and to use this information to identify strategies for mitigating health risks from defective or unsafe devices. See FDC Act § 518A, as added by

FDASIA § 605. FDA is required to clarify procedures for device recall audit checks, and develop criteria for assessing correction or removal actions. It applies to mandatory removals ordered by FDA and voluntary corrections and removals initiated by industry that must be reported to FDA under 21 C.F.R. Part 806.

F. IDE Clinical Holds

Until now, FDA did not have the authority to issue a clinical hold prohibiting the sponsor of a medical device from conducting a clinical investigation using the device. FDASIA amends FDC Act § 520(k) by adding language authorizing FDA to issue a clinical hold if it determines a device represents an unreasonable risk to the subjects' safety or for other reasons established by regulation. See FDC Act § 520(g)(8), as amended by FDASIA § 606. The determination of unreasonable risk must take into account "the qualifications of the clinical investigators, information about the device, the design of the clinical investigation, the condition for which the device is to be investigated, and the health status of the subjects involved." Id. There is no statement governing what other reasons for a clinical hold FDA may by regulation establish. Presumably, these would have to be rationally related to protecting the safety of subjects and/or investigators. A sponsor requesting a removal of a clinical hold would be required to receive a written decision within 30 days. See id. § 520(g)(8)(C), as amended by FDASIA § 606. There is little or no legislative history to explain why this provision was added or what problem it is intended to address.

G. Modification of *de novo* Application Process

A long-standing problem in device regulation has been applying an appropriate premarket pathway to low to moderate risk devices that lack a predicate device but do not belong in Class III subject to premarket approval. In 1997, FDAMA authorized FDA to place such devices in Class I or II without a predicate device. See FDC Act § 513(f)(2) (2011). However, as a prerequisite, the device had to undergo 510(k) review and receive a "not substantially equivalent" decision. Id. This requirement has proved to be a superfluous obstacle to the efficient grant of *de novo* classification.

FDASIA amends FDC Act § 513(f)(2) by eliminating this requirement. See FDASIA § 607(a)(2). A sponsor who finds there is no available predicate device may directly request *de novo* classification. See FDC Act § 513(f)(2)(A)(ii), as amended by FDASIA § 607(a). The sponsor also must include an initial draft proposal for the special controls that would apply, thus potentially easing FDA's burden in identifying such controls, as it is required to do under existing law. See id. § 513(f)(2)(A)(iv), as amended by FDASIA § 607(a). FDA has 120 days to issue a decision. See id. § 513(f)(2)(A)(iii), as amended by FDASIA § 607(a). FDA may decline the request if it concludes that the

device belongs in Class III, that appropriate special controls cannot be developed, or is able to locate an appropriate predicate to place it in Class I or II via the 510(k) process. See id. § 513(f)(2)(A)(iv), as amended by FDASIA § 607(a).

H. Reclassification Procedures

FDASIA would allow FDA, based on new information, to change the classification of a device by administrative order instead of by regulation. See FDC Act § 513(e)(1)(A)(i), as amended by FDASIA § 608(a). FDA may issue orders on its own initiative or upon request from any person. FDA may reclassify a device and revoke any related regulation or requirement in effect under a PMA approval order. The proposed order must be published in the Federal Register and subject to a classification panel meeting. There must also be consideration of comments to a public docket. The published notice must set forth the proposed reclassification order and the basis for it.

There exist numerous procedures allowing for device reclassification by regulation. They have proven so cumbersome that they are rarely used. If FDA takes advantage of this new authority to accomplish the same objective by administrative order, there is great potential to improve the efficiency of FDA's regulatory processes. Hopefully, this new authority will greatly improve FDA's ability to adjust its regulatory classifications based upon new information and postmarket experience.

I. Harmonization

FDASIA § 609 amends the law to provide that FDA may enter into arrangements with nations regarding methods and approaches to harmonizing regulatory requirements for activities, including inspections and common international labeling symbols. See FDC Act § 803(c)(4), as amended by FDASIA § 609. The section added by FDASIA replaces former FDC Act § 803(c)(4), which was limited to harmonizing good manufacturing inspections.

The push for FDA to harmonize labeling symbols is welcome. As an enforcement matter, FDA permits several international symbols in lieu of text for *in vitro* diagnostics ("IVDs"); however, FDA has not taken this approach for other device manufacturers, except for the Rx symbol expressly permitted under 21 C.F.R. § 801.109. While FDA officials have indicated an intention to allow international symbols in all device labeling, they have been slow to act. Hopefully, this statutory change will move FDA forward more quickly.

J. Participation in International Fora

Prior to FDASIA, FDA already had authority to “regularly participate in meetings with representatives of other foreign governments to discuss and reach agreement on methods and approaches to harmonize regulatory requirements.” FDC Act § 803(c)(3) (2011). This section specifies that FDA may participate in international fora, including providing guidance to organizations running them and involving the U.S. public. See FDC Act § 803(c)(3), as amended by FDASIA § 609.

K. Reauthorization of Third-Party Review and Inspection

Congress authorized the third-party (more formally known as Accredited Persons) review program as part of FDAMA. The voluntary program is intended to speed the FDA 510(k) process by providing third-party assistance for more routine reviews. A company required to submit 510(k)s for devices eligible for the program may submit a 510(k) directly to an Accredited Person (a person accredited by FDA to be a third-party reviewer). The Accredited Person reviews the 510(k), then forwards a review, recommendation, and the 510(k) to FDA. FDA must make a final determination within 30 days after receiving the recommendation.

FDASIA reauthorizes the third-party review program until October 1, 2017. See FDC Act § 523(c), as amended by FDASIA § 611(b). It adds that an accreditation to be a third-party reviewer lasts for three years. The provision also addresses reaccreditation, specifying that FDA must respond to a request for reaccreditation within 60 days, and directing FDA to publish criteria to reaccredit or deny reaccreditation to those seeking reaccreditation by November 6, 2012. See id. § 523(b)(2)(E), as amended by FDASIA § 611(a).

Left unchanged are the exclusions of certain devices from the program: (1) Class III devices; (2) a Class II device for which clinical data are required to establish substantial equivalence; and (3) a Class II device intended to be permanently implantable or life sustaining or life supporting.

Under the voluntary third-party inspection program, which is also reauthorized until October 1, 2017, eligible manufacturers of Class II and Class III devices may elect to have an accredited person perform the equivalent of an FDA Quality System inspection. The Accredited Person prepares and forwards the inspection report to FDA, which makes the final classification determination. See id. § 704(g)(11), as amended by FDASIA § 612.

The inspection program is intended to help FDA maximize its inspection resources, provide manufacturers with greater control over the timing of their inspections and, in cases where the authorized persons are recognized by regulatory authorities of other countries, reduce the total number of inspections required.

L. Humanitarian Device Exemptions

The Humanitarian Device Exemption (“HDE”) program allows a device manufacturer to sell a device that would otherwise require a PMA without demonstrating efficacy. A key requirement is that the device must be intended for diseases or conditions that occur in a maximum of 4,000 individuals annually in the U.S. The HDE program, like the orphan drugs program, is intended to encourage device manufacturers to develop devices for rare conditions or diseases.

Until 2007, device firms could set prices at a level calculated to recoup costs, and were not allowed to profit from the sale of HDE devices. In 2007, to motivate the development of pediatric devices, Congress amended the law as part of FDAAA to allow manufacturers a limited profit on pediatric HDE devices. See FDC Act §§ 520(m)(6)(A)(i)-(ii). FDASIA goes a step further, and allows manufacturers to profit from devices intended for a condition or disease that does not occur (or only rarely occurs) in pediatric patients. See FDC Act § 520(m)(6)(A), as amended by FDASIA § 613(a). FDASIA also allows a manufacturer of an HUD designated prior to July 9, 2012 to petition FDA to allow profits on future sales. See FDASIA § 613(b). Unlike the 2007 provision, the amended provision does not cap the number of devices for which the manufacturer may obtain a profit per year at 4,000 devices.

M. Unique Device Identifier

FDASIA requires FDA to issue a proposed rule establishing a Unique Device Identifier (“UDI”) system by December 31, 2012. The mandate is intended to make devices easier to identify for adverse event and recall tracking. FDA must publish the final rule no later than 6 months after the close of the comment period, and must implement the final regulations for implantable, life-saving and life-sustaining devices no later than two years after FDA promulgates the rule, “taking into account patient access.” FDC Act § 519(f), as amended by FDASIA § 614.

This provision is similar to one enacted 5 years ago under FDAAA. It appears that the provision may have affected FDA’s implementation of the UDI mandate even prior to the President’s signing of FDASIA. Until recently, FDA managed to solicit general public comment and hold a public hearing, but not much more. In particular, until recently, FDA had not even issued a proposed rule. However, after the House and Senate

passed FDASIA, but before the President signed it into law, FDA unveiled a proposed rule to implement the UDI mandate. See 77 Fed. Reg. 40,735 (July 10, 2012).

N. Sentinel

FDASIA expands the drug “Sentinel” postmarket risk analysis and identification system established under FDC Act § 505(k)(3)(C) to apply generally to medical devices. This expansion would require FDA to establish and maintain procedures for risk identification and analysis based on electronic health data, and to provide for electronic “active adverse event surveillance” using government and private sector databases. It would also require FDA to identify trends and patterns in the data, and to report on the same. See FDC Act § 519(h), as amended by FDASIA § 615. The law does not otherwise specify what FDA should do with this new information. The provision directs the FDA to consult with stakeholders in setting up the system.

O. Postmarket Surveillance

FDA has authority to order postmarket surveillance for four types of Class II and Class III devices. Those four types of devices include devices: (1) for which failure would reasonably have serious adverse health consequences; (2) expected to have significant use in pediatric populations; (3) intended for implantation (more than 1 year); or (4) intended to be life-sustaining or life-supporting (used outside a device user facility).

FDASIA addresses the timing of a postmarket surveillance order. It provides explicit authority to order post-market surveillance for all four categories of eligible devices at the time of FDA clearance/approval or any time afterward. See FDC Act § 522, as amended by FDASIA § 616.

The new law adds a requirement that the manufacturer begin the surveillance within 15 months of an FDA order. See id. § 522(b)(1), as amended by FDASIA § 616. The device manufacturer must submit a postmarket surveillance plan to FDA within 30 days of receiving the order. FDA has 60 days from receiving the plan to review the plan. The surveillance period can last 36 months, or more if the manufacturer and FDA agree to a longer period, or if the device is expected to have significant use in pediatric populations. FDA has issued guidance that provides examples of the types of potential data sources for the post-market surveillance.

P. Custom Devices

FDASIA § 617 revises the definition of a “custom” device that may be provided to a patient without adhering to FDA premarket approval or performance standard requirements.

