

A Guide to the Food and Drug Administration Safety and Innovation Act



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Having been passed by Congress, and signed July 9 by President Obama (Pub. L. No. 112-144), the Food and Drug Administration Safety and Innovation Act (FDASIA or the Act) reauthorizes the Prescription Drug User Fee Act and the Medical Device User Fee Act, and authorizes new user fees via the Generic Drug User Fee Act (GDUFA) and the Biosimilar User Fee Act (BSUFA). Beyond user fees, FDASIA addresses a range of other significant regulatory changes.

In the drug area, the legislation amends the Federal Food, Drug, and Cosmetic Act (FFDCA) to expand drug supply chain requirements affecting both foreign and domestic facilities. FDASIA requires these facilities to include unique facility identifiers in their establishment

registration.¹ In addition, for domestic establishments the Secretary must conduct inspections on a risk-based schedule, no longer distinguishing between prescription and non-prescription products.² Unlike in the past when manufacturers were only required upon notice to allow inspectors in at reasonable times to review records, under FDASIA records required for inspection will need to be submitted to FDA at the manufacturers' expense.³ The Act addresses the intentional adulteration of drug products, providing severe new penalties.⁴

FDASIA also amends the expedited drug development and review process⁵ by providing a fast track designation for drugs with "serious or life-threatening disease" indications and those defined as "breakthrough therapies."⁶ The Secretary will be required to issue draft guidance for these processes.⁷ The Act seeks to increase incentives for the development of certain qualified infectious disease products (QIDPs). The Act provides for an additional 5 years of exclusivity for QIDPs, and the Secretary must provide guidance regarding the clinical trial protocols for new infectious disease therapies.⁸ The FFDCA is amended to strengthen FDA's response to drug shortages, expanding notification of any

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¹ Food and Drug Administration Safety and Innovation Act (FDASIA) §§ 701, 702.

² *Id.* § 705.

³ *Id.* § 706.

⁴ *Id.* § 716.

⁵ FFDCA § 506(a).

⁶ FDASIA §§ 901, 902.

⁷ *Id.*

⁸ *Id.* §§ 801, 804.

permanent discontinuance or interruption that could affect the U.S. supply of products covered by this section.⁹

In the device realm, FDASIA will increase the number of devices exempt from performance standards and premarket approval,¹⁰ and amend the *de novo* application process such that certain new devices will be eligible for classification by the Secretary.¹¹ In addition, the Act will require FDA to clarify when sponsors are required to notify the Agency for changes made to currently marketed devices.¹² The Secretary will be tasked with implementing a recall system for devices that identifies trends related to defective devices and modifying post-market systems such as Sentinel to include information on medical devices.¹³ The Act also requires FDA to develop and publish a strategy for regulating mobile medical applications and other health information technology (Health IT).

FDASIA also addresses a variety of other issues, such as the codification of FDA's regulation of medical gas products, nanotechnology, enhancing recruitment of FDA advisory committee members and reauthorization of Critical Path Public-Private Partnerships.

This report reviews key provisions from each title of the legislation.

I. USER FEE REAUTHORIZATION (PDUFA V and MDUFA III)

TITLE I—FEES RELATING TO DRUGS

The reauthorized Prescription Drug User Fee Act (PDUFA V) will continue the collection of application, establishment and product fees from industry to support FDA's review of human drug applications. The expected fee revenue under PDUFA V for FY2013 is \$693 million.¹⁴ FDA will continue to calculate inflation and workload adjustments annually, however under PDUFA V the Agency will modify the calculation to account accurately for personnel and benefit costs. Exceptions from prescription drug product fees have been amended such that "the same product as another product that was approved under an application filed under section 505(b) or 505(j)," must also not be contained "in the list of discontinued products compiled under section 505(j)(7)" to receive the fee exception.¹⁵

As with previous user fee legislation, in return for payment of the assessed fees FDA will have certain obligations based on performance goals forwarded to Congress by the Agency. At the end of the five-year period covered by PDUFA V, FDA must act on at least 90% of standard new molecular entity (NME) new drug

applications (NDAs) and original biologic license applications (BLAs) within 10 months of the 60 day filing date, and at least 90% of all priority NME NDAs and original BLAs within 6 months of the 60 day filing date.¹⁶ The review clock for all NME NDA and BLA submissions will begin after a 60 day filing review period commencing on the date of the original submission.

