

E-ALERT | Food & Drug

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FOOD AND DRUG ADMINISTRATION SAFETY AND INNOVATION ACT OF 2012

On July 9, 2012, President Barack Obama signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA).¹ This law, containing 11 titles, reauthorizes and amends both the prescription drug user fee program and the medical device user fee program. It also authorizes new user fees for generic drugs and biosimilars. In addition to the provisions relating to user fees, the FDASIA amends the Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Service Act (PHSA) in ways intended to, among other things, encourage the development of pediatric drugs, combat potential drug product shortages, and enhance patients' access to medical treatments and participation in medical product regulation. This memorandum summarizes the FDASIA, presenting the law's provisions in the order of the FDASIA's titles.

TITLE I — PRESCRIPTION DRUG USER FEE AMENDMENTS OF 2012

Title I reauthorizes the Prescription Drug User Fee Act (PDUFA) through fiscal year 2017.² The reauthorization includes a target of \$633,099,000 in total fees for fiscal year 2013, with revised inflation and workload adjustments for subsequent years. The reauthorization keeps many of the previous limits on fees, including the "reverse trigger" that could reduce fee levels if FDA's total appropriations are increased (adjusted for inflation) for the years after 2013. The reauthorization also alters an exception to the product fee for drugs that are the same as another product already approved under a new drug application (NDA) or abbreviated new drug application (ANDA). The law now specifies that such previously approved products must not be on the "list of discontinued products compiled under section 505(j)(7)."³

As was the case in previous versions of PDUFA, FDA must provide yearly reports that detail the progress FDA has made in meeting FDA's performance goals. The "goals letter" posted on FDA's website describes these performance goals.⁴ Under the FDASIA, however, FDA now will be required to provide detailed data on the progress of drug approvals at CDER and CBER, including data on the number of applications of various types that were submitted and approved over a given fiscal year.⁵

Some of the FDA performance goals have changed in comparison to the performance goals under PDUFA IV. For original NDA applications, the performance goals are largely the same, in particular the requirement that FDA must act on at least 90% of non-New Molecular Entity (NME) NDAs within 10 months. FDA has created a new review model, however, for NME NDAs and original biologics

¹ Pub. L. No. 112-144, 126 Stat. 993 (2012).

² FDASIA § 103 (amending FDCA § 736). FDA must make available to the public a transcript of any negotiations with the regulated industry prior to presenting Congress with recommendations for PDUFA VI. Further, FDA must provide its recommendations for PDUFA VI for public comment prior to presenting the recommendations to Congress. FDCA § 736B(d).

³ *Id.* (amending FDCA § 736(a)(3)).

⁴ FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, available [here](#) [hereinafter PDUFA Performance Goals].

⁵ FDASIA § 104 (amending FDCA § 736B(a)).

license applications (BLAs) that are received on or after October 1, 2012.⁶ This new review model includes a recommended pre-submission meeting,⁷ mid-cycle communication, and a late-cycle status meeting. These applications are subject to different review goals than other original applications, with the time period for review starting after the 60-day filing period of the application, not the receipt date. Further, the new FDA performance goals change the way FDA will handle major amendments. Under the PDUFA IV performance goals, FDA could extend the PDUFA date based on submission of a major amendment only if that amendment was submitted within three months of the PDUFA date. Under the PDUFA V goals, FDA may extend the PDUFA date based on a major amendment submitted at any time during the review process. Finally, the FDA performance goals include provisions for enhancing and expediting drug development.

TITLE II — MEDICAL DEVICE USER FEE AMENDMENTS OF 2012

Title II of the FDASIA reauthorizes and amends FDA's medical device user fee program.⁸ The Medical Device User Fee Amendments (MDUFA) was first enacted in 2002 and reauthorized in 2007 for fiscal years 2008 to 2012. Under the user fee provisions, medical device companies pay user fees when they register and list with FDA and when they submit an application or notification to market a medical device in the United States. MDUFA III will be in effect starting on October 1, 2012 until it sunsets five years later in 2017. Under the new agreement, FDA can collect \$595 million (plus adjustments for inflation) in user fees over the five years.

FDA claims that it will be able to hire more than 200 full-time-equivalent workers with the additional funding by the time MDUFA III sunsets in five years.⁹ In addition to the funding, the Act grants FDA streamlined hiring authority for three years after enactment. Section 208 of the FDASIA adds section 714 to the FDCA to allow FDA to appoint employees to perform, administer, or support MDUFA activities without regard to statutory provisions governing appointments in the competitive service.

MDUFA III expands the definition of the types of manufacturers that must pay a registration fee. Previously, the Act covered only three categories of establishments: manufacturers, single use device reproducers, and specification developers. As amended, "establishments subject to a registration fee" now include all establishments that are required to register with FDA "because such establishment is engaged in the manufacture, preparation, propagation, compounding, or processing of a device."¹⁰ While subject to some ambiguity, this amendment will likely mean that establishments such as relabelers, repackagers, and initial importers that currently are required to register with FDA but do not pay the establishment fee,¹¹ may now be required to pay establishment fees.

MDUFA III increases the base fee and total revenue amounts.¹² Fees relating to premarket submissions are set as a percentage of the Premarket Application (PMA) fee. The 510(k) fee will rise from 1.84% to 2% of the PMA fee, but all other fee percentages will remain the same. Below are the standard and small business fees for FY 2013:

⁶ PDUFA Performance Goals, at 5-11. More details on the new review model for NME NDAs and original BLAs are available [here](#).

⁷ FDA and the applicant can work together during the pre-submission meeting to reach agreement on the content of the complete application. *Id.* at 6.

⁸ FDASIA § 208 (amending FDCA § 738(a)).

⁹ FDA, Fact Sheet: Medical Device User Fee Amendments of 2012, available [here](#).

¹⁰ FDASIA § 202 (amending FDCA § 737).

¹¹ See FDA "Who Must Register, List, and Pay the Fee," available [here](#).

¹² FDASIA § 203 (amending FDCA § 738(b)).

Fee Type	FY 2013 Standard Fee	FY 2013 Small Business Fee
PMA	\$248,000	\$62,000
Efficacy Supplement	\$248,000	\$62,000
Panel-track Supplement	\$186,000	\$46,500
180-Day Supplement	\$37,200	\$9,300
Real-Time Supplement	\$17,360	\$4,340
510(k)	\$4,960	\$2,480
Establishment Registration	\$2,575	\$2,575
Total Revenue	\$97,722,301	

For fiscal year 2014 and the following years, the total revenue amounts will be adjusted for inflation. The below table sets forth the base fee (PMA) amounts, establishment registration fee, and total revenue, which FDA will then adjust for inflation 60 days before the start of the next fiscal year.

	FY 2014	FY 2015	FY 2016	FY 2017
Base Fee	\$252,960	\$258,019	\$263,180	\$268,443
Establishment Registration	\$3,200	\$3,750	\$3,872	\$3,872
Total Revenue	\$112,580,497	\$125,767,107	\$129,339,949	\$130,184,348

MDUFA III also includes a provision permitting FDA to waive or reduce medical device fees. At FDA's sole discretion, FDA may grant a waiver or reduction of these fees if "in the interest of public health;" however, the sum of all waivers and reductions in any fiscal year cannot exceed 2% of the total revenue amount for that year.¹³

In addition, FDA committed to process and timing improvements in its MDUFA Performance Goals and Procedures ("MDUFA Performance Goals").¹⁴ For PMAs, Panel-Track Supplements, and Premarket Report Applications, FDA will communicate whether the application has been accepted for filing review within 15 calendar days of receipt. If the application is filed, FDA will communicate with the applicant through a "Substantive Interaction"¹⁵ within 90 calendar days of the filing date of the application for: 65% of submissions received in FY 2013; 75% of submissions received in FY 2014; 85% of submissions received in FY 2015; and 95% of submissions received in FY 2016 through FY 2017. FDA will issue decisions for 90% of submissions received by FY 2017 within 180 days for submissions that do not require Advisory Committee input, and within 320 days for submissions that require Advisory Committee input.

¹³ *Id.* (amending FDCA § 738(f)).

¹⁴ See FDA, MDUFA III Commitment Letter and Performance Goals (Apr. 18, 2012), at 7, available [here](#). [hereinafter MDUFA Performance Goals].

¹⁵ "Substantive Interaction" is defined as "an email, letter, teleconference, video conference, fax, or other form of communication such as a request for Additional Information or Major Deficiency letters by FDA notifying the applicant of substantive deficiencies identified in initial submission review, or a communication stating that FDA has not identified any deficiencies in the initial submission review and any further minor deficiencies will be communicated through interactive review. An approval or clearance letter issued prior to the Substantive Interaction goal date will qualify as a Substantive Interaction." *Id.* at 18.

For 510(k) submissions, FDA commits to communicate whether the submission has been accepted for review within 15 calendar days of receipt.¹⁶ FDA will communicate with the applicant through a “Substantive Interaction” within 60 calendar days of receipt of the submission for: 65% of submissions received in FY 2013; 75% of submissions received in FY 2014; 85% of submissions received in FY 2015; and 95% of submissions received in FY 2016 through FY 2017. FDA commits to issuing a MDUFA decision for 91% of 510(k) submissions within 90 days in FY 2013, increasing to 95% for submissions received in FY 2015 through FY 2017.

Throughout the discussions leading up to the FDASIA, one of the primary issues raised by industry was the overall review time for devices, which FDA calls “Total Time to Decision.” The Total Time to Decision includes both the time FDA expends to review the application or notification and the time the manufacturer spends answering questions raised by FDA.¹⁷ Over the last several years, the Total Time to Decision has increased, even as time spent by FDA reviewing an application met user fee goals. For example, according to FDA’s statistics, the average total number of days to decision for a 510(k) increased from 90 days in 2005 to 151 days in 2010.¹⁸ Accordingly, as stated in the MDUFA III Commitment Letter, “the process improvements outlined in [the MDUFA goals], when implemented by all parties as intended, should reduce the average Total Time to Decision for PMA applications and 510(k) submissions, provided that the total funding of the device review program adheres to the assumptions underlying this agreement.”¹⁹ In addition, one of the most important elements of MDUFA III is the commitment by FDA to report on the total number of days to a MDUFA decision. In its quarterly reports, FDA will report on the “average and quintiles of the number of calendar days to Substantive Interaction” and “average, and quintiles of the number of FDA Days, Industry Days, and Total Days to a MDUFA decision” for 510(k)s and PMAs.²⁰ For annual reports, the Agency will report on the “[p]erformance on the shared outcome goal for average Total Time to decision.”²¹

In addition, FDA will engage an independent expert to conduct a comprehensive assessment of the process for the review of device applications.²² The scope of the assessment will include (1) identification of process improvements and best practices for conducting predictable, efficient, and consistent premarket reviews; (2) analysis of elements of the review process that consume or save time to facilitate a more efficient process; (3) assessment of FDA methods and controls for collecting and reporting information on premarket review process resource use and performance; (4) assessment of effectiveness of FDA’s Reviewer Training Program implementation; and (5) recommendations for ongoing periodic assessments and any additional, more detailed or focused assessments. The assessment will be conducted in two phases. For the first phase, FDA will award the contract no later than the second quarter of FY 2013. Findings on high-priority recommendations – those likely to have a significant impact on review times – will be published within six months of the award, and final comprehensive findings will be published within one year. FDA will publish an implementation plan within six months of receipt of the recommendations. For the second phase, the contractor will evaluate FDA’s implementation of the recommendations and

¹⁶ MDUFA Performance Goals at 9.

¹⁷ “Total Time to Decision” is defined as “the number of calendar days from the date of receipt of an accepted or filed submission to a MDUFA decision.” *Id.* at 19. FDA’s MDUFA Performance Goals document describes how FDA will calculate Total Time to Decision for 510(k)s and PMAs. *Id.*

¹⁸ See Statement of Jeffrey Shuren, M.D., J.D., Director CDRH Before the Committee on Energy and Commerce, Subcommittee on Health, U.S. House of Representatives (Feb. 15, 2012).

¹⁹ MDUFA Performance Goals at 11.

²⁰ For original PMAs, a “MDUFA decision” includes the following: Approval, Approvable, Approvable Pending GMP Inspection, Not Approvable, Withdrawal, and Denial. For 510(k)s, a MDUFA decision includes substantially equivalent (SE) or not substantially equivalent (NSE) determinations.

²¹ *Id.* at 15.

²² *Id.* at 12.

publish a written assessment no later than February 1, 2016. In addition to incorporating the findings and recommendations into its management of the premarket review program, FDA will incorporate the results of the assessment into a Good Review Management Practices (GRMP) guidance document. To implement the guidance, FDA will conduct training of FDA staff and periodic audits of compliance.

TITLE III — GENERIC DRUG USER FEE AMENDMENTS OF 2012

Title III of the FDASIA contains the Generic Drug User Fee Act (GDUFA), a first ever user fee program for generic drugs.²³ Like PDUFA and MDUFA, GDUFA sunsets in 2017.²⁴ It includes a target of \$299 million in total fees for fiscal year 2013, with inflation and workload adjustments for subsequent years. Fifty million of the total fees will be from a one-time ANDA backlog fee, while the remaining \$249 million will come from several other fees that are similar to fees applied under PDUFA. The fees established by GDUFA are as follows:

The first fee is the one-time ANDA backlog fee.²⁵ GDUFA imposes this fee on all sponsors of ANDA applications that are pending on October 1, 2012.²⁶ FDA will calculate this fee by dividing \$50 million by the total number of ANDAs pending on October 1, 2012. Thus, all sponsors of pending applications must contribute to help lessen the backlog of existing applications. The ANDA backlog fee is due within 30 days of publication of notice of the fee in the Federal Register. Failure to pay will result in placing the ANDA owner on a publicly available arrears list, “such that no new abbreviated new drug applications or supplement submitted on or after October 1, 2012, from that person, or any affiliate of that person, will be received . . . until such outstanding fee is paid.”²⁷

The new law also imposes a one-time drug master file fee.²⁸ Each holder of a Type II active pharmaceutical ingredient (“API”) drug master file that is referenced on or after October 1, 2012 must pay this fee. The total amount of drug master file fees will be 6% of the \$249 million, including inflation adjustments. Failure to pay this fee, which is due on the date of first reference to the drug master file, will result in that drug master file not being “available” for reference.