The statute has long defined a custom device as one created or modified in order to comply with the order of an individual physician or dentist (or any other specially qualified person designated under regulations FDA issues after an opportunity for an oral hearing). The statute also provides that the device may not be generally available in the U.S. in finished form through labeling or advertising by the manufacturer, importer, or distributor for commercial distribution, and must be intended to meet the special needs of the physician or dentist or other specially qualified person in the course of his or her professional practice. The device must be intended for use by an individual patient named in the order of the physician or dentist (or other specially qualified person) and is to be made in a specific form for the patient. The device must not be “generally available to or generally used by other physicians or dentists (or other specially qualified persons so designated.)” FDC Act § 520(b). FDA’s implementing regulations at 21 C.F.R. § 812.3(b) essentially duplicated the statutory language.

FDASIA § 617 retains most of the criteria enumerated for the custom program. It does, however, remove the statutory language requiring that the order must be made in a specific form. It also modifies the language regarding the permissible availability of the device. Under FDASIA, the device must be designed to treat a unique pathology or physiological condition that no other device is domestically available to treat. FDC Act § 520(b)(1), as amended by FDASIA § 617.

This section also adds new language regarding qualification as a custom device. The device must be assembled from components or manufactured and finished on a case-by-case basis to accommodate the unique needs of the particular patient. However, custom devices may have common, standardized design characteristics, chemical and material compositions, and manufacturing processes as commercially distributed devices. See id. This clears up a potential point of confusion under existing law.

Finally, FDASIA § 617 adds that the devices must treat a condition that is rare enough that it would be impractical to conduct clinical investigations on the device, and the manufacturer can make no more than 5 units of the device per year. See id. § 520(b)(2), as amended by FDASIA § 617. This requirement has been one of the factors that FDA has historically considered in determining whether a device was truly a custom device. The 5-unit limitation is new and has the potential to be even more restrictive than

prior law. The manufacturer of a custom device must notify FDA every year that it is manufacturing the device. See id. FDA must issue final guidance implementing the provision by July 9, 2014. See id. § 520(b)(3), as amended by FDASIA § 617. FDA would be wise to revise the regulatory definition as soon as practicable to conform to the new statutory requirements.

Q. Health Information Technology

FDASIA requires FDA to issue a report by January 9, 2014 with a proposed strategy and recommendations on a risk-based health information technology framework, including mobile medical applications, that “promotes innovation, protects patient safety, and avoids regulatory duplication.” FDASIA § 618(a). FDA must consult with the National Coordinator for Health Information Technology and the Chairman of the Federal Communications Commission in issuing the report. See id. FDASIA provides for possible creation of a working group of external stakeholders and experts to advise upon the report. The working group must be geographically diverse and include representatives from a broad cross-section of different types of stakeholders. See FDASIA § 618(b).

Mobile medical applications have been the subject of federal regulatory attention, including issuance of a draft FDA guidance on mobile medical applications in July 2011. In September 2011, the Federal Trade Commission brought its first case targeting health claims related to mobile medical applications, and FDA held a public hearing on medical mobile applications.

R. Good Guidance Practices Relating to Devices

FDASIA § 619 requires that FDA provide an opportunity to comment upon a notice to industry, guidance letter, a notice to industry advisory letter, or any similar notice that sets forth initial interpretations of a regulation or policy or sets forth changes in interpretation or policy. The opportunity to comment must be prior to implementation, unless FDA decides prior public participation is not feasible or appropriate, in which case FDA must provide opportunity for comment at the time of implementation. See FDC Act § 701(h)(1)(C), as amended by FDASIA § 619.

S. Pediatric Device Consortia

FDASIA § 620 reauthorizes through FY 2017 the funding of grant requests to nonprofit consortia for demonstration projects that promote pediatric device development. Specifically, FDASIA authorizes \$5.2 million for FYs 2013-2017. This is a decrease from the \$6 million authorized under FDAAA § 305 for FYs 2008-2012.

This section also directs FDA to issue a proposed rule by December 31, 2012, and a final rule by December 2013, implementing a FDAAA requirement that sponsors of certain applications or protocols include in those documents a description of any pediatric subpopulations that suffer from the disease or condition the device is intended to treat, diagnose, or cure; and the number of affected pediatric patients. See FDC Act § 515A(a)(2), as amended by FDASIA § 620(b).

VII. DRUG SUPPLY CHAIN

FDASIA Title VII makes significant changes to enhance FDA's inspection authority and the drug supply chain. Similar to the medical device UDI system, FDASIA requires FDA to create a Unique Facility Identifier ("UFI") system and to maintain an electronic database containing the registration and listing information of drug facilities. See FDC Act § 510(p), as amended by FDASIA § 704. FDA must ensure the accuracy and coordination of relevant FDA databases in order to identify and inform "risk-based" inspections.

As part of the new UFI system, FDASIA increases the information required for the registration of domestic or foreign drug facilities to include the UFI of each drug establishment and a point of contact e-mail address, in addition to the current requirements of listing the name, place of business, and all establishments. See FDC Act §§ 510(b)(1), 510(i)(A)(i), as amended by FDASIA §§ 701, 702(b)(1)(B). Furthermore, for each drug listed by a drug facility, certain information is required for each drug excipient establishment. See id. § 510(j)(E), as amended by FDASIA § 703(1). While the FDC Act deemed a drug or device misbranded if it was manufactured by a domestic facility that was not registered, the law now deems any drug or device misbranded if it is imported from an unregistered foreign facility. See FDC Act § 502(o), as amended by FDASIA § 702(a). The registration period for domestic and foreign drug manufacturers has also been changed to October 1st to December 31st of each year, instead of the more open-ended period of on or before December 31st of each year.

Under FDASIA, a drug will be deemed adulterated if it has been manufactured, processed, packed, or held in any factory, warehouse, or establishment by an owner or operator who has delayed, denied, or limited an inspection, or has refused to permit entry or inspection. See FDC Act § 501(j), as amended by FDASIA § 707(a). By July 9, 2013, FDA must issue a guidance document that defines the circumstances that would constitute delay, denial, or limiting of an inspection, or refusal to permit entry or inspection. See FDASIA § 707(b).

Generally, a drug is deemed adulterated if manufacturing, processing, packaging, or holding of the product does not conform with current good manufacturing practices (“cGMPs”) to assure the quality and purity characteristics. See FDC Act § 501(a)(2)(B). FDASIA specifies that cGMPs include the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. See id., as amended by FDASIA § 711. FDASIA codifies FDA’s current policy that manufacturers implement quality oversight over their suppliers. However, the new law may increase the burden on manufacturers to implement such oversight earlier in the drug development process.

Regarding inspections, FDASIA maintains the biennial inspection schedule for Class II or III devices, and replaces the biennial inspection schedule for drugs with a “risk-based” inspection schedule. See FDC Act § 510(h), as amended by FDASIA § 705. Congress believed that a risk-based inspection schedule could focus resources on high-risk facilities that present the greatest risk and could help ensure inspection parity of domestic and foreign drug facilities. See H.R. Rep. No. 112-495, at 31. FDASIA enumerates certain safety risk factors that FDA must consider in determining whether to inspect a drug establishment. See FDC Act § 510(h)(4), as amended by FDASIA § 705.

FDA must make publicly available on its website an annual report regarding: (1) the number of registered domestic and foreign establishments; (2) the number of domestic and foreign establishments inspected in the previous year; (3) the number of each type of establishment that manufactures, prepares, propagates, compounds, or processes an active ingredient of a drug, a finished drug product, and a drug excipient; and (4) the percentage of the FDA budget used for inspections. See id. § 510(h)(6), as amended by FDASIA § 705. The report must be available no later than February 1st of each year beginning with Calendar Year 2014.

FDASIA authorizes FDA to enter into agreements with foreign governments to recognize inspections of FDA-registered foreign establishments to facilitate in risk-based inspections. See FDC Act § 809(a), as amended by FDASIA § 712. Agreements may be entered into with foreign governments that FDA has determined as having the capability of conducting inspections that would meet the requirements of the FDC Act. The results of an inspection conducted by such foreign government may be used as evidence of compliance with cGMPs or for any other purpose determined by FDA. See id. § 809(b), as amended by FDASIA § 712.

In addition to FDA’s current inspection authority, FDASIA may require a drug manufacturer to provide, in advance or in lieu of an inspection, any records or other information to FDA that the Agency may otherwise inspect at the facility, in either electronic or physical form and at the expense of the drug manufacturer. See FDC Act

§ 704(a), as amended by FDASIA § 706. FDA must clearly describe the records requested and confirm receipt of the records submitted by the drug manufacturer. See id. § 704(a), as amended by FDASIA § 706.

FDA is not required to disclose, under FOIA, information obtained from a foreign government if: (1) “the information concerns the inspection of a facility, is part of an investigation, alerts the United States to the potential need for an investigation, or concerns a drug that has a reasonable probability of causing serious adverse health consequences or death to humans or animals;” (2) it is released to FDA on a condition that the information not be released to the public; and (3) it is subject to a written agreement. FDC Act § 708(b)(1), as amended by FDASIA § 710(2). The written agreement between FDA and the foreign government must specify the time period in which the information is not disclosable, and if no date is specified, the time period restricting disclosure cannot exceed 36 months. See id. § 708(b)(2), as amended by FDASIA § 710.

FDASIA also permits FDA, pursuant to a written agreement, to provide information to a foreign government, but only if the FDA Commissioner has certified that the foreign government has the ability to protect trade secret information. See FDC Act § 708(c)(1), as amended by FDASIA § 710. The written agreement must include a commitment by the foreign government to protect confidential information unless the sponsor permits disclosure or FDA declares a public health emergency that is relevant to the information. See id. § 708(c)(2), as amended by FDASIA § 710. FDA’s disclosure to a foreign government is limited to information regarding an inspection of a facility if FDA believes the foreign government has authority to obtain the information and will use it for civil regulatory purposes. See id. § 708(c)(3)(A), as amended by FDASIA § 710. FDA is also permitted to disclose to a foreign government information that may be part of an investigation or to alert the need of an investigation, if FDA has reasonable belief that a drug may cause serious adverse health consequences or death to humans or animals. See id. § 708(c)(3)(B), as amended by FDASIA § 710.

FDASIA grants FDA extraterritorial jurisdiction over any violation of the FDC Act for any article intended for import into the U.S. See FDC Act § 311, as amended by FDASIA § 718. This amendment, which gives FDA broad inspection authority of overseas facilities, was prompted by the contamination of heparin products imported to the U.S. that caused serious adverse events and deaths. Moreover, FDASIA grants FDA the authority to destroy, without the opportunity for export, any drug that is refused admission into the U.S. (i.e., counterfeit or adulterated imported drug products) that has not been brought into compliance and that is valued at less than or equal to \$2,500 (the amount of which may be amended by regulation issued by the Department of Treasury). See id. § 801(a), as amended by FDASIA § 708(a). FDA must issue regulations by July

9, 2014 that address the appropriate due process available to the owner, including the introduction of testimony. See FDC Act § 801, as amended by FDASIA § 708(b).