Additionally, as part of the Agency's effort to improve the efficiency of the first cycle of review and enhance review transparency and communication for NME NDAs and BLAs, sponsors are encouraged to participate in pre-submission meetings at least 2 months prior to a planned application submission to allow FDA time for meaningful feedback.¹⁷ During these meetings FDA and the sponsors will discuss the content of the complete application, REMS, and agree to limited components that may be submitted 30 days after submission (i.e., updates to original submission data). FDA will not allow late submission of major components, such as Phase 3 clinical trial data, for all NME NDAs and BLAs.

FDA will provide a review timeline for such applications in the response letter forwarded within 74 calendar days of the submission of the original application. This letter will contain a proposed date for mid-cycle review meetings and discussion on whether an advisory committee meeting is necessary. Within 2 weeks of FDA's mid-cycle review meeting, applicants will receive an update on the status of their review and notice of any significant issues, information requests, safety concerns and/or preliminary REMS considerations, advisory committee plans and any other time related goals for approval of the product.

The Secretary will submit a report each fiscal year concerning the progress of FDA generally in achieving the goals identified above. Under FDASIA, this report will also include future FDA plans for achieving the PDUFA V performance goals.

TITLE II—FEES RELATING TO MEDICAL DEVICES

The reauthorized Medical Device User Fee Act (MDUFA III) allows for a total of \$595 million¹⁸ in fees to be collected from industry over the five-year period of FY2013 through FY2017. MDUFA III broadens the definition of "establishment subject to a registration fee," increasing the number of establishments paying the fee by 37.5%.¹⁹ The establishment fee will be \$2,575

⁹ *Id.* § 1001.

¹⁰ *Id.* § 607.

¹¹ *Id.* § 608.

¹² *Id.* § 604.

¹³ *Id.* §§ 605, 615.

¹⁴ *Id.* § 103.

¹⁵ *Id.* § 103.

¹⁶ See Appendix A.

¹⁷ See "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017," available at <http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf>. (See Appendix B)

¹⁸ FDASIA § 203. (\$97,722,301 for fiscal year 2013; \$112,580,497 for fiscal year 2014; \$125,767,107 for fiscal year 2015; \$129,339,949 for fiscal year 2016; \$130,184,348 for fiscal year 2017.)

¹⁹ *Id.* § 202.

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in FY2013 and rise to \$3,872 for FY2016 and FY2017.²⁰ Except for the establishment fee, the amount of each type of user fee (e.g., 510(k) fee) is set as a percentage of the Premarket Application (PMA) fee, referred to in the legislation as the base fee.²¹ The base fee would be \$248,000 in FY2013 and would rise to \$268,443 for FY2017.²² The 510(k) fee would change from 1.84% to 2% of the base fee, however, all other fee percentages will remain the same.²³ As with the human drug fees, MDUFA III fee amounts will be adjusted for inflation.

FDASIA also amends the FDCA to provide waivers or reduction of fees for a PMA or establishment fee “if the waiver is in the interest of public health.”²⁴ Waivers and fee reductions must not exceed 2% of the total revenue fee for any given year.²⁵ Additionally, the legislation will allow FDA to streamline hiring of employees to assist with the review of device applications; this authority will end three years after enactment of this section.