The third and fourth fees are original ANDA fees and prior approval supplement fees.²⁹ These fees must be paid for each ANDA or prior approval supplement application submitted after October 1, 2012. These two fees are due at the time of submission of an ANDA or a prior approval supplement application; however, there is a “special rule” for fiscal year 2013 because of the possibility that the fee publication in the Federal Register and enactment of the corresponding appropriations act may not take place before October 1, 2012. The prior approval supplement fee will be 50% of the cost of an original ANDA fee. The total amount of ANDA and prior approval supplement fees will be 24% of the \$249 million, including inflation adjustments. Failure to pay these fees within 20 days of submission will result in the application not being considered as received by FDA. This would be particularly significant if the application might otherwise be eligible for 180-day exclusivity and the delay allowed a subsequent applicant to become the first filer and eligible for 180-day exclusivity. If

²³ FDASIA § 302 (adding FDCA §§ 744A-744C).

²⁴ FDA must make available to the public a transcript of any negotiations with the generic drug industry prior to presenting recommendations for GDUFA II to Congress. Further, FDA must provide its recommendations for GDUFA II for public comment prior to presenting the recommendations to Congress.

²⁵ *Id.* (adding FDCA § 744B(a)(1)).

²⁶ Sponsors of currently pending ANDAs have the option to withdraw their application before October 1, 2012 and avoid the fee.

²⁷ *Id.* (adding FDCA § 744B(g)(1)).

²⁸ *Id.* (adding FDCA § 744B(a)(2)).

²⁹ *Id.* (adding FDCA § 744B(a)(3)).

the application involves information from the manufacturer of an API that is not included by reference to a Type II drug master file, the applicant will be required to pay additional fees.

The last two fees are facilities fees — a finished dosage form facility fee and an API facility fee.³⁰ This annual fee must be paid by each person that owns a facility that produces either a final dosage form or API and is listed in a generic drug submission. The total amount of the facilities fees will be 70% of the \$249 million, including inflation adjustments. The fees for the finished dosage form facilities will be higher than those for the API facilities. Foreign facilities identified in generic drug applications will be assessed an additional fee between \$15,000 to \$30,000. Any facility that produces both API and finished dosage form products must pay both the API facility fee and the finished dosage form facility fee.

Penalties for failure to pay the facilities fees are severe. First, no new ANDA or supplement application will be received by FDA from the person responsible for the fee (or any affiliate). Second, FDA will not receive any new generic drug submission that references such a facility if the outstanding fee is not paid within 20 calendar days from FDA providing notification to the sponsor of the failure of the owner of the facility to pay the fee. In addition, all drugs or API that are manufactured at such a facility, or containing an ingredient manufactured in such facility, will be deemed to be misbranded. Further, unlike under PDUFA or BSUFA, there are no waivers for the fees imposed by GDUFA. In particular, there is no small business exception under the GDUFA provisions.

The GDUFA Program Performance Goals and Procedures (“GDUFA Performance Goals”) contain detailed information on the ANDA review and action goals FDA agreed to meet.³¹ Although FDA agreed to performance goals, the goals initially are not as specific as those for other user fee programs. For example, for fiscal years 2013 and 2014, the Agency does not commit to a specific review goal but states it “will 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.”³² Starting in FY 2015, FDA sets timelines for ANDA review with a target of acting on at least 90% of all complete ANDAs within 10 months of submission by fiscal year 2017.

Finally, GDUFA also imposes significant reporting requirements on FDA.³³ FDA must submit an annual report to Congress that details the progress of FDA in meeting its performance goals under GDUFA. Further, FDA must submit detailed statistics regarding the number of ANDAs submitted in a given year, the amount of time that applications are pending, and the amount of time before for approvals. FDA must also make these reports available to the public.

TITLE IV — BIOSIMILAR USER FEE ACT OF 2012

The last user fee act included in the FDASIA is the Biosimilar User Fee Act of 2012 (BSUFA).³⁴ Like PDUFA, MDUFA, and GDUFA, BSUFA extends through fiscal year 2017.³⁵ It imposes four separate types of fees, each of which is tied directly to the amounts of PDUFA V fees.

³⁰ *Id.* (adding FDCA § 744B(a)(4)). For a facility that produces both an API and a finished dosage form, both fees will be assessed against the applicant. *Id.*

³¹ FDA, Generic Drug User Fee Act Program Performance Goals and Procedures, available [here](#) [hereinafter GDUFA Performance Goals].

³² *Id.* at 6, 10.

³³ FDASIA § 303 (adding FDCA § 744C(a)); *Id.* § 308 (amending FDCA § 715).

³⁴ FDASIA § 402 (adding FDCA § 744H).

³⁵ FDA must make available to the public a transcript of any negotiations with the regulated industry prior to presenting recommendations for BSUFA II to Congress. Further, FDA must provide its recommendations for BSUFA II for public comment prior to presenting the recommendations to Congress.

The first fee created under BSUFA is the biosimilar development program fee, equal to 10% of the application fee under PDUFA for the applicable fiscal year.³⁶ The initial biosimilar development program fee is due upon either (1) the date of submission of a clinical protocol for an IND pursuant to § 505(i) intended to support a biosimilar biological product application as determined by FDA,³⁷ or (2) within five days of FDA granting a biosimilar biological product development meeting. Companies that submitted an applicable IND pursuant to § 505(i) prior to the enactment of FDASIA must still pay the initial biosimilar development fee. An annual fee is then due for each year that the sponsor remains in the biological development program.³⁸ The annual fee will be due until either the person has submitted a marketing application for the biological product or discontinued participation in the development program. If the sponsor discontinues participation then seeks to reactivate participation in the program, the sponsor will have to pay a significant fee, equal to 20% of the application fee FDA establishes under PDUFA for that particular fiscal year. If a sponsor fails to pay the biosimilar development fee, the sponsor may not take part in a biological product development meeting, will lose the ability to have an IND reviewed under § 505(i), will have a “financial hold” placed upon the IND that prohibits continuation of clinical investigations on the biosimilar product, and will not be able to have any other biosimilar applications reviewed until the fee is paid. For the biosimilar development program fee, there are no waivers or exemptions.

The second fee under BSUFA is an application and supplement fee, which is similar to the PDUFA application and supplement fees.³⁹ These fees must be paid at the time of submission of any biosimilar application or supplement. The amount of the fee is tied to the fee for a human drug application under PDUFA. However, if the biosimilar application does not require clinical safety or effectiveness data, the fee is only half of the PDUFA application fees. Also, the application fee will be reduced by an amount equal to the cumulative biosimilar biological product development fees previously paid by the sponsor.

The third fee under BSUFA is a product establishment fee.⁴⁰ This annual fee is assessed against each applicant for each product establishment identified in an application. The establishment fee will be imposed only once per establishment, regardless of the number of different biological products produced at that establishment. The amount of the fee is tied to the establishment fee for a human drug application under PDUFA.

The final fee under BSUFA is the biosimilar biological product fee.⁴¹ This annual fee is assessed against each person named in a biosimilar application. The product fee will only be paid once annually for each product. The amount of the fee will be the same as the product fee for a human drug application under PDUFA.

Failure to pay any of the fees discussed above will result in the biosimilar application being considered incomplete.⁴² BSUFA provides for a small business fee waiver for the first biosimilar biological product application submitted by a “small business” or affiliate. To qualify, the small business must have fewer than 500 employees and must not have any other drug products approved under human drug or biosimilar applications.

³⁶ *Id.* (adding FDCA § 744H(b)(1)(A) & (B)).

³⁷ This would include clinical investigations that FDA determines are necessary to support a biosimilar application under § 262(k).

³⁸ *Id.* (adding FDCA § 744H(a)(1)(B)).

³⁹ *Id.* (adding FDCA § 744H(a)(2)).

⁴⁰ *Id.* (adding FDCA § 744H(a)(3)).

⁴¹ *Id.* (adding FDCA § 744H(a)(4)).

⁴² *Id.* (adding FDCA § 744H(d)).

The Biosimilar Biological Product Authorization Performance Goals and Procedures (“BSUFA Performance Goals”) set forth concrete FDA review goals for fiscal years 2013 to 2017.⁴³ In fiscal year 2013, FDA has a target of reviewing 70% of original biosimilar biological product application submissions within 10 months of receipt, with that target rising to 90% by fiscal year 2017. In addition, the Agency has a target of reviewing 70% of resubmitted original biosimilar biological product applications within six months, and rising to 90% by fiscal year 2017.

Finally, BSUFA imposes significant reporting requirements on FDA.⁴⁴ FDA must submit an annual report to Congress that details the progress of FDA in meeting its performance goals under BSUFA. Further, FDA must submit detailed statistics regarding the number of § 351(k) applications submitted in a given year and the percentage of applications approved for that year. FDA must also make these reports available to the public.

TITLE V — PEDIATRIC DRUGS AND DEVICES

Title V of the FDASIA strikes the sunset provisions for the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), thus making both Acts permanent.⁴⁵ The FDASIA also creates new provisions governing deferral extensions under the PREA. On its own initiative or upon request, FDA may grant an extension of a pediatric study deferral, provided that the applicable PREA criteria for deferral are still met and the applicant submits certain materials in support of the extension.⁴⁶ Applicants must submit requests for deferral extensions to FDA not less than 90 days before the date the deferral would otherwise expire. If an applicant fails to comply with specific PREA obligations, FDA must issue a non-compliance letter to the sponsor, the sponsor must respond in writing, and FDA must make both documents publicly available. If, however, FDA determines that the letter was issued in error, these requirements do not apply.

Section 506 of the FDASIA amends the FDCA to include specific requirements for pediatric study plans. Under the law, an applicant must submit an initial pediatric study plan — including any requests for deferral or waiver — before the date the applicant submits a required assessment, and within 60 days after the applicant’s end-of-Phase 2 meeting, or at another agreed-upon time.⁴⁷ FDA must provide comments on the initial plan, and, within 90 days of receiving comments from FDA, the applicant must submit a revised plan. Within 30 days thereafter, FDA must confirm in writing that it agrees with the revised plan. Either FDA or the applicant may initiate amendments to the study plan, subject to these same procedures.

Title V also makes a variety of technical amendments to the FDCA.⁴⁸ Section 509 of the FDASIA revises section 505A(o) of the FDCA, which governs the requirements for generic drug labeling that omits pediatric labeling protected by exclusivity. Under the law, FDA may require such generic labeling to include — in addition to the current information on pediatric contraindications, warnings, and precautions — “other information that [FDA] considers necessary to assure safe use.”⁴⁹ Additionally, the FDASIA amends FDCA section 505A(n) on referrals of pediatric study needs to the National Institutes of Health (NIH). Under the new law, FDA is no longer required to refer studies to the NIH when a sponsor (with unexpired listed patents or certain unexpired exclusivities) declines a written request for pediatric studies or has not submitted study reports by the date specified in the

⁴³ FDA, Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2013 Through 2012, available [here](#).

⁴⁴ FDASIA § 403 (adding FDCA § 744I); *Id.* § 408 (amending FDCA § 715).

⁴⁵ *Id.* § 501 (amending FDCA §§ 505A & 505B).

⁴⁶ *Id.* § 505(a) (adding FDCA § 505B(a)(3)(B)).

⁴⁷ *Id.* § 506(a) (amending FDCA § 505B(e)).

⁴⁸ *Id.* § 509 (amending FDCA §§ 505A & 505B; PHS § 409I).

⁴⁹ *Id.* § 509(a)(4) (amending FDCA § 505A(o)).

request. Instead, FDA determines whether an assessment shall be required under the PREA. Further, section 509 of the FDASIA:

- extends the adverse event reporting period, and subsequent review of the reports by the Pediatric Advisory Committee (PAC), from one year to 18 months after a pediatric labeling change;
- eliminates certain preconditions formerly required before FDA could require sponsors of marketed drugs and biologics conduct pediatric assessments of those products (e.g., reference to a declined written request not referred to the NIH);
- extends the deadline for FDA to invoke its statutory dispute resolution procedure with respect to pediatric labeling negotiations for drugs receiving a standard review;
- permits the Director of the NIH to submit to FDA a proposed pediatric study request for a biosimilar application approved under PHSA section 351(k); and
- provides that the effective date for any amendment made by the FDASIA to the BPCA or the PREA is the date of the FDASIA's enactment, July 9, 2012.

Within one year of enactment of the FDASIA, FDA must issue internal standard operating procedures for the Pediatric Review Committee's review of significant changes to written requests for pediatric studies and pediatric study plans.⁵⁰ FDA must make these procedures publicly available by posting them to the Agency's website. Further, within three years of the FDASIA's enactment, FDA must publicly release certain specified review documents and written requests for pediatric studies submitted between 2002 and September 2007 that resulted in pediatric exclusivity and labeling changes.⁵¹

The FDASIA also addresses a number of procedural and administrative issues. Beginning four years after the FDASIA's enactment, and every five years thereafter, FDA must receive public comment and report to Congress regarding the effectiveness of the BPCA and the PREA.⁵² Also, the FDASIA provides that FDA must hold a public meeting and issue a report on strategies to accelerate the development of therapies for treating pediatric rare diseases.⁵³ Further, it requires that the staff of the Office of Pediatric Therapeutics must include one or more individuals with expertise in neonatology and pediatric epidemiology.⁵⁴ Section 507 of the FDASIA permanently reauthorizes the PAC under the BPCA, and reauthorizes the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) for the duration of ODAC's operation.⁵⁵ It also amends section 520(m) of the FDCA to extend to 2017 the provision allowing a profit on sales of pediatric devices under a humanitarian device exemption (HDE).

Finally, the FDASIA revises section 505A(h) of the FDCA. Among other changes, FDCA section 505A(h) now states that written requests for pediatric studies under the BPCA "may consist of a study or studies required under [PREA]."⁵⁶ Further, it amends the Biologics Price Competition and Innovation Act (BPCIA) to cross-reference FDCA sections 505A(h) and 505A(n),⁵⁷ thereby making these provisions applicable to biologics "to the same extent and in the same manner" as they apply

⁵⁰ *Id.* § 503.

⁵¹ *Id.* § 504.

⁵² *Id.* § 508.

⁵³ *Id.* § 510.

⁵⁴ *Id.* § 511 (amending BPCA § 6).

⁵⁵ *Id.* § 507 (amending BPCA §§ 14(d), 15(a)(3)).

⁵⁶ *Id.* § 502(a)(1) (amending FDCA § 505A(h)).

⁵⁷ *Id.* § 502(a)(2) (amending PHSA § 351(m)(1)).

to drugs. If a written request from FDA does not include studies in neonates, section 502(b) of the FDASIA requires FDA to include a statement describing the rationale for not requesting such a study.

TITLE VI — MEDICAL DEVICE REGULATORY IMPROVEMENTS

A. Investigational Device Exemptions

Section 601 amends section 520(g) of the FDCA regarding investigational device exemptions (IDEs). First, the FDASIA amends the conditions for granting an IDE to clarify that “safety or effectiveness” data obtained as a result of the investigational use of the device must be submitted to FDA.