In addition to FDA's current authority to detain a device or tobacco product found during an inspection that FDA believes is adulterated or misbranded, FDASIA permits FDA to detain for a reasonable period drug products that the Agency believes are adulterated or misbranded based on an inspection. See id. § 304(g), as amended by FDASIA § 709. FDA must promulgate regulations by July 9, 2014 to implement administrative detention authority of drugs.

A commercial importer of drugs must now register with FDA and submit a unique identifier for its principal place of business. See FDC Act § 801(s)(1), as amended by FDASIA § 714(b). Any drug imported or offered for import by a commercial importer of drugs that is not properly registered will be considered misbranded. See id. § 502(o), as amended by FDASIA § 714(c). By July 9, 2015, FDA, in consultation with the Department of Homeland Security, must issue regulations "to establish good importer practices that specify the measures an importer shall take to ensure imported drugs are in compliance with" the FDC Act and PHS Act. See id. § 801(s)(2)(A), as amended by FDASIA §§ 714(b), (d). FDA must discontinue the registration of any commercial drug importer that does not comply with the regulations.

FDASIA creates a new standard of admission for drug products intended to be imported into the U.S. This new standard will permit FDA to take a risk-based approach to screening imported drug products. As a condition of granting admission, FDA may require the importer to submit certain information electronically demonstrating the drug's compliance with the FDC Act. See FDC Act § 801(r)(1), as amended by FDASIA § 713(2). Information requirements may be satisfied, at FDA's discretion, through an inspection conducted by or representations made by a foreign government that has standards and practices determined appropriate by FDA, or by any other appropriate documentation. See id. § 801(r)(3), as amended by FDASIA § 713(2). By January 9, 2014, FDA is required to adopt final regulations implementing these standards.

FDASIA requires a "regulated person" to notify FDA upon knowledge: (1) that the use of a drug may result in serious injury or death; (2) of a significant loss or known theft of such drug intended for use in the U.S.; (3) or that such drug has been or is being counterfeited and that product is in commerce in the U.S, or has been, is being, or may reasonably be imported into the U.S. See FDC Act § 568(a), as amended by FDASIA § 715(b). A "regulated person" is defined as a domestic or foreign drug establishment that must be registered with FDA, a commercial drug importer, a wholesale drug distributor, or any other person that distributes drugs except a person that distributes drugs exclusively for retail sale. See id. § 568(d), as amended by FDASIA § 715(b).

FDA is authorized to specify the procedure for notification by the regulated person to the Agency through either regulation or guidance.

Finally, FDASIA adds penalties for any person who knowingly and intentionally adulterates a drug that results in causing serious adverse health consequences or death to humans or animals. See FDC Act § 303(b), as amended by FDASIA § 716. Penalties include imprisonment of not more than 20 years and monetary penalties of not more than \$1 million, or both. FDASIA also amends the federal criminal code by adding as a criminal offense the trafficking in counterfeit drugs. See 18 U.S.C. § 2320(a)(4), as amended by FDASIA § 717(a)(1). Penalties for the first offense include imprisonment of not more than 20 years and fines of not more than \$5 million, or both, for any individual who intentionally trafficks a counterfeit drug. FDASIA directs the Attorney General to give increased priority to investigate and prosecute cases that involve counterfeit drugs and the U.S. Sentencing Commission to review and amend its guidelines and policy statements applicable to persons convicted of trafficking in counterfeit drugs to reflect Congressional intent of enhanced penalties for such offenses. See FDASIA §§ 717(a)(4), (b).

VIII. GENERATING ANTIBIOTIC INCENTIVES NOW

FDASIA Title VIII includes several provisions based on legislation known as the Generating Antibiotic Incentives Now Act (“GAIN Act”) that are intended to encourage the development of antibacterial and antifungal drug products that treat pathogens that cause serious and life-threatening infections. Title VIII also builds on provisions included in FDAAA intended to improve antibiotic access and innovation, and addresses issues raised since the enactment of FDAAA. See, e.g., U.S. Gov’t Accountability Office, GAO-12-218, Antibiotics: FDA Needs to Do More to Ensure That Drug Labels Contain Up-to-Date Information 19 (2012).

FDASIA § 801 amends the FDC Act to create new Section 505E, which, among other things, grants an additional 5 years of marketing exclusivity upon the approval of an NDA for a drug product designated by FDA as a Qualified Infectious Disease Product (“QIDP”). Thus, for a QIDP, the periods of 5-year New Chemical Entity (“NCE”) exclusivity under FDC Act §§ 505(c)(3)(E)(ii) and (j)(5)(F)(ii), 3-year new clinical investigation exclusivity under FDC Act §§ 505(c)(3)(E)(iii)-(iv) and 505(j)(5)(F)(iii)-(iv), and 7-year orphan drug exclusivity under FDC Act § 527 become 10 years, 8 years, and 12 years, respectively. See FDC Act § 505E(a), as amended by FDASIA § 801(a). In addition, for a QIDP with NCE exclusivity, the period during which an ANDA containing a Paragraph IV certification to an Orange Book-listed patent on the QIDP cannot be submitted is extended from 4 years after QIDP NDA approval to 9 years after

QIDP NDA approval. See id. Pediatric exclusivity granted pursuant to FDC Act § 505A would extend the various QIDP exclusivity periods by 6 months. See id. § 505E(b), as amended by FDASIA § 801(a).

New FDC Act § 505E, which applies only with respect to a drug that is first approved under FDC Act § 505(c) on or after July 9, 2012, see FDASIA § 801(b), limits the 5-year QIDP exclusivity extension, such that it does not apply to the approval of:

- (1) a supplement to an application under [FDC Act § 505(b)] for any [QIDP] for which an extension described in [FDC Act § 505E(a)] is in effect or has expired;
- (2) a subsequent application filed with respect to a product approved under [FDC Act § 505] for a change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or
- (3) a product that does not meet the definition of a [QIDP] under [FDC Act § 505E(g)] based upon its approved uses.

FDC Act § 505E(c), as amended by FDASIA § 801(a).

While the limitation provisions clearly act to prevent application of a QIDP exclusivity extension to NDA supplements for drug products previously awarded such exclusivity, it is unclear how the limitation provisions act to block QIDP-qualifying improvements to a post-FDASIA drug not originally approved with a QIDP exclusivity extension. While the limitation provisions seek to block a QIDP exclusivity extension from applying to a drug submitted in a “subsequent application,” it is unclear what the application must be subsequent to. Moreover, a new indication is usually submitted for approval via an NDA supplement rather than an original NDA. Therefore, a second indication that otherwise qualifies for a QIDP exclusivity extension and that is submitted as an NDA supplement to a non-QIDP NDA first approved on or after July 9, 2012 would seem to receive the QIDP exclusivity extension.

A QIDP is defined in the new law to mean “an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by – (1) an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens;” or (2) certain “qualifying pathogens.” FDC Act § 505E(g), as amended by FDASIA § 801(a). A “qualifying pathogen” is a pathogen that has the potential to pose a serious threat to public health (e.g., resistant gram positive pathogens, multi-drug resistant gram negative bacteria, multi-drug resistant tuberculosis, and

Clostridium difficile) and that is included in a list established and maintained by FDA. See id. § 505E(f), as amended by FDASIA § 801(a). In establishing and maintaining a list of “qualifying pathogens,” FDA must, among other things, take into consideration “the impact on the public health due to drug-resistant organisms in humans” and “the rate of growth of drug-resistant organisms in humans,” and must “consult with experts in infectious diseases and antibiotic resistance. . . .” See id. § 505E(f)(2)(B), as amended by FDASIA § 801(a).

A drug sponsor may request FDA to designate its product as a QIDP any time before the submission of an NDA. See FDC Act § 505E(d)(1), as amended by FDASIA § 801(a). FDA must make a QIDP determination within 60 days of the designation request. See id. QIDP designation cannot be withdrawn “for any reason,” except that if FDA determines that the designation request contained an untrue statement of material fact, the Agency may revoke a designation. Id. § 505E(d)(2)-(3), as amended by FDASIA § 801(a). FDA is required to promulgate final regulations implementing FDC Act § 505E, as well as develop a list of “qualifying pathogens,” not later than July 9, 2014. See id. 505E(e)(1)-(3), as amended by FDASIA § 801(a). Prior to promulgating final regulations, FDA may designate drugs as QIDPs provided the drug meets the QIDP definition at FDC Act § 505E(g). See id. § 505E(e)(4), as amended by FDASIA § 801(a).

FDASIA § 802 amends the FDC Act to create new Section 524A, which states that FDA will grant prior review to an NDA for a drug designated as a QIDP. See FDC Act § 524A, as added by FDASIA § 802(a). Such priority review designation applies only with respect to an NDA that is submitted on or after July 9, 2012. See FDASIA § 802(b). In addition, a QIDP can qualify for “fast track” status under FDC Act § 506. See id. § 803.

FDASIA § 804 requires FDA to review and revise (as appropriate) not fewer than three guidance documents per year, including reviewing guidance “for the conduct of clinical trials with respect to antibacterial and antifungal drugs,” and “revising such guidance documents to reflect developments in scientific and medical information and technology and to ensure clarity regarding the procedures and requirements for approval of antibacterial and antifungal drugs.” FDASIA § 804(a)(1). At a minimum, FDA’s guidance document review must address “the appropriate animal models of infection, in vitro techniques, valid microbiological surrogate markers, the use of noninferiority versus superiority trials, trial enrollment, data requirements, and appropriate delta values for noninferiority trials.” Id. § 804(a)(2). In addition, not later than June 30, 2012, FDA must issue draft guidance that: “(1) specifies how preclinical and clinical data can be utilized to inform an efficient and streamlined pathogen-focused antibacterial drug development program that meets the approval standards of the [FDA]; and (2) provides

advice on approaches for the development of antibacterial drugs that target a more limited spectrum of pathogens.” FDASIA § 806(a). Such guidance must be finalized and issued not later than December 31, 2014. See id. § 806(b).

A would-be QIDP sponsor may request that FDA provide written recommendations “for nonclinical and clinical investigations which the Secretary believes may be necessary to be conducted with the drug before such drug may be approved.” FDASIA § 804(b)(1). FDA must provide written recommendations “on the basis of information available to the Secretary at the time of the request” if the Agency “has reason to believe that a drug for which a request is made” is a QIDP. Id. § 804(b)(2).

FDASIA § 805 requires FDA to report to Congress not later than July 9, 2017 on certain measures, including QIDP designations and product approvals, and to recommend any changes to the law, among other things. See FDASIA § 805(a).

IX. DRUG APPROVAL AND PATIENT ACCESS

A. Enhancement of Accelerated Patient Access to New Medical Treatments

FDASIA § 901 amends certain provisions of FDC Act § 506 to encourage FDA “to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs.” FDASIA § 901(a). Specifically, FDASIA expands the scope of products that qualify for expedited development and review and the range of endpoints that may be used to gain such approval. However, it is unclear given other limitations, whether the changes will have their intended effect of fostering innovation and improving access to products where approval might otherwise be slowed by the regulatory process.