Second, newly-added section 520(g)(4)(C) of the FDCA narrows the circumstances when FDA may disapprove an IDE, stating that FDA shall *not* disapprove an application because FDA determines that:

- (i) the investigation may not support a substantial equivalence or de novo classification determination or approval of the device; (ii) the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or (iii) an additional or different investigation may be necessary to support clearance or approval of the device.⁵⁸

B. Clarification of Least Burdensome Standard

The “least burdensome” principle was originally added to the FDCA in the Food and Drug Administration Modernization Act of 1997 (FDAMA) and instructs FDA to consider the “least burdensome” means to achieve a premarket objective, such as clearance of a 510(k) or approval of a PMA.⁵⁹ However, in recent years, controversy has emerged about whether the least burdensome principle remained a meaningful statutory provision. For example, in 2011, a group of lawmakers submitted a letter to FDA questioning whether FDA was honoring the least burdensome principle.⁶⁰

In light of that background, the FDASIA amends FDCA section 513(a)(3)(D) concerning the type of valid scientific evidence necessary to demonstrate the effectiveness of an application for premarket approval. Section 602 provides that for purposes of this clause, the term “necessary” means “the minimum required information that would support a determination by [FDA] that [a PMA] provides reasonable assurance of the effectiveness of the device.”⁶¹

Similarly, for premarket notifications under section 510(k), the FDASIA amends section 513(i)(1)(D) to state that “necessary” means “the minimum required information that would support a determination of substantial equivalence between a new device and a predicate device.”⁶² The amendment clarifies that these changes to the law do not alter the criteria or standard for evaluating a PMA or 510(k).

C. Agency Documentation and Review of Significant Decisions

Section 603 adds new section 517A to the FDCA, “Agency Documentation and Review of Significant Decisions Regarding Devices.” Upon request, FDA must provide a “substantive summary of the

⁵⁸ *Id.* § 601, (adding FDCA § 520(g)(4)(C)).

⁵⁹ FDAMA § 205 (Pub. Law No. 105-115) (amending FDCA § 513).

⁶⁰ See Letter from Fred Upton, Chairman, Committee on Energy and Commerce, U.S. House of Representatives (Jun. 23, 2011).

⁶¹ FDASIA § 602 (amending FDCA § 513(a)(3)(D)).

⁶² *Id.* (amending FDCA § 513(i)(1)(D)).

scientific and regulatory rationale for any significant decision” of CDRH regarding submission or review of a 510(k) report, an application for premarket approval under section 515, or an application for exemption for investigational use under section 520(g) to the person who submitted the report or application. “Significant decision” is not defined.

In addition, “[a]ny person” may request a supervisory review of this decision. The review “may be conducted at the next supervisory level or higher above the individual who made the significant decision.”⁶³ New section 517A applies time deadlines to the process of requesting supervisory review. To request review, a person must submit a request to FDA not later than 30 days after the decision, and indicate whether he seeks an in-person meeting or teleconference review. Except for cases that are referred to experts outside FDA, the Agency must schedule the review not later than 30 days after the request and issue a decision not later than 45 days after the request or 30 days after the meeting or teleconference.

D. Device Modifications Requiring Premarket Notification Prior to Marketing

FDASIA section 604 amends FDCA section 510(n) to add new provisions regarding device modifications.⁶⁴ First, new section 510(n)(2)(A) requires FDA to submit a report to Congress on when a 510(k) should be submitted for a modification to a legally marketed device. The report must be submitted within 18 months of enactment (by January 9, 2014). The report must include FDA’s interpretation of the following terms: (1) “could significantly affect the safety or effectiveness of the device;” (2) “a significant change or modification in design, material, chemical composition, energy source, or manufacturing process;” and (3) “major change or modification in the intended use of the device.”⁶⁵ In addition, the report must discuss possible processes for industry to use to determine whether a new 510(k) submission is required. It must also analyze how to leverage existing quality system requirements to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of safety and effectiveness of modified devices. FDA must consider the input of interested stakeholders in developing the report.

Second, newly-added section 510(n)(2)(B) requires FDA to withdraw and cease reliance on the July 27, 2011 draft guidance entitled “Guidance for Industry and FDA Staff—510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device.” Further, FDA shall not issue any draft guidance or proposed regulation on this topic until submitting the required report to Congress. In addition, FDA may not issue any final guidance or regulation until one year after the report is submitted. Instead, FDA’s January 10, 1997 guidance, “Deciding When to Submit a 510(k) for a Change to an Existing Device,” will be in effect until a new guidance or regulation is finalized. FDA must interpret the guidance “in a manner that is consistent with the manner in which [FDA] has interpreted such guidance since 1997.”⁶⁶

E. Program to Improve the Device Recall System

The FDASIA adds section 518A, “Program to Improve the Device Recall System.” The section applies to recalls initiated by FDA and to removal or correction initiated by a device manufacturer or importer. Although a timeline is not given for implementation, FDA must “establish a program to routinely and systematically assess information relating to device recalls and use such information to proactively identify strategies for mitigating health risks presented by defective or unsafe devices.”⁶⁷ In addition, FDA is required to clarify procedures for conducting recall audit checks, develop

⁶³ *Id.* § 603 (adding FDCA § 517A).

⁶⁴ *Id.* § 604 (adding FDCA § 510(n)(2)(A)-(C)).

⁶⁵ *Id.* (adding FDCA § 501(n)(2)(A)).

⁶⁶ *Id.* (adding FDCA § 510(n)(2)(C)).

⁶⁷ *Id.* § 605 (adding FDCA § 518A).

“detailed criteria” to assess whether a recall contained an effective correction or action plan, and document the basis for termination of a recall by FDA. At a minimum, the program must identify “(1) trends in the number and types of device recalls; (2) devices that are most frequently the subject of a recall; and (3) underlying causes of device recalls.”⁶⁸

F. Clinical Holds

Section 606 amends section 520(g) of the FDCA to give FDA authority to issue a clinical hold on a trial conducted under an IDE. FDA may issue a clinical hold if it finds that the “device involved represents an unreasonable risk to the safety” of the trial participants.⁶⁹ FDA also may establish other reasons (by regulation) for imposing a clinical hold. FDA is required to make a decision within 30 days on a request from a sponsor that the clinic hold be lifted.

Previously, FDA lacked express statutory authority to issue a clinical hold for IDEs. The language of section 606 is similar to the language added by FDAMA with respect to human drugs.

G. Modification of the De Novo Process

Section 513(f)(2) of the FDCA has allowed a sponsor that received a determination that a proposed new device was not substantially equivalent (NSE) to a predicate to request that FDA reclassify the device from class III to a lower classification. Originally enacted as part of FDAMA, this “de novo” reclassification process was intended to provide a relatively quick and simple way to reclassify a device that is placed into class III due to lack of a sufficient predicate device. In practice, however, the de novo process proved to be somewhat cumbersome, due in part to the requirement to submit a 510(k) that the sponsor expected to be rejected. In an October 2011 draft guidance document, FDA attempted to streamline this process by providing for additional opportunities for early interaction between FDA and sponsors and proposing other procedural changes.⁷⁰

FDASIA section 607 implements additional changes to the de novo process.⁷¹ Most importantly, under newly amended section 513(f)(2)(A), a person may submit a de novo petition “in lieu” of a 510(k), rather than having to wait for an NSE determination before submitting a de novo petition. In addition, the statute directs FDA to classify the device within 120 days following receipt of the de novo application. If the sponsor seeks reclassification into class II, the sponsor must include a draft proposal for special controls that are necessary to provide a reasonable assurance of the safety and effectiveness of the device. The amendment clarifies that FDA may “decline to undertake a classification” if FDA either (1) identifies a legally marketed predicate device that would be appropriate for a 510(k), or (2) determines that the device is not low-moderate risk or that general controls would be inadequate to control the risks and special controls cannot be developed.

H. Reclassification Procedures

In addition to amending the de novo classification process, the FDASIA makes significant amendments to the process described in section 513(e) of the FDCA for reclassifying devices. Prior to the FDASIA, section 513(e) required FDA to reclassify devices through notice-and-comment rulemaking. Due to the administrative burden of issuing such regulations, however, FDA has reclassified relatively few devices through this process.

⁶⁸ *Id.*

⁶⁹ *Id.* § 606 (amending FDCA § 520(g)).

⁷⁰ FDA Draft Guidance, *De Novo Classification Process (Evaluation of Automatic Class III Designation)*, (Oct. 3, 2011), available [here](#).

⁷¹ FDASIA § 607 (amending FDCA § 513(f)(2)).

Section 608 of the FDASIA amends section 513(e) of the FDCA to allow FDA to change a device's classification through administrative order, instead of promulgating a regulation.⁷² Amended section 513(e)(1)(A)(i) states that FDA may publish an administrative order in the Federal Register to reclassify a device following publication of a proposed order, a meeting of the device classification panel, and consideration of comments filed to a public docket. The order may be issued on FDA's own initiative or in response to a petition. The proposed order is required to set forth a substantive summary of valid scientific evidence, including the public health benefits and risks of the device, an explanation of why general and special controls are insufficient to reasonably assure safety and efficacy for switches from class II to class III, and an explanation of why general and special controls are sufficient to reasonably assure safety and efficacy for switches from class III to class II. Like pre-existing law, FDA may order that the classification is not effective until a performance standard is established under section 514 for the device. Authority to issue the order cannot be delegated below the director of CDRH, acting in consultation with the Commissioner.

Section 608 also amends FDCA section 515 to allow FDA to require PMAs for pre-amendment class III devices by administrative order, rather than regulation.

I. International Harmonization and Participation in International Fora

Sections 609 and 610 of the FDASIA amend section 803(c) of the FDCA in two ways.⁷³ First, section 803(c)(4) is amended to permit FDA to enter into arrangements with other nations regarding methods for harmonizing device-related regulatory requirements, including inspections and the use of common international labeling symbols. Second, section 610 amends FDCA section 803(c)(3) to allow FDA to participate in international fora, including the International Medical Device Regulators forum.

J. Reauthorization of 510(k) Third-Party Reviews and Inspections

FDASIA section 611 reauthorizes the 510(k) third-party review program first created by FDAMA for an additional five years.⁷⁴ The purpose of the program was to improve the efficiency and timeliness of FDA's 510(k) process. Under the program, FDA accredits third parties who are authorized to conduct the primary review of 510(k)s for eligible devices. Persons who are required to submit 510(k)s for these devices may elect to contract with an "Accredited Person" and submit a 510(k) directly to the Accredited Person. The Accredited Person conducts the primary review of the 510(k), then forwards its review, recommendation, and the 510(k) to FDA, which is required to make a final determination 30 days after receiving the recommendation. Section 611 also amends section 523(b)(2) to specify that accreditation lasts three years and requires FDA to publish a list of criteria to reaccredit or deny reaccreditation to third party reviewers.

Section 612 reauthorizes the third-party inspection program for medical devices.⁷⁵ This program was originally added to the FDCA by the Medical Device User Fee and Modernization Act of 2002.

K. Humanitarian Device Exemption

Section 613 of the FDASIA makes several revisions to the Humanitarian Device Exemption (HDE) program codified in section 520(m) of the FDCA. An HDE allows a device sponsor to market a device normally subject to PMA approval by demonstrating that: (1) the device is designed to treat a condition that affects fewer than 4,000 individuals in the United States; (2) no comparable devices

⁷² *Id.* § 608 (amending FDCA § 513(e)(1)).

⁷³ *Id.* §§ 609 & 610 (amending FDCA § 803(c)).

⁷⁴ *Id.* § 611 (amending FDCA § 523(b)(2)).

⁷⁵ *Id.* § 612 (amending FDCA § 704(g)(11)).

are on the market and the device would not be available to patients without an HDE; and (3) the device will not expose patients to an “unreasonable or significant risk of illness or injury[,] and the probable benefit . . . outweighs the risk of injury or illness.”⁷⁶

Section 520(m) generally prohibits an HDE sponsor from making a profit on sales of a device distributed under an HDE, except for devices intended to treat diseases or conditions that occur in pediatric patients or subpopulations. This exception for pediatric humanitarian devices was limited to the number of devices specified by an annual distribution number set by FDA, which by statute could not exceed 4,000 devices.

FDASIA section 613 amends FDCA section 520(m)(6) to broaden these exceptions. New section 520(m)(6)(a)(i)(II) will allow HDE sponsors to make a profit on sales of devices “intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe.”⁷⁷ Further, section 520(m)(6)(A)(ii) now defines the “annual distribution number” as the number “reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States.”⁷⁸ Manufacturers that obtained an HDE prior to enactment of the FDASIA are permitted to seek a determination under one of the provisions allowing profits on sales under amended section 520(m)(6).

L. Unique Device Identifier

Section 614 of the FDASIA requires FDA to issue a proposed rule regarding a unique device identifier (UDI) by December 31, 2012.⁷⁹ FDA must finalize the proposed regulations within six months after close of the comment period, and it is required to implement the rule with respect to implantable, life-saving and life sustaining devices within two years after finalization of the regulations, “taking into account patient access to medical devices and therapies.”⁸⁰

M. Sentinel and Post-Market Surveillance

Section 615 requires FDA to expand Sentinel, a post-market risk identification and analysis system, to medical devices.⁸¹ FDA is required to consult with stakeholders when implementing the system with respect to devices.

Section 616 amends section 522 of FDCA to authorize FDA to order post-market surveillance for certain class II and III devices “at the time of approval or clearance of the device or at any time thereafter.”⁸² Section 522 previously did not specify when FDA was permitted to issue such orders. Section 616 also amends section 522 to specify that manufacturers must commence surveillance within 15 months of a post-market surveillance order.

N. Custom Devices

The FDASIA makes several significant amendments to the statutory requirements for custom devices. Under section 520(b) of the FDCA, a device manufacturer is exempted from compliance

⁷⁶ FDCA § 520(m)(2).

⁷⁷ FDASIA § 613 (amending FDCA § 520(m)(6)).

⁷⁸ *Id.*

⁷⁹ FDA has already issued a proposed UDI regulation, published by the Agency prior to FDASIA being signed into law. Our client alert on the proposed regulation is available [here](#).

⁸⁰ *Id.* § 614 (amending FDCA § 519(f)).

⁸¹ *Id.* § 615 (adding FDCA § 519(h)).

⁸² *Id.* § 616 (amending FDCA § 522).

with sections 514 and 515 (performance standards and PMA approval) for custom devices that meet several criteria. Prior to amendment, section 520(b) required that the device: (1) necessarily deviate from an applicable performance standard or PMA requirement to meet the order of a physician or dentist; (2) not be generally available in finished form for purchase or dispensing upon prescription; (3) not be offered through advertising or labeling; (4) be intended for a specific patient and made in a specific form for that patient, or be intended to meet the special needs of a physician or dentist; and (5) not be generally available or generally used by other physicians or dentists.

Despite the considerable ambiguity in those statutory provisions, FDA never issued a guidance document on the Agency's views on custom devices. Instead, the Agency issued a number of warning and untitled letters, often taking a very restrictive view on when a device qualified as a custom device.

In light of that background, section 617 provides clarifications to the custom device program, including several new requirements. First, the custom device "must be designed to treat a unique pathology or physiological condition that no other device is domestically available to treat."⁸³ The device must also be "assembled from components or manufactured and finished on a case-by-case basis to accommodate the unique needs" of the user.⁸⁴ Nevertheless, custom devices "may have common, standardized design characteristics, chemical and material compositions, and manufacturing processes as commercially distributed devices."⁸⁵ Further, section 617 eliminates the requirement that the device, if built for a specific patient, be built in "a specific form" for the patient.

FDASIA section 617 also amends section 520(b) to specify that custom devices must be for the purpose of treating a "sufficiently rare condition, such that conducting clinical investigations" would be "impractical."⁸⁶ Further, the "production of such device . . . is limited to no more than 5 units per year of a particular device type, provided that such replication otherwise complies with this section."⁸⁷ FDA is required to issue guidance within two years of enactment on the replication of multiple devices. The manufacturer of the custom device must notify FDA on an annual basis of the manufacture of the device.

O. Health Information Technology

FDASIA section 618 requires FDA to issue, in consultation with the National Coordinator for Health Information Technology (HIT) and the Federal Communications Commission, a report that contains a proposed strategy and "risk-based regulatory framework pertaining to health information technology, including mobile medical applications."⁸⁸ The strategy must promote innovation, protect patient safety, and avoid regulatory duplication. FDA is permitted to set up a working group of external stakeholders to advise the Agency. Such a group must include a diverse set of stakeholders, including representatives of patients, health care providers, startup companies, insurance organizations, venture capital investors, and information technology vendors, among other groups.

FDA's position toward the regulation of HIT has been complex and, in many cases, unclear. FDA takes the position that certain types of HIT can meet the definition of a medical device. For example,

⁸³ *Id.* § 617 (amending FDCA § 520(b)).

⁸⁴ *Id.*

⁸⁵ *Id.*

⁸⁶ *Id.*

⁸⁷ Although the replication of a custom device will now be limited to no more than five units per year, FDA's prior warning letters regarding custom devices could be interpreted as permitting no replication. Thus, the inclusion in the statute of a specific number of units may provide helpful clarity in this area.

⁸⁸ *Id.* § 618(a).

FDA has promulgated a regulation classifying medical device data systems, which are devices that transfer, store, convert, and display data from medical devices but are not used for active patient monitoring.⁸⁹ FDA also regulates other types of HIT, including dosing calculators, laboratory information management systems, and radiological image software. For some types of HIT, however, including electronic health records, FDA has said that it will exercise enforcement discretion and not enforce regulatory requirements. Nevertheless, it is unclear how far this enforcement discretion extends, especially when software programs perform functions beyond basic storage and retrieval of health records.

A particularly challenging issue has been the recent proliferation of health-related mobile applications. In 2011, FDA released a draft guidance document regarding its regulation of mobile medical applications.⁹⁰ Some aspects of that draft guidance were controversial, including a proposal to regulate certain types of mobile medical apps that simply automate simple, well-accepted algorithms, such as Apgar scoring. An earlier version of the user fee legislation would have prohibited FDA from finalizing this draft guidance until FDA outlined its proposed strategy for regulation of mobile medical apps in a report to Congress and convened a working group of external stakeholders to provide feedback.

P. Good Guidance Practices

FDASIA section 619 amends FDCA section 701(h)(1)(C) to specify that, for devices, “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” is subject to good guidance practices.⁹¹ These practices require that such documents be subject to comment before implementation, unless public participation is not feasible or appropriate.

Q. Pediatric Device Consortia

Section 620 of FDASIA reauthorizes grant funding under the Pediatric Medical Device Safety and Improvement Act (PMDSIA).⁹² It also requires that FDA issue by December 31, 2012 a proposed rule implementing section 515A(a)(2) of FDCA, which requires information on pediatric subpopulations in HDE applications and product development protocols. FDA must issue a final rule by December 31, 2013.

TITLE VII — DRUG SUPPLY CHAIN

A. Changes to Establishment Registration and Drug Listing Requirements

Title VII expands existing requirements regarding the establishment registration requirements for domestic and foreign drug manufacturers and foreign device manufacturers, as well as the drug listing requirement of the FDCA.⁹³

1. Establishment Registration

Section 701 of the FDASIA changes the annual registration requirements for domestic drug establishments.⁹⁴ Registration information must be submitted between October 1 and December

⁸⁹ See 21 C.F.R. § 880.6310.

⁹⁰ FDA Draft Guidance, Mobile Medical Applications, (Jul. 21, 2011), available [here](#).

⁹¹ FDASIA § 619 (amending FDCA § 701(h)(1)).

⁹² *Id.* § 620 (amending PMDSIA (Pub. Law No. 110–85, § 305(e))).

⁹³ FDCA § 510(b) & (c).

⁹⁴ FDASIA § 701 (amending FDCA §§ 510(b) & (c)).

31 of each year, instead of on or before December 31, as was required previously. Under pre-existing law, submissions had to include only the name of the owner or operator, place of business, and all establishments owned or operated by the registrant. The FDASIA expands the submission requirements to include a unique facility identifier of each establishment and an email address for the point of contact. This section also requires FDA to “specify the unique facility identifier system” to be used by registrants, but it does not provide any additional detail regarding this system. In addition to the annual registration requirements, drug and device manufacturers must also submit complete registration information upon first engaging in the manufacture of a drug or device in any establishment in the United States.

Section 702 of the FDASIA establishes similar requirements for foreign drug and device establishments.⁹⁵ For drugs, the information submitted must include the same information required for domestic establishments, as well as the name of the US agent for each establishment, the name of the importer of each drug that is known to the establishment, and the name of the person who imports or offers for import the drug to the United States. Owners or operators of device establishments should submit the same information, except that they are not required to submit a unique facility identifier or email address for a point of contact.⁹⁶ This section also amends FDCA section 502(o), which provides that a drug or device is misbranded if it was manufactured in a facility that is not registered with FDA. Section 702 expands this provision to apply to drugs and devices manufactured at an unregistered facility anywhere in the world (not just in the United States).⁹⁷

2. Identification of Drug Excipient Information

Section 703 of the FDASIA requires registered owners and operators of drug establishments to include in the drug listing information they submit to FDA the following information about each manufacturer of an excipient of the listed drug: the name and place of business, all establishments used in the production of the excipient, the unique facility identifier for the establishment, and an email address for the point of contact for each manufacturer.⁹⁸

3. Electronic System for Establishment Registration and Drug Listing

Section 704 of the FDASIA requires FDA to, not later than two years after FDA specifies a unique facility identifier system, maintain an electronic database populated with establishment registration and drug listing information.⁹⁹ The database must be searchable (by FDA personnel) by any field of information submitted with an establishment registration. It must also use the unique facility identifier system to link with other relevant FDA databases, including the database for submission of risk information under FDCA section 801(r). FDA must ensure the accuracy of the database and coordination with other databases in order to identify and inform risk-based inspections under section FDCA 510(h).

B. Inspections

Title VII also significantly enhances FDA’s inspection authority over both foreign and domestic establishments that manufacture drugs.

⁹⁵ *Id.* § 702 (amending FDCA §§ 510(i)(1)(A)).

⁹⁶ As noted above, section 614 of the FDASIA requires FDA to issue a proposed rule regarding a unique device identifier (UDI) by December 31, 2012.

⁹⁷ *Id.* (amending FDCA § 502(o)).

⁹⁸ *Id.* § 703 (adding FDCA § 510(j)(1)(E)).

⁹⁹ *Id.* § 704 (amending FDCA § 510(p)).

1. Risk-Based Inspections

Section 705 of the FDASIA amends FDCA section 510(h) to establish a schedule of inspections for every establishment (domestic and foreign) required to be registered with FDA.¹⁰⁰ Device establishments must be inspected at least once every two years. For drug establishments, the new law abandons the once-every-two year schedule for domestic manufacturing facilities. In its place, for both foreign and domestic facilities, FDA must establish a “risk-based schedule” based on the following risk factors:

- the compliance history of the establishment;
- the record, history, and nature of recalls linked to the establishment;
- the risks inherent in the drug(s) manufactured, prepared, propagated, compounded, or processed at the establishment;
- the inspection frequency and history of the establishment, including whether the establishment has been inspected within the last four years;
- whether the establishment has been inspected by a foreign government or an agency thereof recognized under section 809; and
- any other criteria FDA deems necessary and appropriate for purposes of allocating inspection resources.

In establishing the risk-based schedule, FDA may not consider whether the drugs manufactured in the establishment are prescription drugs. Beginning in February 2014 and annually thereafter, FDA must make available on its website a report regarding establishment registrations and inspections. Reports must include:

- the number of domestic and foreign establishments registered in the previous fiscal year;
- the number of domestic and foreign establishments inspected by FDA in the previous fiscal year;
- the number and type of establishments that manufacture an active ingredient of a drug, a finished product, or a drug excipient; and
- the percentage of the FDA budget used to fund inspections.

2. Records for Inspection

Section 704 of the FDCA authorizes FDA to conduct inspections. FDASIA section 706 amends FDCA section 704 by authorizing FDA to require drug manufacturers to submit records or other information otherwise subject to inspection. FDA may require such records or information “in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, and in either electronic or physical form, at the expense of such person.”¹⁰¹ The term “reasonable” is not defined.

3. Prohibition Against Delaying, Denying, Limiting, or Refusing Inspection

¹⁰⁰ *Id.* § 705 (amending FDCA § 510(h)).

¹⁰¹ *Id.* § 706 (amending FDCA § 704(a)(4)(A)).

FDCA section 501 sets forth the ways in which a drug or device can become adulterated. FDASIA amends this provision to add that a drug is considered to be adulterated if it is manufactured, processed, packed, or held in any factory, warehouse, or establishment for which the owner, operator, or agent delays, denies, or limits an inspection or refuses to admit the inspectors.¹⁰² Within one year of enactment of the FDASIA, FDA must issue guidance that define the circumstances that would constitute delaying, denying, or limiting an inspection or refusing to admit the inspectors.¹⁰³

4. Recognition of Foreign Government Inspections

Section 712 adds a new FDCA section 809, authorizing FDA to enter into “arrangements and agreements” with foreign governments to inspect foreign establishments in order to facilitate the risk-based inspection schedule.¹⁰⁴ FDA may enter into such arrangements and agreements only if it has determined that the foreign government is capable of conducting inspections that meet the applicable requirements of the FDCA. FDA is authorized to perform reviews and audits of drug safety programs, systems, and standards of a foreign government in order to make such a determination. The results of inspections performed by foreign governments may be used as evidence that an establishment is operating in compliance with good manufacturing practice (“GMP”) or for any other purpose as determined by FDA.

C. Imported Drugs

Title VII contains several provisions related to the importation of drugs.

1. Counterfeit Drugs Offered for Import

Section 708 amends FDCA section 801 to provide that FDA may destroy, without the opportunity for export, any drug valued at less than \$2,500 that is refused admission for import and not brought into compliance pursuant to FDCA section 801(b).¹⁰⁵ FDA must issue regulations, via notice-and-comment rulemaking, providing for notice and an opportunity for a hearing prior to the destruction of any drug.

2. Standards for Admission of Imported Drugs

FDASIA section 713 amends FDCA section 801(o) to eliminate the existing requirement that registration statements be provided for drugs offered for import.¹⁰⁶ It also adds a new FDCA section 801(r), authorizing FDA to require that as a condition of importing a drug, the importer electronically submit information demonstrating that the drug complies with the applicable requirements of the FDCA.¹⁰⁷ These requirements may be satisfied through (1) representation by a foreign government if the government conducts an inspection using standards and practices determined appropriate by FDA; (2) representation by a foreign government or agency thereof recognized under FDCA section 809; or (3) other appropriate documentation or evidence as determined by FDA.

Not later than 18 months after enactment of the FDASIA, FDA must adopt, via notice-and-comment rulemaking, final regulations implementing the above requirement. The regulations must be appropriate for the type of import (e.g., drugs imported for use in preclinical research or in a clinical

¹⁰² *Id.* § 707(a) (adding FDCA § 501(j)).

¹⁰³ *Id.* § 707(b).

¹⁰⁴ *Id.* § 712 (adding FDCA § 809)).

¹⁰⁵ *Id.* § 708(a) (amending FDCA § 801(a)).

¹⁰⁶ *Id.* § 713 (amending FDCA § 801(o)).

¹⁰⁷ *Id.* (adding FDCA § 801(r)).

investigation under an investigational new drug exemption under FDCA section 505(i)). In promulgating the regulations, FDA may take into account differences among importers and types of imports and, based on the level of risk posed by the imported drug, provide for expedited clearance for those importers that volunteer to participate in a partnership program for highly compliant companies and pass a review of internal controls, including sourcing or foreign manufacturing inputs and plant inspections.

3. Registration of Commercial Importers

Section 714 also adds a new FDCA section 801(s), requiring commercial importers of drugs to (1) be registered with FDA in a form and manner specified by FDA, and (2) submit, at the time of registration, a unique identifier for the importer's principal place of business.¹⁰⁸ Not more than three years after the date of enactment of the FDASIA, FDA, in consultation with the Secretary of Homeland Security, must issue, via notice-and-comment rulemaking, regulations to establish good importer practices that specify the measures an importer must take to ensure that imported drugs are in compliance with the FDCA and the PHSa. FDA must discontinue the registration of any commercial importer that fails to comply with these regulations. FDA must also specify the unique identifier system to be used by registrants.

FDASIA section 714 adds failure to register as a commercial importer to the list of prohibited acts in FDCA section 301.¹⁰⁹ It also amends FDCA section 502, which sets forth the criteria for a misbranded drug or device, to state that a drug is misbranded if it is imported or offered for import by a commercial importer of drugs not duly registered.¹¹⁰

D. Administrative Detention

FDCA section 304(g) provides for administrative detention of devices and tobacco products determined to be adulterated or misbranded during an inspection. FDASIA section 709 expands this requirement to apply to drugs, as well.¹¹¹ It also requires FDA to issue, via notice-and-comment rulemaking, regulations implementing its administrative detention authority within two years of the effective date of FDASIA.

E. Exchange of Information

FDASIA section 710 provides that FDA is not required to disclose under the Freedom of Information Act¹¹² or any other provision of law, any information related to drugs obtained from a foreign government agency if:

- (A) 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;
- (B) the information is provided or made available to the United States Government voluntarily on the condition that it not be released to the public; and
- (C) the information is covered by, and subject to, a written agreement between the Secretary and the foreign government.¹¹³

¹⁰⁸ *Id.* § 714 (adding FDCA § 801(s)).