FDASIA first expands the scope of products that qualify for fast track status to include products that are intended for the “treatment of a serious or life-threatening *disease* or condition.” FDC Act § 506(b)(1), as amended by FDASIA § 901(b) (emphasis added). Previously, the law defined fast track products to include only products that were intended “for the treatment of a serious or life-threatening *condition*” and that demonstrate “the potential to address unmet medical needs for such a condition.” FDC Act § 506(a)(1) (2011) (emphasis added).

FDASIA also provides that FDA may approve an NDA or BLA for a product for a “serious or life-threatening disease or condition,” including a fast track product, based on

“a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.” FDC Act § 506(c)(1)(A), as amended by FDASIA § 901(b). Such approval is referred to as “accelerated approval.” *Id.* Previously, the law permitted FDA to approve a fast track product only upon a determination that the product has “an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit.” FDC Act § 506(b)(1) (2011). “The evidence to support that an endpoint is reasonably likely to predict clinical benefit . . . may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.” *Id.* at § 506(c)(1)(B), as amended by FDASIA § 901(b). Accordingly, the amended provision appears to significantly expand the scope of available endpoints that can be used to demonstrate a product qualifies for accelerated approval.

Whether the changes made to the law by FDASIA will facilitate innovation likely turns on FDA’s interpretation of authority pursuant to the new law’s limitations. Namely, the law retains its previous limitation that FDA require the sponsor to conduct appropriate post-approval studies, but now requires that those studies “verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit” (versus “validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint” under the pre-FDASIA statute). FDC Act § 506(c)(2), as amended by FDASIA § 901(b). This change is reflective of FDA’s more recent, and heavily criticized, notion that proof of efficacy on mortality related endpoints is necessary to obtain approval of drugs intended to treat certain life-threatening diseases or conditions.²⁰ Similarly, FDA may now expedite withdrawal of approval of a product if “a study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the product fails to verify and describe such effect or benefit.” *Id.* § 506(c)(3)(B), as amended by FDASIA § 901(b). FDASIA clarifies that FDA may require the sponsor to file *either* post-approval studies to confirm the effect on the clinical endpoint (as described above) *or* copies of all promotional materials, or both. *Id.* § 506(c)(2), as amended by FDASIA § 901(b).

²⁰ See, e.g., FDA, Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment (Nov. 2010) (requiring demonstration of efficacy on all cause mortality measured at 28 days as a primary endpoint for approval).

FDASIA requires FDA to “establish a program to encourage the development of surrogate and clinical endpoints, including biomarkers, and other scientific methods and tools that can assist the Secretary in determining whether the evidence submitted in an application is reasonably likely to predict clinical benefit for serious or life-threatening conditions for which significant unmet medical needs exist.” Id. § 506(f)(2), as amended by FDASIA § 901(b). FDA is also required to issue draft guidance implementing the amendments to FDC Act § 506, and that shall consider “issues arising under the accelerated approval and fast track processes . . . for drugs designated for a rare disease or conditions” and any “unique issues associated with rare disease.” FDASIA § 901(c). In addition, FDA is required to amend the regulations governing accelerated approval under 21 C.F.R. Part 314 (drugs) and 21 C.F.R. Part 610 (biologics) within one year. Id. at (c)(2)(B).

B. Breakthrough Therapies

FDASIA § 902 significantly amends FDC Act § 506 by permitting FDA to accelerate approval of so-called “breakthrough therapies.” A “breakthrough therapy” is defined as a drug that:

is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

FDC Act § 506(a)(1), as amended by FDASIA § 902(a).

The sponsor of a “breakthrough therapy” may request the Secretary to designate the drug as a breakthrough therapy at the time of or any time after the submission of an IND. See id. § 506(a)(2), as amended by FDASIA § 902(a). Similar to accelerated approval of other products, FDA must decide within 60 days of receipt whether the product meets the definition of a breakthrough therapy, and, if so, take actions that are “appropriate to expedite the development and review of the application for approval,” which may include meetings and product development advice. See id. § 506(a), as amended by FDASIA § 902(a).

FDA must publish guidance no later than January 9, 2014 implementing the new requirements, which shall be finalized no later than one year after the close of the comment period for the draft guidance. See FDASIA § 902(b)(1)(A). In addition, if deemed necessary, FDA’s regulations must be amended not later than July 9, 2014. See id. § 902(b)(1)(B).

C. Consultation With External Experts

While previous law required FDA to provide, upon the sponsor's request, information about clinical and non-clinical investigations that may be needed for approval for certain rare disease treatments, there was no specific provision addressing the use of experts as consultants in the pre-approval period. See FDC Act § 525 (2011). FDASIA amends the FDC Act to address the use of such experts and to promote the efficiency of, and inform the review by, FDA of "new drugs and biological products for rare diseases and drugs and biological products that are genetically targeted." FDC Act § 569, as added by FDASIA § 903(a).

FDA is also required to develop and maintain a list of external experts, who are considered special government employees, with whom to consult regarding specified topics in the review of new drugs and biological products for rare diseases, and drugs and biological products that are genetically targeted, when such consultation is necessary because FDA lacks the requisite expertise. See id. § 569(a)(2), as added by FDASIA § 903(a). The provision was apparently motivated, in part, by FDA's delayed approval of Cayston (aztreonam), an inhaled antibiotic for use in cystic fibrosis patients FDA approved in February 2010 under NDA No. 050814, after an 18-month review process. It is postulated that the review was lengthened by prolonged conversations between FDA and the sponsor that could have been truncated by outreach to external experts.

D. Prescription Drug Container Label Accessibility

As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA"), Pub. L. No. 108-173, 117 Stat. 2066 (2003), Congress called upon FDA to investigate solutions addressing the problem of inaccessible prescription drug labeling. FDA requested comments from industry in May 2004; however, advocates for the visually impaired were dissatisfied with the lack of improvement to access to prescription drug information that flowed from those efforts. See 69 Fed. Reg. 29,139 (May 20, 2004).

FDASIA directs FDA to convene a working group that will develop best practices on access to information on prescription drug labels for individuals who are blind or visually impaired. See FDASIA § 904(a)(1). The working group will consider the use of braille, auditory means (including "talking bottles"), and enhanced visual means such as high contrast printing. See id. § 904(a)(4).

E. Risk-Benefit Framework

FDASIA amends FDC Act § 505(d) to require FDA to “implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs.” FDC Act § 505(d), as amended by FDASIA § 905. The revision could provide greater transparency to the review process.

F. Orphan Drug Grants and Contracts

The Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983), as amended, authorizes the Secretary to provide grants and contracts to public and private entities to defray the costs of qualified testing used for orphan drug development, i.e. drugs for rare diseases and conditions. FDASIA reauthorizes the Orphan Products Grant program and authorizes \$30 million to be appropriated each year for that program through FY 2017. FDASIA § 906(b). In addition, FDASIA deletes the requirement that certain qualified testing costs occur after a product is designated as an orphan drug. See id. § 906(a).

G. Demographic Subgroups Reporting

FDASIA requires that FDA publish on its website and provide to Congress by July 9, 2013 a report “addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups including sex, age, race, and ethnicity, is included in applications submitted to [FDA].” FDASIA § 907(a). During that same one-year window, FDA is required to publish and provide to Congress an action plan that includes recommendations on how to improve the public availability of demographic data to patients, providers and researchers, including recommendations to improve the completeness and quality of analysis of data on demographic subgroups in summaries of product safety and effectiveness data and labeling, as well as recommendations on the inclusion and availability of such data in labeling. See id. § 907(b)(2)(A)-(C).

This provision likely stems from concerns that women and minorities are underrepresented in clinical trials and that there is insufficient record of the population demographic in those trials that may reveal subpopulation trends.

H. Rare Pediatric Disease Priority Review Voucher Program

FDASIA creates a Priority Review Voucher (“PRV”) program for the approval of a product for a “rare pediatric disease,” which is defined in the law to mean a “disease

[that] primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents” and that meets the definition of “rare disease or condition” as set forth in the Orphan Drug Act, FDC Act § 526. FDC Act § 529(a)(3), as added by FDASIA § 908. The program rewards developers of rare pediatric disease treatments by requiring FDA, upon approval, to provide the sponsor with a voucher entitling it to “priority review” of a single human drug application. See id. § 529(a)(2), as added by FDASIA § 908. The new pediatric PRV program is inspired by the existing tropical disease PRV program at FDC Act § 524, as added by FDAAA, but also differs from it in several respects.

The pediatric PRV program requires that to qualify for a voucher, the drug or biological product that is the subject of an application contain “no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application” under the FDC Act or the PHS Act. Id. § 529(a)(4)(A)(ii), as added by FDASIA § 908. In addition, the application must, among other things, be a human drug application, as defined at FDC Act § 735(1), “that relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population,” and “that does not seek approval for an adult indication in the original rare pediatric disease product application.” Id. § 529(a)(4)(D)-(E), as added by FDASIA § 908.

The pediatric PRV program requires the sponsor of an application that will rely on a pediatric PRV to notify FDA of its intent to use the PRV no later than 90 days prior to application submission. See id. § 529(b)(4), as added by FDASIA § 908. This is significantly less than the 365-day notice required for use of a tropical disease PRV. See FDC Act § 524(b)(4). In addition, the user fee assessed with respect to a pediatric PRV is significantly less than that required by a tropical disease PRV. See FDC Act § 529(c)(2), as added by FDASIA § 908. Such fee, however, must be paid upon notification of use of the pediatric PRV, see id. § 529(c)(4), as added by FDASIA § 908, as opposed to the tropical disease PRV, which must be paid upon application submission. See FDC Act § 524(c)(4).

FDASIA § 908 sets forth unique designation provisions that require FDA to determine whether a product qualifies as a product for a rare pediatric disease and whether an application qualifies as a rare pediatric disease product application within 60 days after receiving a request for such a determination. See id. FDC Act § 529(d), as added by FDASIA § 908. The request must be made “at the same time a request for designation of orphan disease status . . . or fast track designation . . . is made.” Id. § 529(d)(2), as added by FDASIA § 908. FDA can revoke a pediatric PRV if the product for which the voucher was awarded is not marketed within 365 days of approval. See id. § 529(e)(1), as added by FDASIA § 908. In addition, a sponsor is required to report to

FDA, within 5 years of product approval, on the estimated population in the U.S. suffering from the disease, the estimated U.S. demand for the product, and the actual product distribution – each in the previous 4 years. See id. § 529(e)(2), as added by FDASIA § 908.

X. DRUG SHORTAGES

A spate of shortages in the U.S. supply of certain prescription drugs led to the inclusion of several new provisions as part of FDASIA. FDASIA Title X incorporates provisions that attempt to address drug shortages, in part by enabling FDA to better manage and track drug shortages and threatened shortages. Specifically, FDASIA: (1) expands drug supply disruption reporting requirements; (2) directs FDA to take specific actions to prevent or mitigate shortages; (3) creates a mechanism for tracking drug shortage data and sharing that information with key stakeholders; and (4) creates a task force to analyze the causes of drug shortages and devise a strategic plan that addresses shortages.