¹⁰⁹ *Id.* (adding FDCA § 301(aaa)).

¹¹⁰ *Id.* (amending FDCA § 502(a)).

¹¹¹ *Id.* § 709 (amending FDCA § 304(g)).

¹¹² 5 U.S.C. § 552.

¹¹³ FDASIA § 710 (amending FDCA § 708(b)(1)).

This section also authorizes FDA to enter into written agreements with foreign governments regarding the exchange of information containing trade secrets.¹¹⁴ To enter into such an agreement, the foreign government must certify its ability to protect trade secret information. Furthermore, the written agreement must include a commitment to protect the information exchanged from disclosure, unless the sponsor gives written permission for disclosure or FDA makes a public health emergency declaration under the section 319 of the PHS Act.

Notwithstanding the foregoing requirements, information may be exchanged only if (1) FDA reasonably believes or the written agreement establishes that the foreign government has the authority to obtain the information, and (2) the written agreement limits the recipient's use of the information to the recipient's civil regulatory purposes. The information may not be exchanged if FDA has reasonable grounds to believe that a drug has a reasonable probability of causing serious adverse health consequences or death to humans or animals.

F. Enhancing the Quality of the Drug Supply

Under FDCA section 501, a drug is adulterated if, among other things, it is not manufactured in accordance with GMPs. FDASIA section 711 revises FDCA section 501 to state that, for purposes of that provision, GMP includes "the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."¹¹⁵

G. Notification

Section 715 adds a new FDCA section 568, authorizing FDA to require notification by "regulated persons" who know (1) that use of the drug in the United States may result in serious injury or death; (2) of the substantial loss or theft of a drug; or (3) that a counterfeit drug is in or could reasonably be expected to be introduced into commerce in the United States or has been, is being, or may be imported into the United States.¹¹⁶ Notification must be made in a manner and by such means as FDA specifies by regulation or in guidance. The term "regulated person" means anyone who is required to register under FDA section 510 or 801(s), a wholesale distributor of a drug product, or any other person that distributes drugs except a person that distributes drugs exclusively for retail sale.

FDASIA section 715 also adds failure to comply with section 568 to the list of prohibited acts in FDCA section 301.

H. Protection Against Intentional Adulteration

FDASIA section 716 amends FDCA section 303(b) by adding a requirement that any person who knowingly and intentionally adulterates a drug, so that the drug has a reasonable probability of causing serious adverse health consequences or death to human or animals, shall be imprisoned for not more than 20 years, fined not more than \$1 million, or both.¹¹⁷

¹¹⁴ *Id.* (amending FDCA § 708(c)).

¹¹⁵ *Id.* § 711 (amending FDCA § 501).

¹¹⁶ *Id.* § 715 (adding FDCA § 568).

¹¹⁷ *Id.* § 716 (adding FDCA § 303(b)(7)).

I. Penalties for Counterfeiting Drugs

FDASIA section 717 amends section 2320 of the United States Criminal Code to add a new offense of trafficking in counterfeit drugs.¹¹⁸ The statute defines a “counterfeit drug” by cross-reference to FDCA section 201. For individuals, penalties for trafficking in counterfeit drugs include imprisonment for 10 years, fines of up to \$2 million, or both. For entities other than individuals, penalties include fines of up to \$5 million. Section 2320 also provides for enhanced penalties for second or subsequent offenses and for causing serious bodily injury or death.

FDASIA section 717 further requires the Attorney General to give increased priority to efforts to investigate and prosecute offenses under section 2320 that involve counterfeit drugs. Finally, section 717 requires the U.S. Sentencing Commission to review and amend, if appropriate, its guidelines applicable to persons convicted of an offense related to drug counterfeiting in order to reflect the intent of Congress that penalties be increased.

J. Extraterritorial Jurisdiction

Section 718 adds a new FDCA section 311, which provides for extraterritorial jurisdiction over any violation of the FDCA relating to an article regulated under the FDCA if (1) the article was intended for import into the United States, or (2) any act in furtherance of the violation was committed in the United States.¹¹⁹

TITLE VIII — GENERATING ANTIBIOTIC INCENTIVES NOW

Title VIII contains provisions from the Generating Antibiotic Incentives Now (GAIN) Act providing incentives for the development of new qualified infectious disease products (“QIDPs”). Among other things, the new law adds five years to specified periods of exclusivity for which such QIDPs otherwise qualify.¹²⁰

A. Definitions

FDASIA section 801 establishes a new FDCA section 505E, which defines a QIDP as 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) qualifying pathogens listed by FDA.¹²¹ A “qualifying pathogen” is listed by FDA due to its “potential to pose a serious threat to the public health,” such as resistant gram positive pathogens, multi-drug resistant gram negative bacteria, multi-drug resistant tuberculosis, and *Clostridium difficile*.¹²² FDA must establish and maintain a list of qualifying pathogens, and must make public the methodology it uses to develop its list. When establishing this list, FDA must consider enumerated properties that focus on the public health, and consult with experts in infectious diseases and antibiotic resistance, including the Centers for Disease Control and Prevention (CDC), FDA, medical professionals, and the clinical research community.¹²³ FDA must, through notice and comment rulemaking, publish final regulations, including a list of qualifying pathogens within two years of enactment. FDA may issue interim guidances prior to issuing its final

¹¹⁸ *Id.* § 717(a) (amending 18 U.S.C. § 2320).

¹¹⁹ *Id.* § 718 (adding FDCA § 311).

¹²⁰ *Id.* § 801 (adding FDCA § 505E(a)).

¹²¹ *Id.* (adding FDCA § 505E(g)).

¹²² *Id.* (adding FDCA § 505E(f)(1)).

¹²³ Specifically, FDA must consider: the impact on public health due to drug resistant organisms in humans; the rate of growth of drug resistant organisms in humans; the increase in resistance rates in humans; and the morbidity and mortality in humans. *Id.* (adding FDCA § 505E(f)(2)).

rule that also list qualifying pathogens. The list of qualifying pathogens must be reviewed and revised every five years, or more often as needed.

B. QIDP Designation

A manufacturer can request that a product be designated as a QIDP at any time prior to submission of an application for approval.¹²⁴ FDA must make a determination within 60 days of the request. Further, FDA may not revoke a QIDP designation absent proof of misrepresentation of material fact during initial approval of the designation. All products that are approved and designated as a QIDP must be given priority review and are eligible for fast track review.¹²⁵

C. Exclusivity Extensions

Subject to a limitation provision, starting July 9, 2012, if FDA “approves an application pursuant to [FDCA] section 505 for a drug that has been designated as a [QIDP],” such drug will be eligible for five years of exclusivity extension.¹²⁶ This includes five-year extensions of (a) five year New Chemical Entity (NCE) NDA exclusivity; (b) four year ANDA Paragraph IV exclusivity; (c) three year new clinical investigation exclusivity; and (d) seven year orphan drug exclusivity. Such five year extensions are in addition to any six month pediatric exclusivity that may be available for the drug product. There are, however, certain limitations on the applicability of the GAIN Act extensions. The five year extension does not apply to the approval of:

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

D. Guidance Documents and Reporting Requirements

Section 804 of the FDASIA states that FDA must review, and revise as appropriate, at least three guidance documents annually.¹²⁷ FDA must review guidance documents for the conduct of clinical trials for antibacterial and antifungal drugs, and revise any guidance as necessary to reflect changes in scientific and medical information and technology and to ensure clarity regarding procedures for approval of antibacterial and antifungal drugs.¹²⁸ Sponsors of a drug intended to be designated as a QIDP can request written recommendations from FDA on non-clinical and clinical investigations that may be necessary for the approval of a QIDP.¹²⁹ FDA is required to provide these written recommendations if, based on the information available at the time of the request, the Agency believes the drug is a QIDP.

¹²⁴ *Id.* (adding FDCA § 505E(d)).

¹²⁵ *Id.* § 802 (adding FDCA § 524A); *Id.* § 803 (amending FDCA § 506(a)(1)).

¹²⁶ *Id.* § 801 (adding FDCA §§ 505E(a) & (b)).

¹²⁷ *Id.* § 804(a).

¹²⁸ At a minimum, FDA must consider issues such as “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.*

¹²⁹ *Id.* § 804(b)(1).

The FDASIA also requires the Department of Health and Human Services (HHS), in consultation with FDA, CDC, and other appropriate agencies, to perform a review of the effectiveness of the GAIN Act and provide Congress with a report within five years of enactment.¹³⁰ The parties must also provide Congress with recommendations for, among other things, how to improve the effectiveness of the GAIN program, highlighting scientific and regulatory challenges that the program faces moving forward.

Finally, FDASIA section 806 requires that, prior to June 30, 2013, FDA must release a draft guidance detailing how to use preclinical and clinical data to streamline pathogen-focused antibacterial drug development and provide advice on approaches for the development of antibacterial drugs that target a more limited spectrum of pathogens. FDA must finalize this guidance, after notice and an opportunity for public comment on the draft guidance, before January 2015.

TITLE IX — DRUG APPROVAL AND PATIENT ACCESS

A. Enhancement of Accelerated Approval Pathway and Designation of “Breakthrough Therapies”

Sections 901 and 902 of the FDASIA amend FDCA section 506 to make explicit the breadth of circumstances under which FDA might use the accelerated approval pathway to speed access to certain drugs. They also create a new product designation, “breakthrough therapy.” A “breakthrough therapy” is defined in the new FDCA section 506(a)(1) as a drug:

intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition [where] 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.¹³¹

Section 902 of the FDASIA provides that a drug sponsor may request that FDA designate its drug as a breakthrough therapy at the time of submission of an IND, or anytime thereafter.¹³² Once a designation is requested, the Secretary has 60 calendar days to determine whether the drug meets the definition of a “breakthrough therapy.” Similar to the fast track product designation process, FDA is required to take “actions” to “expedite the development and review” of an application for approval of a breakthrough therapy. These include, for example, holding meetings with the sponsor and FDA review team, involving senior managers and experienced reviewers in cross-disciplinary review, and ensuring that clinical trials are “as efficient as practical.”¹³³ FDA is required to publish draft guidance on breakthrough therapies by January 9, 2014 (and finalize the guidance no later than one year after the close of the comment period) and, if FDA deems it necessary, revise relevant regulations by July 9, 2014.

Section 901 of the FDASIA arguably expands the situations under which fast track designation can be granted. Previously, fast track designation was limited to drugs intended to treat serious or life-threatening *conditions* and that demonstrated the potential to address unmet medical needs for

¹³⁰ The report must include the number of initial designations of drugs as QIDPs, the number of QIDPs, whether such products address the need for antibacterial and antifungal drugs to treat serious and life-threatening infections, and a list of QIDPs with information on the types of exclusivity granted for each product. Progress made regarding the review and revision of clinical trial guidance documents and the impact of that process has had on review and approval of QIDPs must also be included. *Id.* § 805.

¹³¹ *Id.* § 902(a)(3) (amending FDCA § 506(a)).

¹³² *Id.*

¹³³ *Id.* (amending FDCA § 506(a)(3)(B)).

such a *condition*. FDASIA section 901 adds “disease or” in front of “condition.”¹³⁴ It also makes clear that combination products are eligible for fast track designation if they meet the other requirements. Fast track designation provides the sponsor with the opportunity for more frequent meetings with FDA to discuss the drug’s development plan, as well as rolling review of its NDA.

Further, a drug no longer needs to be designated as a fast track product in order to be granted accelerated approval. Under the revised law, a drug for a serious and life threatening disease may qualify for accelerated approval without demonstrating the potential to address an unmet medical need.

The new law also revises the endpoints on which accelerated approval can be based. Under the prior statutory provision, a fast track product could be approved “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.” This constituted accelerated approval. The FDASIA revises the law to specify that FDA may grant accelerated approval to a product for a “serious or life-threatening disease or condition” (including a fast track product) upon 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.”¹³⁵ The FDASIA also specifies the type of evidence that can be used to support an endpoint that is reasonably likely to predict clinical benefit for purposes of accelerated approval – epidemiological, pathophysiological, therapeutic, and pharmacologic evidence, as well as evidence developed using biomarkers or other scientific methods or tools.

Section 901 of the FDASIA retains the requirement that approval of a product under the accelerated approval pathway might require the sponsor to conduct post approval studies and to submit all promotional materials to FDA at least 30 days prior to disseminating the materials. It notes, however, that the post-approval studies must “verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit,”¹³⁶ rather than “validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint.” Expedited procedures for withdrawal of approval remain applicable.

FDASIA section 901 requires the Secretary to establish a program that encourages the development of surrogate and clinical endpoints, including biomarkers and other scientific methods and tools that can assist FDA in determining whether the evidence submitted in an accelerated approval application is reasonably likely to predict clinical benefit for serious or life-threatening conditions for which significant unmet medical needs exist.¹³⁷ FDA previously was required to establish a program to encourage the development of surrogate endpoints only.

Section 901 of the FDASIA includes a “Construction” provision. Among other things, it states that the amendments are intended to encourage FDA to use “innovative and flexible approaches” to accelerated approval. This dovetails with a “Sense of Congress” provision at the beginning of section 901, which explains that FDA “should apply the accelerated approval and fast track provisions ... to help expedite the development and availability to patients of treatments for serious and life-threatening diseases or conditions while maintaining safety and effectiveness standards for such treatments.” The “Construction” provision also explains that accelerated approval does not change existing FDA safety or effectiveness standards under sections 505(c) and (d) of the FDCA

¹³⁴ *Id.* § 901(b) (amending FDCA § 506(a)(1)).

¹³⁵ *Id.* (amending FDCA § 506(b)(1)(A)).

¹³⁶ *Id.* (amending FDCA § 506(b)(2)(A)).

¹³⁷ *Id.* (amending FDCA § 506(d)(2)).

and section 351(a) of the PHS Act, but reiterates that the Secretary can rely on evidence to support accelerated approval that does not come from adequate and well-controlled investigations.¹³⁸

By July 9, 2013, FDA must issue draft guidance to implement amendments to the accelerated approval pathway, considering issues related to accelerated approval of drugs for rare diseases.¹³⁹ Within one year of publishing the draft guidance, FDA must issue final guidance and amend the accelerated approval regulations (Subpart H of 21 C.F.R. Part 314 and Subpart E of 21 C.F.R. Part 601) as needed.