A. Expanded Reporting Requirement

FDASIA amends the FDC Act to require that manufacturers of all drugs that are life-supporting, life-sustaining, or that are “intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery” (not including a radiopharmaceutical drug product or any other product designated by FDA) to notify the Agency “of a permanent discontinuance in the manufacture of the drug or an interruption of the manufacture of the drug that is likely to lead to a meaningful disruption in the supply of that drug in the United States, and the reasons for such discontinuance or interruption.” FDC Act § 506C(a), as amended by FDASIA § 1001(a). A “meaningful disruption” is defined as “a change in production that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product,” but does not include interruptions in manufacturing due to “routine maintenance or insignificant changes in manufacturing” where the manufacturer “expects to resume operations in a short period of time.” Id. § 506C(h)(3), as amended by FDASIA § 1001(a).

A notice must be submitted to FDA at least 6 months prior to the date of the drug discontinuance or interruption, or as soon as is “practicable.” Id. § 506C(b), as amended by FDASIA § 1001(a). Failure to notify FDA can result in FDA investigating the noncompliance and potentially making it public, unless the manufacturer had a reasonable basis for failing to notify FDA. Id. § 506C(f), as amended by FDASIA § 1001(a). FDA must distribute, “[t]o the maximum extent practicable,” information on

the discontinuation or interruption of drugs to “appropriate organizations,” including physicians, health providers, and patient organizations, id. § 506C(c), as amended by FDASIA § 1001(a), and must establish a mechanism by which these same entities can, in turn, report evidence of a shortage to the Agency. See id. § 506D(d), as amended by FDASIA § 1003. FDA must also “maintain an up-to-date list of drugs that are determined by the Secretary to be in shortage in the United States.” Id. § 506E(a), as amended by FDASIA § 1004.

In the case of a controlled substance, notification of a shortage may generate a “request that the Attorney General increase the aggregate and individual production quotas under section 306 of the Controlled Substances Act applicable to such controlled substance and any ingredient therein to a level the Secretary deems necessary to address a shortage of a controlled substance based on the best available market data.” Id. § 506C(e)(2)(B), as amended by FDASIA § 1001(a). “[I]f the Attorney General determines that the level requested is not necessary to address a shortage of a controlled substance, the Attorney General shall provide to the Secretary a written response detailing the basis for the Attorney General’s determination,” which will be made public. Id. § 506C(e)(2)(C), as amended by FDASIA § 1001(a).

FDASIA also formalizes existing FDA practices designed to prevent or mitigate shortages. For example, FDA must consider the potential impact of any warning letter or other enforcement action on the supply of the drug at issue. Any enforcement action that could have an impact on the drug supply must be vetted by the appropriate FDA Center. See id. § 506D(b)-(c), as amended by FDC Act § 1003.

B. Task Force and Drug Shortage Study

Industry observers disagree on the causes of drug shortages, and consequently on the appropriate measures to prevent and mitigate such shortages. Perhaps in anticipation that further measures may be necessary to prevent and mitigate drug shortages in the future, FDASIA establishes two mechanisms for ongoing drug shortage research and strategic planning.

First, FDASIA requires FDA to create a task force on drug shortages. The task force is to develop and implement a strategic plan for preventing and mitigating shortages, part of which may include a “qualified manufacturing partner program” that designates certain drug manufacturers as “qualified manufacturers” with “the capability and capacity to supply products determined or anticipated to be in shortage.” FDC Act § 506D(a)(1)(C), as amended by FDASIA § 1003. The task force must examine whether “qualified manufacturers” should be eligible for incentives for their participation in the program. Id. § 506D(a)(1)(C)(ii), as amended by FDASIA § 1003.

Second, FDASIA requires the Comptroller General to conduct a study examining the cause of drug shortages. The study is to produce recommendations on how to prevent or alleviate shortages, and its results must be reported to Congress by January 9, 2014. See FDASIA § 1008.

XI. OTHER PROVISIONS

Title XI includes various provisions, including a host of miscellaneous provisions, concerning a range of topics from medical gas, to nanotechnology, to 180-day generic drug marketing exclusivity, to controlled substances.

A. Subtitle A - Reauthorizations

1. Enantiomer Marketing Exclusivity

FDAAA § 1113 amended 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), among other things, to “elect to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug” so as to qualify for a period of 5-year New Chemical Entity (“NCE”) exclusivity. FDC Act § 505(u)(1). Thus far, FDA has not awarded a period of NCE exclusivity based on the election provided for under FDC Act § 505(u), and very little interest has been shown in the provision.²¹ FDC Act § 505(u) was scheduled to sunset on September 30, 2012. See id. § 505(u)(4).

FDASIA § 1107 reauthorizes FDC Act § 505(u) for an additional 5 years, such that the provision is now scheduled to sunset on September 30, 2017.

2. Critical Path Public-Private Partnerships

FDASIA § 1102 amends FDC Act § 566 to authorize \$6 million in appropriations for each of FYs 2013 through 2017. See FDC Act § 566(f), as amended by FDASIA § 1102. FDC Act § 566 was added to the law by FDAAA § 603, and provides for the

²¹ See U.S. Gov’t Accountability Office, GAO-12-218, Antibiotics: FDA Needs to Do More to Ensure That Drug Labels Contain Up-to-Date Information 19 (2012), available at <http://www.gao.gov/assets/590/588022.pdf> (“According to FDA officials, they have received very few inquiries regarding this provision and as of November 2011, no NDAs for antibiotics have been submitted that would qualify for this exclusivity. . . .”).

establishment of certain partnerships between FDA and eligible non-profit and higher education institutions to advance FDA's Critical Path Initiative. 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.

B. Subtitle B - Medical Gas Product Regulation

FDASIA §§ 1111-1113 are intended to streamline and modernize the regulation of medical gases, a class of drug products that have been used for over 100 years to treat certain medical conditions. Although FDA has approved marketing applications for some medical gases, many medical gases have been marketed for years without FDA approval. The FDASIA medical gas provisions are based on legislation introduced in June 2011 by Representative Leonard Lance (R-NJ), who sought, with the Medical Gas Safety Act, H.R. 2227, 112th Cong. (2011) to "create a new, targeted drug application process and regulatory regime specifically for medical gases." Press Release, Rep. Lance Introduces Medical Gas Safety Act (June 17, 2011).

FDASIA § 1111 amends the FDC Act to add Sections 575-577. FDC Act § 575 defines the term "medical gas" to mean a drug that "(A) is manufactured or stored in a liquefied, nonliquefied, or cryogenic state; and (B) is administered as a gas." FDC Act § 575(2), as amended by FDASIA § 1111. It also defines the current core medical gases (*i.e.*, oxygen, nitrogen, nitrous oxide, carbon dioxide, helium, carbon monoxide, and medical air) – each identified as a "designated medical gas" – and provides FDA with the authority to add an additional medical gas as a "designated medical gas" as the Agency deems appropriate, *see* FDC Act § 575(1)(H), but with the caveat that such additional gas "have a history of safe and effective use." H.R. Rep. No. 112-495, at 33. Prior to adding a new "designated medical gas," FDA is required to assess whether there are any pending medical gas Investigational New Drug Applications ("INDs") (for humans or animals). FDA is prohibited from identifying a medical gas as a "designated medical gas" if that gas is subject to an unexpired period of NCE exclusivity, including a period of applicable pediatric exclusivity. *See* FDC Act § 575(1)(H), as amended by FDASIA § 1111.

FDC Act § 576 establishes a process for the filing of a certification with FDA for the designation of a medical gas as a "designated medical gas." Such a certification, the contents of which are specified in FDC Act § 576(a)(1), may be submitted to FDA beginning on January 5, 2013, and is deemed to be granted unless denied by FDA within 60 days of filing. FDA can revoke a certification if the Agency determines that the certification request contains any material omission or falsification. *See id.* § 576(a)(4)(B), as amended by FDASIA § 1111.

A “designated medical gas” subject to a granted certification is deemed to have in effect an approval under FDC Act § 505 (human drug) or FDC Act § 512 (animal drug), “alone or in combination, as medically appropriate, with another designated medical gas or gases for which a certification or certifications have been granted,” for both specific uses listed in the statute and additional uses added by FDA. Id. § 576(a)(3)(A), as amended by FDASIA § 1111. FDA is prohibited from adding additional uses if a designated medical gas is subject to an unexpired period of 3-year exclusivity or orphan drug exclusivity, including a period of applicable pediatric exclusivity. See id. § 576(a)(3)(A)(i)(VIII), as amended by FDASIA § 1111. In addition, a “designated medical gas” with a deemed approval is not eligible “for any period of exclusivity under section 505(c), 505(j), or 527, or the extension of any such period under section 505A, on the basis of such deemed approval.” Id. § 576(a)(3)(B)(i), as amended by FDASIA § 1111.

FDC Act § 576 also requires the labeling on a final use container for a “designated medical gas” to bear the “Rx only” legend, a warning statement concerning the use of the medical gas as determined by FDA by regulation, and appropriate directions and warnings concerning storage and handling. See id. § 576(a)(3)(A)(ii), as amended by FDASIA § 1111. Except for oxygen, the FDC Act’s prescription requirements would continue to apply to a “designated medical gas” unless FDA removes such requirement pursuant to FDC Act § 505(b)(3), the “designated medical gas” is approved for Over-the-Counter (“OTC”) use under a marketing application, or “the use in question is authorized pursuant to another provision of [the FDC Act] relating to use of medical products in emergencies.” Id. § 576(b)(1), as amended by FDASIA § 1111. Oxygen may be provided OTC: (1) “[f]or use in the event of depressurization or other environmental oxygen deficiency;” and (2) “[f]or oxygen deficiency or for use in emergency resuscitation, when administered by properly trained personnel.” See id. § 576(b)(2), as amended by FDASIA § 1111.

FDC Act § 577 provides for the exemption of PDUFA user fees and states: “A designated medical gas, alone or in combination with another designated gas or gases (as medically appropriate) deemed under [FDC Act § 576] to have in effect an approved application shall not be assessed fees under [FDC Act § 736(a)] on the basis of such deemed approval.” See id. § 577, as amended by FDASIA § 1111.

FDASIA § 1112 requires FDA to determine whether any changes are necessary to existing regulations pertaining to drugs as a result of the enactment of the new statutory requirements for medical gases. After obtaining input from medical gas manufacturers and other interested parties regarding the applicability of current federal drug regulations to medical gases, FDA must submit a report to Congress regarding any such changes not later than January 9, 2014. FDASIA § 1112(a). If FDA determines that changes to

federal drug regulations are necessary for medical gases, then FDA must promulgate final regulations not later than July 9, 2016. According to the House Report on these medical gas provisions, FDA is expected to “address longstanding regulatory issues faced by the medical gas industry based on the unique characteristics of medical gases.” H.R. Rep. No. 112-495, at 34.