B. Consultation with External Experts

FDASIA section 903 establishes a new FDCA section 569 on consultation with external experts. It requires FDA to maintain a list of external scientific and medical experts to consult about issues related to the review of new drug applications and biologics license applications for rare diseases and drugs and biological products that are genetically targeted.¹⁴⁰ FDA may consult with these experts to address a specific regulatory question when the Agency lacks the necessary expertise. Such consultations are not intended to delay FDA review of an IND, NDA, or BLA. Thus, before consulting external experts in relation to such an application, FDA must either (1) determine that the consultation will facilitate FDA review and address outstanding deficiencies in the application, or (2) secure the sponsor's consent. For purposes of this section, external experts "are individuals who possess scientific or medical training that the Secretary lacks with respect to one or more rare diseases."¹⁴¹

C. Accessibility of Information on Prescription Drug Container Labels

Section 904 of the FDASIA requires the creation of a stakeholder working group to develop best practices for pharmacies to ensure that blind or visually impaired individuals have safe, consistent, reliable, and independent access to the information on prescription drug container labels.¹⁴² In developing its best practices, the working group will consider, among other things, mechanisms such as braille, digital voice recorders, radio frequency identification tags, and high-contrast printing. The working group must develop these best practices, which are to be made publicly available, by July 9, 2013.

D. Risk-Benefit Framework

FDCA section 505(d) sets out seven criteria that FDA may use to decline to approve an NDA. Section 905 of the FDASIA amends section 505(d) to state at the end that FDA will "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."¹⁴³ This new requirement does not "alter the criteria for evaluating an application for premarket approval of a drug."¹⁴⁴

¹³⁸ *Id.* (adding FDCA § 506(e)(2)).

¹³⁹ *Id.* § 901(c).

¹⁴⁰ *Id.* § 903 (adding FDCA § 569(a)(2)(A)).

¹⁴¹ *Id.* (adding FDCA § 569(a)(2)(B)).

¹⁴² *Id.* §§ 904(a)(1) & (3)(A).

¹⁴³ *Id.* § 905 (amending FDCA § 505(d)).

¹⁴⁴ *Id.*

E. Orphan Drug Development Grants and Contracts

Under the Orphan Products Grant Program, the Secretary may make grants to (and enter into contracts with) public and private entities to defray the costs of “qualified testing” in connection with the development of drugs for rare diseases or conditions.¹⁴⁵ Section 906 of the FDASIA reauthorizes an appropriation of \$30 million for the Orphan Products Grant Program for each of fiscal years 2013 through 2017. It also amends the Orphan Drug Act to remove the requirement that to constitute “qualified testing,” the testing must have occurred after the drug received orphan drug designation.¹⁴⁶

F. Demographic Subgroups Reporting

Section 907 of the FDASIA requires FDA to post on FDA’s website 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.¹⁴⁷ The posting of the report on FDA’s website must be consistent with FDA’s public disclosure regulations regarding confidential commercial information.

Within one year of publication of the report, FDA must post an action plan on FDA’s website and submit the action plan to Congress. The action plan must include recommendations, as appropriate, (and by product type), on the following areas: (1) improving the completeness and quality of analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling; (2) including such data, or the lack of availability of such data, in labeling; and (3) otherwise improving the public availability of such data to patients, health care providers, and researchers.

G. Rare Pediatric Disease Priority Review Voucher

Section 908 of the FDASIA establishes a rare pediatric disease priority review voucher (RPDPRV) in section 529 of the FDCA, similar to the existing voucher program under section 524 for tropical diseases. Under the program, when FDA approves a rare pediatric disease product application, it shall award the sponsor of that application with an RPDPRV. The sponsor (or a transferee) can use the voucher to obtain priority review of a single NDA or BLA.

Under new section 529, a rare pediatric disease is defined as a disease that “primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents” and qualifies as a rare disease or condition under section 526 of the FDCA (Orphan Drug Act). To be eligible for award of a voucher, an application must be for treatment or prevention of a rare pediatric disease, contain “no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application,” be submitted under section 505(b)(1) of the FDCA or section 351(a) of the PHS Act, be eligible for priority review, rely on data derived from studies examining a pediatric population (and dosages of the drug intended for that population), not seek approval for an adult indication in the original rare pediatric disease product application, and be approved by FDA after the enactment of the Prescription Drug User Fee Amendments of 2012.

A sponsor that wishes to use an RPDPRV must give notice of its intent to submit an application at least 90 days before submission. By contrast, a sponsor using a tropical disease priority review voucher is required to give notice one year in advance.

¹⁴⁵ 21 U.S.C. § 360ee(a)(1).

¹⁴⁶ FDASIA § 906(a) (amending 21 U.S.C. § 360ee(b)(1)(A)(ii)).

¹⁴⁷ *Id.* § 907(a)(1).

New FDCA section 529 establishes a special user fee for RPDPRVs. The amount and timing of the special fee differs from the fee associated with the tropical disease program. The RPDPRV fee – set by FDA each fiscal year – is equal to the difference between the average cost FDA incurs to conduct a priority review and the average cost of conducting a standard review.¹⁴⁸ The special fee must be paid upon giving notice to FDA of an intent to use the voucher, and it must be paid in addition to normal user fees (which are due upon submission of the application). This is less than the special fee assessed under the tropical disease program.

Under FDCA section 529(d), sponsors may utilize a unique “designation” process that requires FDA to inform the sponsor whether a drug or application will meet the statutory criteria for award of a voucher. A request for designation must be made at the same time as a request for orphan disease designation or fast track designation would be made.¹⁴⁹

New section 529 also specifies several post-market commitments for voucher awardees.¹⁵⁰ For example, FDA may revoke a voucher if the rare pediatric disease drug is not marketed within one year of approval. Additionally, voucher awardees must submit a report to FDA within five years of approval that estimates the prevalence of the rare pediatric disease, the demand for the rare pediatric drug, and the actual amount of drug supplied.

FDA’s authority to issue an RPDPRV ceases one year after FDA awards the third RPDPRV.¹⁵¹ After this third voucher is issued, the Government Accountability Office (GAO) is directed to complete a study on the effectiveness of the RPDPRV program.

TITLE X — DRUG SHORTAGES

Title X contains several provisions intended to help alleviate the current problems associated with drug shortages in the United States and prevent future shortages. A drug shortage is defined as a period of time when the demand or projected demand for a drug in the United States exceeds the supply of the drug.¹⁵²

A. Discontinuance or Interruption in the Production of Life-Saving Drugs

FDCA section 506C requires sole manufacturers of drugs that are life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition to report to FDA any discontinuance of the manufacture of that drug. FDASIA section 1001 expands this provision to require all manufacturers to report the permanent discontinuance of the manufacture of a drug or any interruption of the manufacture of the drug that is likely to lead to a meaningful disruption in the US supply.¹⁵³ Such manufacturers must also report the reasons for the discontinuance or interruption. The scope of section 506C is also expanded to require notification for drugs used in emergency medical care or during surgery, except that radio pharmaceutical drug products and any other product designated by FDA are not covered by the notification requirement. A “meaningful disruption” means a change in production that is reasonably likely to lead to a reduction in the supply of a drug by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product.¹⁵⁴ A meaningful disruption

¹⁴⁸ *Id.* § 908 (adding FDCA § 529(c)).

¹⁴⁹ *Id.* (adding FDCA § 529(d)).

¹⁵⁰ *Id.* (adding FDCA § 529(e)).

¹⁵¹ *Id.* (adding FDCA § 529(b)(5)).

¹⁵² *Id.* § 1001(a) (adding FDCA § 506C(h)).

¹⁵³ *Id.* (adding FDCA § 506C(a)).

¹⁵⁴ *Id.* (adding FDCA § 506C(h)).

does not include interruptions in manufacturing due to routine maintenance or insignificant changes in manufacturing, so long as the manufacturer expects to resume operations in a short time.

Manufacturers must notify FDA at least six months before the date of the discontinuance or interruption, or as soon as practicable if six months' notice is not possible.¹⁵⁵ To the maximum extent practicable, FDA must distribute information about the discontinuance or interruption to "appropriate organizations," including physician, health provider, and patient organizations.

If, based on the notification, FDA determines that there is likely to be a drug shortage, the Agency may expedite (1) the review of an ANDA or a supplement to an ANDA or an NDA that could help mitigate or prevent the shortage, or (2) an inspection or re-inspection of an establishment that could help mitigate or prevent the shortage.¹⁵⁶ If FDA determines that the notification pertains to a controlled substance subject to a production quota, it must request that the Attorney General increase the production quotas to a level necessary to address a shortage based on the best available market data. If the Attorney General determines that the level requested is not necessary to address a shortage, the Attorney General must provide a written explanation, which must be posted on FDA's website.

If a manufacturer fails to notify FDA of a discontinuance or interruption, FDA must issue a letter to the manufacturer informing it of the failure. FDA must publish the manufacturer's response on its website, unless the Agency determines that the initial letter was issued in error or that the manufacturer had a reasonable basis for not notifying FDA.¹⁵⁷

Not later than 18 months after enactment of the FDASIA, FDA must adopt regulations implementing this section. The statutory requirements described above do not initially apply to biological products, as defined in section 351 of the PHS Act. FDA's implementing regulations may, however, require notifications by manufacturers of biological products. In doing so, the Agency must consider whether the notification requirement would be satisfied by submitting a notification to the CDC pursuant to the CDC's vaccine shortage notification program.

B. Annual Reporting on Drug Shortages

FDASIA section 1002 adds a new FDCA section 506C-1, which requires FDA to submit, by the end of 2013, and annually thereafter, a report to Congress on drug shortages.¹⁵⁸ The new section specifies the content for the report, including the number of manufacturers that notified FDA of a discontinuance or interruption, the significant actions taken by FDA to prevent or mitigate drug shortages, and the instances in which FDA exercised "regulatory flexibility and discretion" to prevent or alleviate a drug shortage.

C. Coordination; Task Force and Strategic Plan

FDASIA section 1003 adds a new FDCA section 506D, which requires FDA to establish a task force to develop and implement a strategic plan for enhancing FDA's response to preventing and mitigating drug shortages. The strategic plan must include plans for interagency and intra-agency communication and coordination, plans for ensuring that FDA considers drug shortages when taking regulatory action, plans for effective communication with outside stakeholders, plans for considering the impact of drug shortages on research and clinical trials, and an examination of whether to

¹⁵⁵ *Id.* (amending FDCA § 506C(b)).

¹⁵⁶ *Id.* (amending FDCA § 506C(g)).

¹⁵⁷ *Id.* (amending FDCA § 506C(f)).

¹⁵⁸ *Id.* § 1002 (adding FDCA § 506C-1).

establish a “qualified manufacturing partner program.”¹⁵⁹ Under such a program, a qualified manufacturer would have the capability and capacity to supply products determined or anticipated to be in shortage within a rapid timeframe. As part of the strategic plan, FDA must also consider whether incentives are necessary to encourage manufacturers to participate in such a program. The task force must publish and submit its plan to Congress within one year of enactment of the FDASIA.

FDA must also ensure that before taking any enforcement action or issuing a warning letter that could reasonably lead to a meaningful disruption in the supply of a drug, there is communication with the appropriate FDA office with expertise in drug shortages regarding whether the enforcement action or warning letter could cause or exacerbate a shortage.¹⁶⁰ If, after the communication, FDA determines that such an outcome is possible, the Agency must evaluate the risks associated with the shortage and the risks associated with the violation before taking action or issuing a letter, “unless there is imminent risk of serious adverse health consequences or death to humans.”¹⁶¹

FDA must also identify or establish a mechanism by which health care providers and other third-party organizations can report evidence of drug shortages.¹⁶² The requirements for a task force and strategic plan and communication within FDA regarding enforcement actions sunset five years after the enactment of the FDASIA.

D. Drug Shortage List

FDASIA section 1004 adds a new FDCA section 506E, which requires FDA to maintain an up-to-date list of drugs that it determines are in shortage in the United States. For each drug on the list, FDA must include the following: the name and National Drug Code (NDC) of the drug, the name of the manufacturer, the reason for the shortage (selecting from a list of categories), and the estimated duration of the shortage.¹⁶³ The list must be publicly available, except that FDA may not disclose information containing trade secrets or confidential information. In addition, FDA may choose not to make the list public if the Agency determines that disclosure of the information would adversely affect the public health (e.g., by increasing the possibility of hoarding).

E. Quotas Applicable to Drugs in Shortage

FDASIA section 1005 amends section 306 of the Controlled Substances Act (CSA) to add a new subsection (h), which allows manufacturers of schedule II controlled substances subject to production quotas to request an increase in the quotas (both aggregate and individual) to address a shortage.¹⁶⁴ The Attorney General must respond to such a request within 30 days. If the Attorney General determines that the level requested is not necessary to address the shortage, the Attorney General must provide a written explanation, which must be posted on FDA’s website.

F. Attorney General Report on Drug Shortages

FDASIA section 1006 requires the Attorney General to, not more than six months after enactment of the FDASIA, submit to Congress a report on drug shortages.¹⁶⁵ The report must:

¹⁵⁹ *Id.* § 1003 (adding FDCA § 506D(a)(1)).

¹⁶⁰ *Id.* (adding FDCA § 506D(b)).

¹⁶¹ *Id.* (adding FDCA § 506D(c)).

¹⁶² *Id.* (adding FDCA § 506D(d)).

¹⁶³ *Id.* § 1004 (adding FDCA § 506E(b)).

¹⁶⁴ *Id.* § 1005 (adding 21 U.S.C. § 826(h)).

¹⁶⁵ *Id.* § 1006.

- identify the number of requests received under the new CSA section 306(h), the average review time for such requests, the number of requests granted and denied, and, for each of the requests denied, the basis for the denial;
- describe the coordination between the Drug Enforcement Administration and FDA on efforts to prevent or alleviate drug shortages; and
- identify drugs containing a controlled substance subject to CSA section 306 that are determined by FDA to be in shortage.

G. Hospital Repackaging of Drugs in Shortage

FDASIA section 1007 adds a new FDCA section 506F, which addresses hospitals that repackage drugs (other than controlled substances) for transfer to another hospital within the same health system.¹⁶⁶ Under new section 506F, hospitals do not constitute establishments subject to registration in accordance with FDCA section 510 solely by virtue of such transfer, provided the drug is on FDA’s drug shortage list or the repackaging occurs within 60 days of the drug appearing on the shortage list. This exemption from the registration requirement applies only if the following conditions are met: (1) the repackaged drug is not sold or otherwise distributed by the health system or a hospital within the system to an entity or individual that is not a hospital within the health system, and (2) repackaging of the drug is done in compliance with applicable requirements of the state in which the drug is repackaged and received. For purposes of this section, “repackage” means to divide the volume of a drug into smaller amounts in order to extend the supply of a drug in shortage or facilitate access to the drug by hospitals in the same health system. This provision does not apply on or after the date on which FDA “issues final guidance that clarifies the policy of [FDA] regarding hospital pharmacies repackaging and safely transferring repackaged drugs to other hospitals within the same health system during a drug shortage.”¹⁶⁷

H. Study on Drug Shortages

FDASIA section 1008 requires the Comptroller General of the United States to conduct a study on the causes of drug shortages and develop recommendations to prevent or alleviate shortages.¹⁶⁸ In conducting the study, the Comptroller General must consult with relevant stakeholders. The Comptroller General must submit a report with its recommendations to Congress by January 9, 2014.