FDASIA § 1113 provides certain rules of construction with respect to FDASIA §§ 1111-1112 and the changes made to the FDC Act that are intended to “preserve the NDA process for medical gases,” and “maintain the incentive to innovate and develop new uses for a new medical gas added to the list of Designated Medical Gases.” *Id.* Specifically, the law provides that FDASIA’s medical gas provisions do not apply to: (1) a drug that is approved under FDC Act § 505 or § 512 prior to May 1, 2012; (2) any core medical gases (*i.e.*, oxygen, nitrogen, nitrous oxide, carbon dioxide, helium, carbon monoxide, and medical air) or any combination of any such gases for an indication that is not included in, or is different from, those specified in FDC Act § 576(a)(3)(A)(i)(I)-(VII) of such Act and that is approved under FDC Act § 505 or § 512 on or after May 1, 2012; or (3) any “designated medical gas” added by FDA pursuant to FDC Act § 575(1)(H) that is not included in, or is different from, those originally added pursuant to FDC Act § 575(1)(H) and FDC Act § 576(a)(3)(A)(i)(VIII) and that is approved under FDC Act § 505 or § 512 on or after May 1, 2012. *See* FDASIA § 113.

C. Subtitle C - Miscellaneous Provisions

1. Internet Product Promotion

FDASIA § 1121 requires FDA to issue guidance describing its policy regarding use of the internet (including social media) in the promotion of medical products. FDA has two years to issue this guidance.

2. Combating Prescription Drug Abuse

As part of its effort to combat prescription drug abuse, Congress, through FDASIA, requires the Secretary to review federal initiatives and “identify gaps and opportunities” for: (1) ensuring the safe use of prescription drugs that have the potential for abuse; and (2) treatment of prescription drug dependence. FDASIA § 1122(a). In addition, by July 9, 2013 the Secretary must post a report on the Department of Health and Human Services (“HHS”) website that includes certain findings and recommendations. *See id.* Further, by January 9, 2013, the Secretary must promulgate guidance on the development of “abuse deterrent” drug products. *Id.* § 1122(c).

The Senate and final versions of the bill deleted the requirement that the Secretary consider the safe disposal of prescription drugs. In addition, the House version would have required FDA to promulgate guidance on “tamper deterrent” versus “abuse deterrent” drugs. See FDA Reform Act of 2012, H.R. 5651, 112th Cong. § 866(a), (c).

3. Optimizing Global Clinical Trials

This section amends the FDC Act to add a requirement for the Secretary to work with other regulators around the world, medical research companies, and international organizations to foster uniform, scientifically driven clinical trial standards, and to enhance the commitment to provide consistent scientific advice to manufacturers in order to reduce duplication of studies necessary for premarket approval of drugs, biologics, and medical devices without altering the current standards for premarket review of such medical products. See FDC Act § 569A, as added by FDASIA § 1123. It would also require the Secretary to accept foreign clinical data if the applicant demonstrates that such data are adequate to support approval, licensure or clearance under applicable FDA standards, or notify the sponsor of its rationale for concluding that the data are not adequate. See id. § 569B, as added by FDASIA § 1123.

4. Advancing Regulatory Science

By July 9, 2013, the Secretary must establish a strategy and implementation plan for advancing regulatory science in order to promote the public health and advance innovation in regulatory decision-making. See FDASIA § 1124(a). The strategy and implementation plan must identify a “clear vision of the fundamental role of efficient, consistent, and predictable, science-based decisions throughout [FDA] regulatory decisionmaking . . . with respect to medical products,” include FDA’s regulatory science priorities related to medical product decision-making, and identify regulatory and scientific gaps “that impede the timely development and review of, and regulatory certainty with respect to, the approval, licensure, or clearance of medical products.” Id. § 1124(b). The Secretary must report on the progress made towards achieving these goals.

5. Information Technology

FDASIA § 1125 requires the Secretary to issue a report describing a comprehensive information technology strategy plan, including an inventory of current systems, use of the systems, and ways in which FDA can modernize its projects and activities.

6. Nanotechnology

FDASIA requires FDA to “intensify and expand activities related to enhancing scientific knowledge regarding nanomaterials included or intended for inclusion in products regulated” under the FDC Act. FDASIA § 1126(a). In doing so, FDA may assess the potential toxicology of nanomaterials, their potential benefits in new therapies, and their effect on and interaction with biological systems in a variety of ways. See id. § 1126(b).

7. Online Pharmacy Report to Congress

By July 9, 2013, the GAO must issue a report describing “any problems posed by pharmacy Internet Web sites that violate Federal or State law.” FDASIA § 1127. Among other things, this report must include the methods by which online pharmacies sell prescription drugs in violation of state or federal law or established industry standards, the harm to patients, efforts to investigate and prosecute the owners or operators of online pharmacies and to protect patients, and whether additional laws could assist Federal, State, and local governments in investigating and prosecuting the owners and operators of pharmacy Internet Web sites. See id.

8. Report on Small Businesses

By July 9, 2013, FDA must submit a report to Congress regarding issues related to small businesses, including opportunities and resources that FDA makes available to small businesses. See FDASIA § 1128. Congress is particularly interested in the number of marketing applications for orphan drugs made by small businesses, the number of applications approved for orphan drug research grants, and the number of companies receiving protocol assistance for the development of drugs for rare diseases and disorders. The report must also describe the “barriers small businesses encounter in the drug and medical device approval process.” Id.

9. Whistleblower Protections

FDASIA amends PHS Act § 221(a) (42 U.S.C. § 213a(a)) to extend whistleblower protections to the Commissioned Corps of the Public Health Service Act. See FDASIA § 1129.

10. OTC Sunscreen Drug Products

FDASIA requires FDA to comply with certain requirements for labeling and effectiveness testing for certain OTC sunscreen drug products containing specified active

ingredients and marketed without approved applications. FDA discussed these requirements in a June 2011 final rule and established effective dates of June 18, 2012 (for OTC sunscreen drug products with annual sales of \$25,000 or more) and June 17, 2013 (for OTC sunscreen drug products with annual sales of less than \$25,000). See 76 Fed. Reg. 35,620 (June 17, 2011).

In May 2012, FDA announced a delay in the 2011 final rule's compliance dates "because information received after publication of the 2011 final rule indicates that full implementation of the 2011 final rule's requirements for all affected products will require an additional 6 months." 77 Fed. Reg. 27,591 (May 11, 2012). Instead, compliance with the requirements in the June 2011 rule would be December 17, 2012 (for OTC sunscreen drug products with annual sales of \$25,000 or more) and December 17, 2013 (for OTC sunscreen drug products with annual sales of less than \$25,000).

FDASIA § 1130 is intended to prevent further delay in the effective date of FDA's June 2011 rule, and states that a product subject to the final rule "shall comply with such rule not later than – (1) December 17, 2013, for products subject to such rule with annual sales of less than \$25,000 and (2) December 17, 2012, for all other products subject to such rule." FDASIA § 1130.

11. Strategic Integrated Management Plan

FDASIA § 1131 requires the Secretary to submit to Congress a "strategic integrated management plan" for the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health. The "strategic integrated management plan" must: (1) "identify strategic institutional goals, priorities, and mechanisms to improve efficiency" among the Centers; (2) "describe the actions the Secretary will take to recruit, retain, train, and continue to develop the workforce at the [Centers] to fulfill the public health mission of the Food and Drug Administration," and (3) "identify results-oriented, outcome-based measures that the Secretary will use to measure the progress of achieving" the items and actions under (1) and (2), "including metrics to ensure that managers and reviewers of the [Centers] are familiar with and appropriately and consistently apply the requirements under the [FDC Act]," including new requirements under PDUFA, MDUFA, GDUFA, and BsUFA.

This section is one component of a broader bill – the Promoting Accountability, Transparency, Innovation, Efficiency, and Timeliness at FDA Act of 2012 (or the ("PATIENTS' FDA Act") (S. 2292) – Senator Richard Burr (R-NC) introduced in April 2012 that was intended to enhance FDA transparency and accountability. FDASIA § 1131 finds its roots in a February 2010 GAO report finding that FDA does not fully use

established practices for effective strategic planning and management. See U.S. Gov't Accountability Office, GAO-10-279, FDA: Opportunities Exist to Better Address Management Challenges (2010), available at <http://www.gao.gov/assets/310/300950.pdf>.

12. REMS Assessment and Modification

FDASIA amends FDC Act § 505-1(g) to make the REMS system created by FDAAA more efficient by allowing for minor modifications of a drug's REMS. Some drugs and biologics are required by FDA to have a REMS to ensure that the benefits of the drug outweigh the risks. Under the law, the sponsor must submit periodic assessments of the REMS to determine whether the goals established in the REMS are being met. The current law ties modifications of the REMS to an assessment. FDASIA amends the FDC Act to clarify that a sponsor may propose a modification to an approved REMS at any time. See FDC Act § 505-1(g)(4), as amended by FDASIA § 1132(a)(4). The law is further amended to clarify that FDA would have 180 days to review and act on the proposed modification, unless the modification was deemed to be "minor," in which case FDA would have 60 days to act. See id. § 505-1(h), as amended by FDASIA § 1132(b)(5)(A). FDA has one year to issue guidance describing minor modifications. FDA must also implement guidance describing certain modifications to an approved REMS that can be made following simple notification to the Agency. In addition, FDASIA requires FDA to issue an action letter describing the actions taken by FDA in response to a proposed modification of a approved REMS.

13. Extension of ANDA Tentative Approval Period

FDASIA § 1133 concerns FDC Act § 505(j)(5)(D)(i)(IV), which is one of the six 180-day generic drug exclusivity forfeiture provisions added to the FDC Act by Title XI of the MMA. Under FDC Act § 505(j)(5)(D)(i)(IV), 180-day exclusivity eligibility is forfeited if:

The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

FDAAA clarified FDC Act § 505(j)(5)(D)(i)(IV), such that if "approval of the [ANDA] was delayed because of a [citizen] petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final Agency action on the petition (inclusive of such beginning and ending dates)" FDC Act § 505(q)(1)(G).

FDA has very strictly and narrowly interpreted FDC Act § 505(j)(5)(D)(i)(IV). For example, FDA interprets FDC Act § 505(j)(5)(D)(i)(IV) such that when an ANDA sponsor who amends a long-pending ANDA to include a Paragraph IV certification to an Orange Book-listed patent and qualifies as a “first applicant,” that sponsor may simultaneously forfeit 180-day exclusivity eligibility for failure to obtain timely tentative approval because FDA counts 30 months from the ANDA submission date and not from the first Paragraph IV certification date. Moreover, FDA’s growing median ANDA approval time – about 32-33 months today – has led to concerns about first applicants forfeiting 180-day exclusivity eligibility as a result of FDA delays.

FDASIA § 1133 is intended to address the above-referenced concerns expressed by the generic drug industry. Specifically, FDASIA § 1133 would provide that the time to obtain timely tentative approval (or final approval if tentative approval is not warranted) under FDC Act § 505(j)(5)(D)(i)(IV) for an ANDA submitted to FDA between January 9, 2010 and July 9, 2012 initially containing a Paragraph IV certification to a patent listed in the Orange Book for the Reference Listed Drug (“RLD”), or that is amended between January 9, 2010 and July 9, 2012 to first contain a Paragraph IV certification to a patent listed in the Orange Book for the RLD, is 40 months during the period of July 9, 2012 and September 30, 2015, and not 30 months. During the period beginning on October 1, 2015 and ending on September 30, 2016, the period under FDC Act § 505(j)(5)(D)(i)(IV) is 36 months and not 30 months. See FDASIA § 1133(a). A conforming amendment is made to FDC Act § 505(q)(1)(G) concerning extension of the tentative approval period under FDC Act § 505(j)(5)(D)(i)(IV). See id. § 1133(b).

While FDASIA § 1133(a) concerns 180-day exclusivity only for ANDAs submitted or amended up to July 9, 2012, FDASIA § 1133(b) concerns 180-day exclusivity for ANDAs first amended after July 9, 2012 to contain a Paragraph IV certification. Specifically, this subsection provides that for an ANDA submitted to FDA prior to July 9, 2012 that is first amended on July 10, 2012 and up to September 30, 2017 to contain a Paragraph IV certification to a patent listed in the Orange Book for the RLD, thereby qualifying the applicant as a “first applicant” eligible for a period of 180-day exclusivity, “the date of the filing of such amendment (rather than the date of the filing of such application) shall be treated as the beginning of the 30-month period described in [FDC Act § 505(j)(5)(D)(i)(IV)].” Id.

14. Discontinuation Citizen Petition Decision Deadline

Under FDC Act § 505(j)(4)(I), FDA may refuse to approve an ANDA if the Agency determines that the RLD was withdrawn from sale for reasons of safety or

effectiveness. In addition, FDA can withdraw (or suspend) approval of an ANDA if the RLD is withdrawn from sale for reasons of safety or effectiveness. See FDC Act § 505(j)(6). In that case, the RLD is removed from the Orange Book. See id. § 505(j)(7)(C).

FDA acknowledged in the preamble to the Agency's July 1989 proposed regulations implementing the 1984 Hatch-Waxman Amendments that the law does not "specify procedures to be followed in determining whether a drug that is voluntarily withdrawn from sale by its manufacturer is withdrawn for safety or effectiveness reasons." 54 Fed. Reg. 28,872, 28,907 (July 10, 1989). As such, FDA took it upon itself to create such a procedure. FDA's interpretation of the Hatch-Waxman Amendments is embodied in the Agency's regulations at 21 C.F.R. § 314.161.

FDA has not had a specific timeframe for responding to withdrawal petitions. In some cases FDA has responded within months (see, e.g., Docket No. FDA-2011-P-0128), while in other cases it has taken FDA more than three years to respond (see, e.g., Docket No. FDA-2008-P-0527). One likely explanation for FDA's different response timeframes is that the Agency only responds to such a petition when it becomes necessary to do so; that is, when the Agency is poised to make an approval decision.

In what is widely believed to be an effort to make FDASIA compliant with the Statutory Pay-As-You-Go Act of 2010, FDASIA amends FDC Act § 505 to add a new subsection to require FDA to issue a final, substantive determination on a petition submitted pursuant to 21 C.F.R. § 314.161(b) "no later than 270 days after the date the petition is submitted." FDC Act § 505(w), as amended by FDASIA § 1134(a). The new requirement applies to any petition that is submitted pursuant to 21 C.F.R. § 314.161(b) on or after July 9, 2012. See FDASIA § 1134(b).

15. FDC Act § 505(q) Citizen Petitions

Another provision added to the FDC Act that is widely believed to be a pay-for for other FDASIA provisions is FDASIA § 1135. FDASIA § 1135 amends FDC Act § 505(q) to shorten the timeframe FDA has to respond to certain citizen petitions, and to expand the reach of the provision.

FDC Act § 505(q), which was added to the law as part of FDAAA, provides that FDA shall not delay approval of a pending ANDA or 505(b)(2) application as a result of a citizen petition submitted to the Agency pursuant to 21 C.F.R. § 10.30 (citizen petition) or § 10.35 (petition for stay of action), unless FDA "determines, upon reviewing the petition, that a delay is necessary to protect the public health." FDC Act § 505(q)(1)(A)(ii). Prior to the enactment of FDASIA, FDC Act § 505(q) stated that

“[FDA] shall take final agency action on a petition not later than 180 days after the date on which the petition is submitted.” FDA may not extend the period “for any reason,” including consent of the petitioner, and may summarily deny a petition submitted with the primary purpose of delaying ANDA or 505(b)(2) application approval. *Id.* §§ 505(q)(1)(E), (F). FDA only rarely misses the 180-day timeframe.

FDASIA § 1135 amends FDC Act § 505(q) to reduce the 180-day citizen petition response timeframe to 150 days. *See* FDC Act §§ 505(q)(1)(F), 505(q)(2)(A), as amended by FDASIA § 1135. It also makes FDC Act § 505(q) applicable not only to citizen petitions concerning pending ANDAs and 505(b)(2) applications, but also to citizen petitions concerning biosimilar applications submitted to FDA pursuant to PHS Act § 351(k). *See id.* § 505(q)(1)(A), as amended by FDASIA § 1135. Finally, FDASIA § 1135 provides that FDC Act § 505(q)(2), which concerns exhaustion of administrative remedies, “does not apply to a petition addressing issues concerning an application submitted pursuant to [PHS Act § 351(k)].” *Id.* § 505(q)(4)(B), as amended by FDASIA § 1135.

FDASIA § 1135 appears to be intended to realize greater savings from generic drug and biosimilar approvals as a result of quicker FDA decisions on citizen petitions. FDC Act § 505(q) petition decisions, however, often are not keyed to generic drug approval decisions. As such, it seems more likely that FDA, with a 150-day response timeframe, will issue more non-response petition denials.

16. Electronic Submission of Applications

With respect to drug and biologic submissions under FDC Act § 505(b) (NDAs), FDC Act § 505(i) (INDs), FDC Act § 505(j) (ANDAs), PHS Act § 351(a) (Reference Product BLAs), and PHS Act § 351(k) (Biosimilar BLAs), electronic submissions to FDA will be required beginning no earlier than 24 months after FDA issues final guidance. *See* FDC Act § 745A(a)(1), as amended by FDASIA § 1136. In such guidance, FDA may provide a timetable of further electronic submission standards, as well as waiver criteria and exemptions. *See id.* § 745A(a)(2), as amended by FDASIA § 1136. So-called Compassionate Use INDs submitted under FDC Act § 561 are excepted from the electronic submission requirements. *See id.* § 745A(a)(3), as amended by FDASIA § 1136. This section is presumably intended to complete the evolution of electronic submissions that began about two decades ago. *See generally* FDA, Electronic Submissions and the Electronic Common Technical Document eCTD, available at <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM275455.pdf>.

With respect to medical device submissions, FDASIA § 1136 requires an electronic copy for device pre-submissions and submissions submitted under FDC Act

§ 510(k), § 513(f)(2)(A), § 515(c), § 515(d), § 515(f), § 520(g), § 520(m), § 564, or PHS Act § 351 following issuance of final FDA guidance. FDC Act § 745A(b)(1), as amended by FDASIA § 1136. Such guidance may provide electronic copy submission standards and set forth criteria waivers and exemptions criteria. See id. § 745A(b)(2), as amended by FDASIA § 1136.

17. Patient Participation in Medical Product Discussions

FDASIA amends the FDC Act to require the Secretary “to develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions.” FDC Act § 569C(a), as added by FDASIA § 1137. This could include allowing a patient representative in FDA meetings with medical product sponsors and investigators, and trying to identify patient representatives who do not have extensive financial interests in the medical products industry. The law is not intended to affect the protection of confidential commercial or trade secret information, or to create a right for such consultation.

18. Ensuring Adequate Drug Information

FDA is required to develop a communication plan “to inform and educate health care providers and patients on the benefits and risks of medical products, with particular focus on underrepresented subpopulations, including racial subgroups.” FDASIA § 1138(a). This plan must be issued by July 9, 2013.

19. Hydrocodone Scheduling

In FDASIA’s final legislative stages, Congress amended one of its more controversial provisions that would have required the rescheduling of combination hydrocodone products from Schedule III to Schedule II under the Controlled Substances Act (“CSA”). The CSA controls substances of abuse under 5 schedules determined by, upon other things, the drug’s potential for abuse. See 21 U.S.C. § 812. Schedule II substances are considered to have a greater potential for abuse than those in schedule III. See id. In addition, Schedule II substances are subject to stricter controls than those in Schedules III, IV, and V, including ordering, recordkeeping, dispensing, and storage requirements. The legislative hydrocodone rescheduling provision ran into opposition from patient advocacy and pharmacy groups who wrote letters to Congress expressing concerns that rescheduling would unduly restrict legitimate patient access to needed medications and impose burdens upon pharmacies.

Legislatively rescheduling the combination hydrocodone products through FDASIA would have bypassed the administrative proceedings that the Drug Enforcement Administration (“DEA”) is otherwise required to follow when scheduling, rescheduling or descheduling a drug.²² Instead, FDASIA requires FDA to “hold a public meeting to solicit advice and recommendations to assist in conducting a scientific and medical evaluation in connection with a scheduling recommendation to the DEA regarding drug products containing hydrocodone combined with other analgesics or as an antitussive.” FDASIA § 1139(a).

FDA published notice of a public meeting of the Drug Safety and Risk Management Committee to be held on October 29 and 30, 2012 to discuss “the public health benefits and risks, including the potential for abuse, of drugs containing hydrocodone either combined with other analgesics or as an antitussive.” 77 Fed. Reg. 34,051 (June 8, 2012). The Notice states that FDA is calling for the meeting because DEA requested HHS to conduct a scientific and medical evaluation, and scheduling recommendation, for hydrocodone combination products, “in response to continued reports of misuse, abuse, and addiction related to these products.” *Id.* The completion of a scientific and medical evaluation by FDA is a significant step to DEA’s administrative rulemaking proceedings to reschedule the hydrocodone products. See 21 U.S.C. § 811(b).

FDASIA further requires the Secretary to solicit stakeholder input “regarding the health benefits and risks, including the potential for abuse and the impact of up-scheduling of these products.” FDASIA § 1139. In conducting any rescheduling evaluation, DEA must consider 8 factors. See 21 U.S.C. § 811(c). Outside of FDASIA, however, FDA is not required to obtain such outsider input for DEA rescheduling. See id. § 811.