TITLE XI — OTHER PROVISIONS

A. Subtitle A — Reauthorizations

1. Exclusivity of Certain Drugs Containing Single Enantiomers

Section 505(u) of the FDCA permits, if certain conditions are met, a manufacturer of a single enantiomer of a previously approved racemic drug to elect to have the single enantiomer “not be considered the same active ingredient as that contained in the approved racemic drug.”¹⁶⁹ The provision originally was available only for applications submitted between September 27, 2007 and

¹⁶⁶ *Id.* § 1007 (adding FDCA § 506F).

¹⁶⁷ *Id.* (adding FDCA § 506F(d)).

¹⁶⁸ *Id.* § 1008(a).

¹⁶⁹ FDCA § 505(u)(1).

October 1, 2012.¹⁷⁰ Section 1101 of the FDASIA extends this latter date to October 1, 2017.¹⁷¹ Section 1101 also clarifies the required conditions for making such an election.¹⁷²

2. Critical Path Public-Private Partnerships

Section 1102 of the FDASIA amends FDCA subsection 566(f). The amendment authorizes the appropriation of \$6 million for each fiscal year 2013 through 2017 to implement FDA's Critical Path Initiative.¹⁷³

B. Subtitle B – Medical Gas Product Regulation

Section 1111 of the FDASIA adds a new subchapter G to chapter V of the FDCA for the regulation of certain medical gases.¹⁷⁴ Under new FDCA section 576, beginning 180 days after the FDASIA's enactment, any person may file with FDA a request for certification of a medical gas as a "designated medical gas."¹⁷⁵ Such requests for certification must contain:

- a description of the medical gas;
- the sponsor's name and address;
- the name and address of the facility where the gas is or will be manufactured; and
- any other information deemed appropriate by FDA.

Unless FDA makes certain findings within 60 days of the request for certification, the request is deemed granted. A medical gas that is granted certification as a designated medical gas is deemed approved, alone or in combination with other certified medical gasses where medically appropriate, for certain indications for use specified in FDCA section 576(a)(3).¹⁷⁶ FDA may add additional indications for use unless the designated medical gas is subject to certain unexpired periods of exclusivity. Subject to certain exceptions, particularly for the use of oxygen, a designated medical gas is subject to prescription drug requirements under section 503(b)(1) of the FDCA. FDA has the authority to withdraw or suspend approval of a certified medical gas, and may revoke the grant of certification if the request contains any material omission or falsification.¹⁷⁷

According to FDASIA section 1111, a designated medical gas deemed approved under FDCA section 576 is ineligible for any period of exclusivity under sections 505(c), 505(j), 527, or 505A of the FDCA on the basis of such approval.¹⁷⁸ Additionally, subject to certain exceptions, drug product exclusivity periods granted under the aforementioned sections of the FDCA cannot impede the submission,

¹⁷⁰ *Id.* § 505(u)(4).

¹⁷¹ FDASIA § 1101(a) (amending FDCA § 505(u)(4)).

¹⁷² *Id.* § 1101(b) (amending FDCA § 505(u)(1)(A)(ii)(II)).

¹⁷³ *Id.* § 1102 (amending FDCA § 566(f)).

¹⁷⁴ Under subchapter G, "medical gas" means a drug that is "manufactured or stored as a liquefied, nonliquefied, or cryogenic state and is administered as a gas." *Id.* § 1111 (adding FDCA § 575).

¹⁷⁵ A "designated medical gas" means oxygen, nitrogen, nitrous oxide, carbon dioxide, helium, carbon monoxide, or medical air, that "meets the standards set forth in an official compendium," or any other medical gas deemed appropriate by the Secretary under certain conditions. *Id.* Subchapter G does not apply to certain drugs and gases, depending on when the drug or gas was approved, what use the drug or gas was approved for, and what section of the FDCA the drug or gas was approved under. See *Id.* § 1113.

¹⁷⁶ *Id.* § 1111 (adding FDCA § 576(a)(3)(A)(i)). For example, a certification for nitrogen approves the medical gas for use in hypoxic challenge testing, and a certification for carbon monoxide approves the medical gas for use in lung diffusion testing.

¹⁷⁷ *Id.* (adding FDCA § 576(a)(4)).

¹⁷⁸ *Id.* (adding FDCA § 576(a)(3)(B)).

grant, or effect of a certification for a medical gas. FDASIA section 1111 exempts approved designated medical gases from being assessed fees under section 736(a) of the FDCA on the basis of such approval.¹⁷⁹

Within 18 months of the FDASIA's enactment, FDA must submit a report to congressional committees regarding any necessary changes to medical gas federal regulations.¹⁸⁰ In preparing this report, FDA must obtain input from interested third parties (including medical gas manufacturers). Further, within four years of the FDASIA's enactment, FDA must issue final regulations implementing these identified changes.

C. Subtitle C – Miscellaneous Provisions

1. Guidance Regarding Product Promotion on the Internet

Section 1121 of the FDASIA requires FDA to publish guidance on the promotion of FDA-regulated medical products using the Internet (including social media) no later than July 9, 2014.¹⁸¹

2. Prescription Drug Abuse

Section 1122 of the FDASIA requires FDA to develop and post on the HHS website a report that includes findings and recommendations on ways to combat prescription drug abuse. Specifically, the report must include findings and recommendations on how best to: (1) leverage existing federal data sources to create a centralized data clearinghouse and early warning tool; (2) develop and disseminate best practice models to states for achieving greater interoperability and effectiveness of prescription drug monitoring programs; and (3) develop provider, pharmacist, and patient education tools.¹⁸² Additionally, within six months of the FDASIA's enactment, FDA must promulgate guidance on the development of abuse-deterrent drug products.¹⁸³

3. Optimizing Global Clinical Trials

FDASIA section 1123 adds new section 569A to the FDCA. This new provision requires FDA to work with various international organizations to encourage uniform clinical trial standards for medical products (drugs, devices, and biologics) and provide parallel scientific advice to manufacturers seeking simultaneous global development of new products. Section 1123 also adds new section 569B to the FDCA, which requires FDA to accept data from clinical trials conducted outside of the United States, provided that the applicant successfully demonstrates that the data are adequate under FDA's approval standards. Any finding from FDA that such data are inadequate must be accompanied by a notice to the sponsor explaining the Agency's rationale.¹⁸⁴

4. Advancing Regulatory Science

FDASIA section 1124 requires FDA to develop, by July 9, 2013, a regulatory strategy and science implementation plan for advancing regulatory science and innovation in regulatory decisionmaking.¹⁸⁵ The plan must be consistent with FDA's user fee performance goals and must address, among other things, regulatory and scientific gaps that impede development of regulatory

¹⁷⁹ *Id.* (adding FDCA § 577).

¹⁸⁰ *Id.* § 1112.

¹⁸¹ *Id.* § 1121.

¹⁸² *Id.* § 1122(b).

¹⁸³ *Id.* § 1122(c).

¹⁸⁴ *Id.* § 1123 (adding FDCA § 569B).

¹⁸⁵ *Id.* § 1124.

certainty, metrics for progress, and ways to ensure advances are implemented. This section also requires FDA to report to Congress, as part of the annual user fee performance reports, progress in advancing, integrating, and adopting advances in regulatory science.

5. Information Technology

FDASIA section 1125 requires HHS to issue a report to Congress addressing a comprehensive information technology (IT) strategic plan.¹⁸⁶ The plan must address milestones and a completion date to align the IT systems of FDA, efforts to complete an inventory of FDA IT systems, the ways that the plan will guide modernization projects, and the extent to which FDA has implemented GAO recommendations on this issue. FDA also must develop an enterprise architecture program management plan and a gap analysis. Section 1125 requires the GAO to issue a report regarding the strategic plan and FDA's progress implementing it.

6. Nanotechnology

FDASIA section 1126 requires FDA to “intensify and expand activities” relating to scientific understanding of nanotechnology and associated regulatory issues, such as potential benefits, toxicology, and interaction with biological systems.¹⁸⁷ This section also lists a number of activities FDA may undertake, including cooperating with other agencies, promoting FDA programs, and reviewing literature. FDA has been active in the area of nanotechnology; the Agency has adopted a “Nanotechnology Regulatory Science Research Plan” and released draft guidance documents on use of nanotechnology by the food and cosmetics industries.

7. Online Pharmacy Report

FDASIA section 1127 requires the GAO to submit a report to Congress that describes problems posed by internet Internet pharmacies that violate federal and state law.¹⁸⁸ The report must describe methods by which such internet sites illegally sell prescription drugs, the resulting harmful effects to patients, the degree to which governments have been able to address the problem, and additional laws and policies that would assist in combating the problem.

8. Report on Small Businesses

FDASIA section 1128 requires FDA to submit a report on small business activities, including staffing levels of small business offices, status of partnerships between FDA and the Small Business Association, summary of outreach efforts, small business utilization of Orphan Drug Act benefits, small business involvement with grant programs, and barriers for small businesses to achieve approval of drugs and devices.¹⁸⁹

9. Protections for the Commissioned Corps of the PHS

FDASIA section 1129 adds retaliation protection to the statutory list of rights and benefits to which the Commissioned Corps of the Public Health Service is entitled.¹⁹⁰ The Commissioned Corps consists of health professionals (e.g., doctors, nurses) that are detailed to federal agencies, including FDA.

¹⁸⁶ *Id.* § 1125.

¹⁸⁷ *Id.* § 1126.

¹⁸⁸ *Id.* § 1127.

¹⁸⁹ *Id.* § 1128.

¹⁹⁰ *Id.* § 1129 (adding PHSA § 221(a)(18)).

10. Compliance Date for Sunscreen Rule

Section 1130 establishes a statutory effectiveness date for FDA's final rule, "Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use."¹⁹¹ The Final Rule describes the permitted and required claims for sunscreen, testing procedures on which those claims must be based, and claims that are not permitted or that would render a sunscreen product misbranded.¹⁹² FDA had issued a federal register notice in May of 2012 delaying the compliance date for this rule until December 17, 2013 for products with sales less than \$25,000 per year, and December 17, 2012 for all other products subject to the rule. Section 1130 requires compliance with the final rule by these dates.

11. Strategic Integrated Management Plan

Section 1131 requires FDA to submit to Congress a strategic integrated management plan for CDER, CBER, and CDRH. The plan must identify goals to promote efficiency, describe actions to develop FDA's workforce, and identify methods to measure whether the reviewers and managers are appropriately and consistently applying the requirements of the FDCA.¹⁹³

12. REMS Assessment and Modification

Section 1132 of the FDASIA amends section 505-1(g) & (h) of the FDCA, which provide for assessments and modifications to risk evaluation and mitigation strategies (REMS).

FDASIA amends section 505-1(g) so that a responsible person (i.e., a person submitting a BLA, an NDA or an ANDA for a prescription drug, or holder of such approved application)¹⁹⁴ can now propose modifications to add, modify, or remove any component of its REMS without submitting an assessment of the REMS at the same time.¹⁹⁵ Previously, a responsible person could only submit a REMS modification in conjunction with an assessment. On its own initiative, FDA can require that a responsible person submit a proposed modification to a REMS within 120 days (or within such other reasonable time specified by FDA), if FDA determines that the approved REMS should be modified to: (1) ensure the benefits of the drug outweigh the risks of the drug, or (2) minimize the burden on the health care delivery system of complying with the strategy.¹⁹⁶

Unless certain dispute resolution procedures apply, in most cases FDA must review and act on requests for modification to a REMS within 180 days. If, however, the requested modification is for a "minor" modification, FDA must review and act on the request within 60 days. Similarly, if the proposed modification is to "conform the strategy to approved safety label changes, including safety labeling changes initiated by the sponsor in accordance with FDA regulatory requirements, or to a safety label change that the Secretary has directed the holder of the application to make pursuant to [FDCA] section 505(o)(4)," FDA must review and act on the request within 60 days.¹⁹⁷ Through guidance, FDA must establish (1) what modifications constitute "minor" modifications, and (2) that responsible person(s) may implement certain REMS modifications following notice to FDA.

Section 1132 also changes the grounds upon which FDA can require the responsible person to submit a REMS assessment. Under the prior law, FDA could require that the responsible person

¹⁹¹ *Id.* § 1130.

¹⁹² See our client alert, available [here](#), for more information.

¹⁹³ *Id.* § 1131.

¹⁹⁴ FDCA § 505-1(b)(7).

¹⁹⁵ FDASIA § 1132(a)(4) (amending FDCA § 505-1(g)(4)).

¹⁹⁶ *Id.* The latter criterion is a new basis for modifying a REMS.

¹⁹⁷ *Id.* § 1132(b)(5)(A) (amending FDCA § 505-1(h)(2)(A)(iii)).

submit an assessment “within a time period to be determined by the Secretary” if “new safety or effectiveness information” indicated that certain REMS elements should be modified. As revised by the FDASIA, a responsible person must submit a REMS assessment (within a time period determined by FDA) if FDA determines that an assessment is needed to evaluate whether the approved REMS should be modified to: (1) ensure the benefits of the drug outweigh the risks of the drug, or (2) minimize the burden on the health care delivery system of complying with the strategy.¹⁹⁸ The FDASIA also strikes a provision under which FDA could require a REMS assessment within 15 days if it determined there may be cause to withdraw approval of the drug under FDCA section 505(e).

A responsible person can submit a voluntary assessment at any time without proposing a modification to the approved REMS. A REMS assessment no longer needs to include information about post-approval studies or clinical trials required under FDCA 505(o).

FDA is now required to “promptly” initiate discussions with the responsible person about REMS, assessments, and proposed modifications to REMS.¹⁹⁹ Previously, FDA was given 60 days after submission to initiate discussions with the responsible person.

FDASIA section 1132(b)(5)(A) deletes the provision that required FDA to describe a REMS, or modification to a REMS, in “the action letter on the application” or in “an order,” and that FDA make those documents publicly available. FDA must now make publicly available “an action letter” describing FDA’s decision about a proposed REMS or REMS modification.²⁰⁰ Finally, the FDASIA revises the timing for responsible persons to request review of certain REMS submissions by the Drug Safety Oversight Board (DSOB).²⁰¹

13. Extension Period for Obtaining Tentative Approval Without Forfeiting 180-Day Exclusivity

Section 505(j)(5)(D)(i)(IV) of the FDCA provides that a “first” ANDA application forfeits its 180-day exclusivity if it 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, requirements for approval imposed after the application was filed. Section 505(q)(1)(G) adds that this period can be extended if approval is delayed by a citizen petition. Generic applicants have voiced concerns that FDA delays in reviewing ANDAs have unfairly caused first applicants to forfeit 180-day exclusivity.