20. Study on Drug Labeling by Electronic Means

By July 9, 2013, the Comptroller General must submit to Congress a report on the on the benefits and efficiencies of electronic patient labeling of prescription drugs, as a complete or partial substitute for patient labeling in paper form. See FDASIA § 1140. The study must address the implementation costs to the different levels of the distribution system, logistical barriers to utilizing a system of electronic patient labeling, and any anticipated public health impact of movement to electronic labeling. See id. § 1140 (a). The provision likely stems from urging by industry that FDA speed revised drug product

²² See 21 U.S.C. § 811; see also 28 C.F.R. § 0.100(b) (delegating authority to the Administrator from the Attorney General to reschedule a drug); Touby v. United States, 500 U.S. 160 (1991) (upholding that delegation as constitutional).

labeling requirements to formally establish the National Library of Medicine's DailyMed Web Site as the primary authoritative source for product information.

21. Recommendations on Interoperability Standards

State-operated Prescription Drug Monitoring Programs ("PDMPs") have emerged as a popular tool to combat prescription drug abuse. These programs track prescribing and dispensing of certain controlled substances to patients by prescriber and can be used to identify behaviors indicative of diversion or abuse such as "doctor shopping" and overprescribing, and they can assist law-enforcement and regulators in detecting diversion and insurance fraud. PDMPs can also help avoid unintended drug interactions. PDMPs typically require reporting by physicians and pharmacists and the prescribing/dispensing records can be viewed by practitioners as well as law-enforcement officers, under certain restrictions. See Fact Sheet, Office of National Drug Control Policy, Prescription Drug Monitoring Programs, Fact Sheet (Apr. 2011), available at http://www.whitehouse.gov/sites/default/files/ondcp/Fact_Sheets/pdmp_fact_sheet_4-8-11.pdf.

In 2011, 35 states had operational PDMPs and 12 additional jurisdictions had legislation authorizing the operation of PDMPs. See id. However, mechanisms do not currently exist that would enable interstate PDMP communication. Interstate communication could assist in the detection of diversion that occurs between states, where drug-seeking patients travel to obtain controlled substances for other than legitimate medical purposes from areas with less stringent anti-diversion controls to evade potential detection.

FDASIA § 1141 seeks to enhance communication and the interoperability between state PDMPs by allowing the Secretary to facilitate (with consultation by the Attorney General) standards for the exchange of information between states that receive federal funds for their PDMPs through: (1) DOJ's Harold Rogers Prescription Drug Monitoring Program; and (2) HHS's Controlled Substance Monitoring Program. See FDASIA § 1141(a). In facilitating those standards, FDASIA § 1141(b) requires the Secretary to take into account several considerations enumerated in the law.

The Secretary must submit by July 9, 2012 a report to Congress on enhancing the interoperability of state PDMPs with other technologies and databases used to detect and reduce fraud, diversion, and prescription drug abuse. See id. § 1141(c). The report must assess the legal, technical, fiscal, privacy or security challenges that impact interoperability; discuss how state PDMPs could increase the production and distribution of unsolicited reports to practitioners, law-enforcement officials and regulators; provide

recommendations that address challenges that impact interoperability; and assess the extent to which providers use PDMPs. See id.

22. Conflicts of Interest

Effective October 1, 2012, FDASIA § 1142 significantly amends FDC Act § 712 to improve FDA's conflict of interest rules to enable FDA's advisory committees to have access to the most knowledgeable experts. See FDASIA § 1142(b). FDAAA included a provision designed to limit conflicts of interest and restrict those eligible to serve on FDA advisory committees. Congress believes this provision discouraged the use of the most qualified experts from serving on FDA advisory committees, thus preventing the advisory committees from providing the best guidance to FDA on important scientific issues. See H.R. Rep. No. 112-495, at 25.

FDASIA strikes FDC Act §§ 712(b) and (c), which govern recruitment and limits on waivers. In their place, the new law requires FDA to actively recruit to fill the Agency's advisory committees in order to have access to the most current expert advice. See FDC Act § 712(b), as amended by FDASIA § 1142.

The new law also requires FDA to provide transparency regarding the type, nature, and magnitude of relevant financial interests of advisory committee members. Specifically, it retains FDA's current prohibition regarding conflicts of interest and associated waiver for essential expertise, as well as the requirements to disclose such waivers either 15 or more days in advance or less than 30 days in advance of the meeting, depending on when the financial interest becomes known. See id. § 712(c), as amended by FDASIA § 1142. Written determinations and written certifications are still required to be disclosed on FDA's website, but the new law adds that the Secretary's reasons for the determination or certification may include the public health interest in having the member's expertise with respect to the particular matter before the committee. See id. The new law retains the requirement that the public record and transcript of each advisory committee include the required waiver disclosure. See id. § 712(d), as amended by FDASIA § 1142.

FDASIA changes the types of information that the Secretary is required to report annually to Congress under FDC Act § 712(e). With respect to information on the FY that ended on September 30 of the previous year, the law retains only the requirement to report the number of vacancies and adds requirements to report: (1) the number of persons nominated for participation in meetings for each advisory committee; (2) the number of persons so nominated, and willing to serve; and (3) the number of persons contacted for service as members of each advisory committee meeting for each advisory committee who did not participate because of the potential for participation to constitute

a disqualifying financial interest. See id. § 712(e)(1)(A), as amended by FDASIA § 1142.

With respect to the current year, the new law removes the existing reporting requirements and instead requires reporting of the number of members contacted for service who did not participate for reasons *other than* the potential for participation to constitute a disqualifying financial interest, the number of members attending meetings for each advisory committee, and the aggregate number of disclosures required and the percentage of individuals to whom such disclosures did not apply who served on the committee. See id. § 712(e)(1), as amended by FDASIA § 1142. The Secretary is required to make the report available to the public within 30 days of its submission to Congress. See id. § 712(e)(2), as amended by FDASIA § 1142.

Finally, FDASIA § 1142 requires the Secretary to issue guidance that describes how the Secretary reviewed the financial interests and involvement of advisory committee members that are disclosed pursuant to FDC Act § 712(c) but that the Secretary determined did not meet the definition of a disqualifying interest. See id. § 712(g), as amended by FDASIA § 1142.

23. Laboratory Developed Tests

FDASIA requires FDA to notify Congress at least 60 days prior to issuing a draft or final guidance on the regulation of Laboratory Developed Tests (“LDTs”). The notice must include anticipated details of the action. The requirement sunsets in 5 years.

As background, an LDT is a diagnostic test developed and performed by a single laboratory. This category includes virtually all genetic tests and many tests for rare conditions and companion diagnostics (used in conjunction with pharmaceuticals). Starting in 1992, FDA asserted that all LDTs are devices subject to regulation under the FDC Act. Since then, FDA said it was exercising its enforcement discretion and not regulating LDTs, leaving primary federal regulation of laboratories to a separate law that governs laboratories. FDA announced in June 2010 that it was revisiting its years-long policy of exercising enforcement discretion over LDTs. FDA officials subsequently indicated a plan to more actively regulate LDTs under a risk-based framework, to be issued for comment as guidance. Members of the laboratory community have expressed concerns about the particulars of such a framework. The draft framework is believed to be under OMB review.

D. Subtitle D – Synthetic Drugs

In a provision that DEA commended Congress for including in the final bill, FDASIA amends the CSA by legislatively scheduling 26 synthetic substances under Schedule I. See News Release, DEA, Congress Agrees to Add 26 Synthetic Drugs to the Controlled Substances Act (June 19, 2012) available at <http://www.justice.gov/dea/pubs/pressrel/pr061912.html>. Schedule I controlled substances have a high potential for abuse, no currently accepted medical use in treatment in the U.S., and a lack of accepted safety for use under medical supervision. See 21 U.S.C. § 812(b)(1). Marijuana is a Schedule I controlled substance. See id. § 812(c).

FDASIA amends the CSA by adding a new subsection to control any material, compound, mixture or preparation unless specifically exempted or scheduled elsewhere, that contains any quantity of “cannabimimetic agents” under Schedule I. See 21 U.S.C. § 812(d)(1), as amended by FDASIA § 1152. In so doing, the CSA, by default, now controls substances that meet the new statutory definition. FDASIA amends the law to define “cannabimimetic agents” as any substance that “is a cannabinoid receptor type 1 (CB1 receptor) agonist as demonstrated by binding studies and functional assays” that falls within the five specifically identified structural classes. Id. 21 U.S.C. § 812(d)(2), as amended by FDASIA § 1152. FDASIA identifies 15 specific agents that meet this definition. See id. § 812(d)(2)(B), as amended by FDASIA § 1152. In addition, FDASIA amends subsection 21 U.S.C. § 812(c), which designates marijuana, mescaline, peyote and psilocybin as a Schedule I controlled substances, to include 11 additional substances.

DEA already placed some of the substances scheduled in FDASIA in Schedule I through the Agency’s temporary emergency scheduling authorization. Section 811(h) authorizes the Attorney General to immediately and temporarily control a drug or other substance, without following notice-and-comment rulemaking procedures, in Schedule I if he finds that scheduling “is necessary to avoid an imminent hazard to the public safety.” Id. § 811(h)(1). Prior to FDASIA, the scheduling of a drug or other substance pursuant to that provision expired after one year, yet during its pendency, could have been extended by the Attorney General for up to 6 months. See id. § 811(h)(2). FDASIA § 1153, however, extends the temporary scheduling period to 2 years, with extensions up to 1 year.

On March 1, 2011 DEA temporarily scheduled 5 agents used to create the fake-marijuana products popularly dubbed as “K-2” and “Spice,” all of which are scheduled under FDASIA. Contemporaneous with that scheduling, the DEA Administrator explained that the action, “while temporary, will reduce the number of young people being seen in hospital emergency rooms after ingesting these synthetic chemicals to get

high.” News Release, DEA, Chemicals Used in “Spice” and “K2” Type Products Under Federal Control and Regulation (Mar. 1, 2011), available at <http://www.justice.gov/dea/pubs/pressrel/pr030111.html>. DEA extended temporary placement of those substances in Schedule I. See 77 Fed. Reg. 12,201 (Feb. 29, 2012). The next day, DEA published a Notice of Proposed Rulemaking to permanently place the 5 chemicals in Schedule I. See 77 Fed. Reg. 12,508 (Mar. 1, 2012).

FDASIA’s legislative scheduling ends these DEA rulemaking proceedings, which would have required the Agency to make specific findings regarding the substances’ potential for abuse, their pharmacological effect, and their psychic and physiological dependence liability. See 21 U.S.C. § 811. FDASIA’s scheduling also removes the requirement that the Secretary issue a scientific and medical evaluation and the possibility of DEA holding an administrative hearing. See id. Instead, the drugs that were previously scheduled pursuant to DEA’s emergency scheduling provision are now permanently scheduled, as are other substances named in the new provision and those that meet the new statutory definition of “cannabimimetic agents.”

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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 FDASIA, please contact Kurt R. Karst (202.737.7544), David B. Clissold (202.737.7545), or Jeffrey K. Shapiro (202.737.9633).