FDASIA section 1133 temporarily extends the period in which a first ANDA applicant must obtain tentative approval to avoid forfeiting 180-day exclusivity. For ANDA applicants that have made a “paragraph IV certification” during the period of January 9, 2010 through July 9, 2012 – either in an original application or by amendment of a pending application – the 30-month period in which they must obtain tentative approval of the drug to be entitled to 180-day exclusivity is extended: (1) to 40 months during the period of enactment to September 30, 2015, and (2) to 36 months during the period of October 1, 2015 until September 30, 2016.²⁰² Further, for ANDAs filed before enactment of the FDASIA but amended after enactment and before September 30, 2017 to contain a paragraph IV certification, the 30-month period is treated as beginning on the date of the amendment.²⁰³

¹⁹⁸ *Id.* § 1132(a)(2)(B) (amending FDCA § 505-1(g)(2)(C)).

¹⁹⁹ *Id.* § 1132(b)(2) (amending FDCA § 505-1(h)(1)).

²⁰⁰ *Id.* § 1132(b)(5)(B) (amending FDCA § 505-1(h)(2)(C)).

²⁰¹ *Id.* § 1132(b)(6)(A) (amending FDCA § 505-1(h)(4)(A)(i)).

²⁰² *Id.* § 1133(a).

²⁰³ *Id.* § 1133(b).

14. Deadline for Determination on Certain Citizen Petitions

Section 505(j)(4) of the FDCA specifies the grounds upon which FDA may refuse to approve an ANDA. One of these is if the reference listed drug (RLD) was withdrawn for reasons of safety or effectiveness.²⁰⁴ Thus, FDA regulations allow submission of citizen petitions to FDA requesting a determination whether a given RLD was voluntarily withdrawn for reasons of safety and/or effectiveness.²⁰⁵ Although FDA's citizen petition regulations require FDA to provide a response to citizen petitions within 180 days,²⁰⁶ FDA often takes substantially longer to issue a final decision on these petitions. FDASIA section 1134 therefore adds a new subsection (w) to section 505 of the FDCA, requiring FDA to respond to petitions requesting a determination of the circumstances for withdrawal of an RLD within 270 days after submission.²⁰⁷ The amendment applies to petitions filed on or after July 9, 2012.

15. Section 505(q) Citizen Petitions

Section 505(q) of the FDCA prohibits FDA from delaying approval of an ANDA or a 505(b)(2) application as a result of actions requested in a citizen petition unless FDA determines that delay is necessary to protect the public health.²⁰⁸ Prior to enactment of the FDASIA, it also required that FDA respond to such citizen petitions within 180 days. FDASIA section 1135 amends section 505(q) of the FDCA in several ways.²⁰⁹ First, it shortens the period in which FDA must respond to such citizen petitions from 180 days to 150. Second, it extends the application of section 505(q) to citizen petitions relating to pending biosimilar applications under 351(k) of the PHSa. Section 1135 specifies, however, that section 505(q)(2) — concerning exhaustion of administrative remedies and final agency action if FDA does not respond within the 150-day period — does not apply to petitions regarding biosimilar applications.

16. Electronic Submission of Applications

Section 1136 of the FDASIA amends the FDCA to require sponsors to electronically submit NDAs, INDs (but not expanded access INDs), ANDAs, BLAs, and applications for biosimilar products.²¹⁰ The requirement does not go into effect until at least two years after FDA issues final guidance that provides a timetable for FDA to establish further standards for electronic submission of the specified applications and sets forth criteria for waivers and exemptions from the electronic submission requirement.

Section 1136 also amends the FDCA to require sponsors to submit an electronic copy of medical device pre-submissions and submissions under 510(k), 513(f)(2)(A), 515(c), 515(d), 515(f), 520(g), 520(m), 564, and section 351 of the PHSa, along with any supplements to such pre-submissions or submissions.²¹¹ This requirement goes into effect after FDA issues the final guidance described above.

²⁰⁴ FDCA § 505(j)(4)(I).

²⁰⁵ 21 C.F.R. § 314.161(b).

²⁰⁶ 21 C.F.R. § 10.30(e)(2).

²⁰⁷ FDASIA § 1134 (adding FDCA § 505(w)).

²⁰⁸ FDCA § 505(q)(1)(A).

²⁰⁹ FDASIA § 1135 (amending FDCA § 505(q)).

²¹⁰ *Id.* § 1136 (adding FDCA §§ 745A(a)(1) & (3)).

²¹¹ *Id.* (adding FDCA § 745A(b)(1) & (3)).

17. Patient Participation in Medical Product Discussion

FDASIA section 1137 establishes a new section 569C of the FDCA requiring FDA to develop strategies to solicit views of patient representatives during the medical product development process.²¹² Such strategies shall include “fostering participation” of a patient representative who may serve as a special government employee in appropriate Agency meetings with sponsors. New section 569C specifies that it is not intended to affect current protections for propriety information and trade secrets or create a legal right or obligation for consultation with any particular expert or stakeholder.

18. Adequate Information Regarding Pharmaceuticals for Underrepresented Subpopulations

FDASIA section 1138 requires FDA to review and modify, as necessary, its communication plan to inform and educate healthcare providers and patients on the risks and benefits of medical products.²¹³ FDA’s plan must focus on underrepresented subpopulations, including racial subgroups, and take into account the goals and principles set forth in the Strategic Action Plan to Reduce Racial and Ethnic Health Disparities issued by HHS. The plan must also take into account the nature of the medical product, and health and disease information available from other HHS departments. FDA must post its plan on FDA’s website and seek public comment.

19. Scheduling of Hydrocodone

FDASIA section 1139 requires FDA, by September 7, 2012, to hold a public meeting to solicit advice and recommendations for making a scheduling recommendation to the Drug Enforcement Agency (DEA) regarding products that contain hydrocodone combined with other drugs, such as analgesics or antitussives.²¹⁴ FDA is required to solicit views from CDC, the National Institute on Drug Abuse, and the DEA. An earlier version of the legislation scheduled all hydrocodone products as Schedule II drugs,²¹⁵ but this provision reportedly met resistance during the reconciliation process.

20. Study on Labeling by Electronic Means

Section 1140 requires the GAO, by July 9, 2013, to complete a study on the benefits and efficiencies of electronic patient labeling for prescription drugs as a complete or partial substitute for traditional paper labeling. 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 on movement to electronic labeling.”²¹⁶

21. Recommendations on Interoperability Standards

FDASIA section 1141 permits HHS and the Department of Justice (DOJ) to collaborate and develop recommendations for interoperability standards for the exchange of prescription information by states receiving grants under the Harold Rogers Prescription Drug Monitoring Program and the Controlled Substance Monitoring Program.²¹⁷ These grant programs are aimed at combating prescription drug diversion. HHS and the DOJ must address a number of considerations, including open standards, exchange intermediaries, transmission security, access control methodologies, and

²¹² *Id.* § 1137 (adding FDCA § 569C).

²¹³ *Id.* § 1138.

²¹⁴ *Id.* § 1139.

²¹⁵ 158 Cong. Rec. S3607 (daily ed. May 24, 2012) (text of section 1141).

²¹⁶ FDASIA § 1140(a).

²¹⁷ *Id.* § 1141.

model standards. HHS and the DOJ must submit a report to Congress on the issue within one year of enactment.

22. Conflicts of Interest

FDASIA section 1142 amends section 712 of the FDCA, which governs the management of conflicts of interest on FDA advisory committees. An “advisory committee” is defined as any advisory committee under the Federal Advisory Committee Act (FACA) that provides advice or recommendations to the Secretary regarding activities of FDA.²¹⁸

The Food and Drug Administration Amendments Act (FDAAA) amended the FDCA to include provisions designed to limit conflicts of interest and restrict those eligible to serve on FDA advisory committees.²¹⁹ The FDASIA largely eliminates those provisions. There is no longer a limit on the number of “exceptions” that can be granted by FDA for an individual to participate with respect to a particular matter considered in an advisory committee meeting.²²⁰ Furthermore, when making appointments to an FDA advisory committee, FDA is no longer required to take steps to reduce the likelihood that an appointed individual would later require a written determination under 18 U.S.C. § 208(b)(1) or a written certification under 18 U.S.C. § 208(b)(3) for service on the committee at a meeting of the committee.²²¹

FDASIA section 1142 does not repeal or amend 18 U.S.C. § 208, which governs federal employee conflicts of interest more broadly and also applies to FDA advisory committee members. Section 208 of title 18 is a criminal statute that prohibits government employees, including special government employees, from participating personally and substantially in a particular government matter that will have a direct and predictable effect on their financial interests (or the financial interests of others that are attributed to the federal employee, e.g., spouse or minor child).

The amendments to the FDCA made by section 1142 of FDASIA take effect on October 1, 2012.

■ Recruitment

FDASIA section 1142 revises the provisions of the FDCA governing the activities the Secretary must engage in to recruit individuals to serve as advisory committee members.²²² These activities include seeking input from professional medical and scientific societies to determine the most effective informational and recruitment activities and may include developing a process through which entities that receive funding from the NIH, Agency for Healthcare Research and Quality (AHRQ), CDC, or the Department of Veterans Affairs (VA) can identify persons for FDA to contact regarding nominations.²²³ FDASIA adds a new requirement for the Secretary to request referrals for advisory committee members from various stakeholders, including product developers, patient groups, disease advocacy organizations and relevant professional societies, academia, and medical societies at least every 180 days.²²⁴

²¹⁸ FDCA § 712(a)(1).

²¹⁹ FDAAA § 701(a).

²²⁰ FDASIA § 1142(a)(1).

²²¹ *Id.*

²²² FDASIA § 1142(a)(1)(amending FDCA § 712(b)).

²²³ *Id.*

²²⁴ *Id.* (adding FDCA § 712(b)(1)(C)).

■ Disclosures

FDASIA maintains the requirement for the Secretary to disclose, no later than 15 days prior to an advisory committee meeting, the type, nature, and magnitude of the financial interests of any member to whom the Secretary has made a written determination or a written certification, as well as the Secretary's reasons for the determination or the certification.²²⁵ If a financial interest becomes known to the Secretary fewer than 30 days prior to the meeting, the Secretary must make these disclosures as soon as practicable after the determination or certification decision is made, but in no event later than the date of the meeting.²²⁶

The FDAAA required the Secretary to submit a report to Congress each year. The FDASIA changes the content of this report. FDA must now include the following information: (1) with respect to the previous fiscal year, the number of individuals contacted to participate on an advisory committee who did not participate because of the potential for such participation to constitute a disqualifying financial interest under 18 U.S.C. § 208 or who did not participate for other reasons, and (2) the number of members attending each advisory committee meeting.²²⁷ FDA is no longer required to include: (1) how FDA plans to reduce the number of vacancies on advisory committees, and (2) the methods that will be used to encourage the nomination of individuals to serve on an advisory committee. FDA must make the annual report publicly available no later than 30 days after submitting it to Congress.²²⁸

The Secretary must review and update as necessary, and at least once every five years, FDA guidance regarding disclosure of conflicts of interest and the application of section 208 of title 18 of the United States Code, to ensure FDA has appropriate access to needed scientific expertise.²²⁹ The Secretary must also issue new guidance describing how the Secretary reviews the financial interests and involvement of advisory members to which a determination or certification applies but that the Secretary determines do not meet the definition of disqualifying interest under 18 U.S.C. § 208.²³⁰

23. Notification of FDA Intent to Regulate Laboratory Developed Tests

FDASIA section 1143 requires FDA to notify Congress 60 days before issuing a draft or final guidance document regarding the regulation of laboratory developed tests (LDTs).²³¹ LDTs are diagnostic tests that are developed, validated, and performed by individual laboratories, and are not commercially distributed to other laboratories. LDTs can be distinguished from commercially available in vitro diagnostic (IVDs) test kits, which are developed by diagnostic manufacturers and sold to clinical laboratories. LDTs have often been developed to respond to emerging public health threats or in situations where an IVD kit may not be commercially feasible. Clinical laboratories that develop and use LDTs are subject to oversight and regulation under the Clinical Laboratories Improvement Amendments (CLIA). While historically FDA did not regulate LDTs as medical devices, since the early 1990s, FDA has asserted that LDTs are medical devices subject to regulation under the FDCA. However, the Agency has not sought to impose on LDTs the regulations that apply to medical devices, explaining that it was exercising enforcement discretion because LDTs are subject to CLIA regulation.

²²⁵ *Id.* § 1142(a)(1)(amending FDCA § 712(c)).

²²⁶ *Id.*

²²⁷ *Id.* § 1142(a)(3) (amending FDCA § 712(e)(1)).

²²⁸ *Id.* (adding FDCA § 712(e)(2)).

²²⁹ *Id.* § 1142(a)(4) (amending FDCA § 712(f)).

²³⁰ *Id.* § 1142(a)(5) (adding FDCA § 712(g)).

²³¹ *Id.* § 1143.

In recent years, however, FDA has attempted to assert some regulatory oversight over certain types of LDTs.²³² And in 2010, FDA announced that it intended to regulate *all* LDTs as medical devices.²³³ Agency officials announced that they would phase in this regulation under a risk-based approach that would be described in future guidance documents. This proposal was met with significant criticism from clinical laboratories, among others. To date, FDA has not issued the guidance documents it described. Section 1143 requires FDA to notify Congress of the “anticipated details” of any such guidance documents, presumably allowing Congress the opportunity to review and evaluate FDA’s actions.

D. Subtitle D – Synthetic Drugs

Subtitle D schedules numerous synthetic cannabis agents as Schedule I under 21 U.S.C. § 812(c). Subtitle D also extends the effectiveness period for temporary scheduling actions (from one year to two years) and the permissible extension period of temporary scheduling actions (from six months to one year).²³⁴

* * *

This information is not intended as legal advice, which may often turn on specific facts. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein. If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food & Drug Practice Group:

Scott Cunningham	202.662.5275	scunningham@cov.com
Scott Danzis	202.662.5209	sdanzis@cov.com
Ellen Flannery	202.662.5484	eflannery@cov.com
Michael Labson	202.662.5220	mlabson@cov.com
Erika Lietzan	202.662.5165	elietzan@cov.com
Stefanie Doeblner	202.662.5271	sdoeblner@cov.com

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²³² Additional background and a description of FDA’s attempts to regulate LDTs are described [here](#).

²³³ 75 Fed. Reg. 34,463 (June 17, 2010).

²³⁴ FDASIA § 1152.