In return for payment of the assessed fees, FDA will have new performance goals and obligations. By 2017, FDA will issue decisions on at least 90% of the PMA submissions that do not require Advisory Committee input within 180 days, and at least 80% of the PMA submissions that require Advisory Committee input within 320 days.²⁶

As with prior user fee reauthorizations, the amendments made by Title I and II will take effect on October 1, 2012 and sunset on October 1, 2017 if not renewed.²⁷

II. USER FEE AUTHORIZATION (GDUFA and BSUFA)

TITLE III – FEES RELATING TO GENERIC DRUGS

FDASIA authorizes FDA to assess and collect new fees related to the manufacture and review of human generic drugs.²⁸ Similar to the other user fee arrangements, industry has agreed to pay various fees in return for, among other things, specified review times for applications. GDUFA authorizes FDA to collect \$299M in fees during each of the next five fiscal years, adjusted for inflation. There are five separate fees contemplated by the legislation.

Currently, FDA’s Office of Generic Drugs has a backlog of roughly 2,000 submissions awaiting review. FDA will distribute \$50M of the first year of GDUFA fees among those submissions in the backlog. Sponsors of those submissions will have the option to withdraw their submission rather than be subject to the fee; as a result, the precise persubmission fee will not be known until all sponsors have decided whether to keep their submissions open and FDA has published the final fees

in the *Federal Register*, which it must do by the end of October. This backlog fee will be a one-time fee. In addition, each holder of a Drug Master File (DMF) for an active pharmaceutical ingredient first referenced by an application on or after October 1st will be assessed a fee. The total fees from DMF holders are to account for roughly 6% of the total (non-backlog) fees collected under GDUFA each year.

Sponsors will also be assessed a fee for submitting an abbreviated new drug application (ANDA) or a prior approval supplement. These fees will account for roughly 24% of the total (non-backlog) fees each year. Each facility that manufactures human generic drug products, and each facility that manufactures an active pharmaceutical ingredient contained in such products will be assessed an annual fee accounting for roughly 56% and 14%, respectively, of the total (non-backlog) fees collected each year under GDUFA. Facility fees for foreign facilities must be at least \$15,000, but no more than \$30,000, higher than fees for domestic facilities in order to account for differences in inspection costs to FDA. FDA is required to conduct risk-based inspections of facilities once every two years, and, important to U.S. drug substance and drug product manufacturers, attain parity between foreign and domestic inspection rates by 2017.

Congress must continue to appropriate funds for the review of human generic drugs at or above the FY2009 budget levels, adjusted for inflation. FDA, at the end of the five year period covered by GDUFA, must act on at least 90% of all complete ANDAs within 10 months of submission, at least 90% of all pending applications, amendments, and supplements.

TITLE IV – FEES RELATING TO BIOSIMILAR BIOLOGICAL PRODUCTS

BSUFA authorizes FDA to assess and collect various fees, calculated as percentages of the PDUFA V fees, related to the manufacture and review of biosimilars. FDA will charge a fee of 10% of the human drug application fee for requests for development meetings or clinical protocol meetings. Each year while the biosimilar is under development, FDA will assess an additional charge of 10% of the human drug application fee. Sponsors may elect to discontinue this annual fee if the Investigational New Drug application (IND) for the biosimilar has been withdrawn or the sponsor certifies that it will not be submitting anything to FDA during that year. In the event that a sponsor reactivates an IND that has been discontinued, they are assessed a fee equal to 20% of the human drug application fee.

Biosimilar BLAs or supplements will be assessed an application fee equal to the full NDA fee minus the total amount of annual product development fees paid for that application. Manufacturers of a biosimilar product will be assessed an annual establishment fee equal to the establishment fees paid for human drug product establishments. Each approved biosimilar will be assessed an annual product fee equal to the human drug product fees paid by holders of human drug approvals. The product development and application fees are waived for the first biosimilar product submitted by businesses of less than 500 employees, provided the company has not previously received approval for a human drug or biologic.

As with all other user fee arrangements with FDA, in return for receiving these fees from sponsors and

²⁰ *Id.* § 203. (Appendix C—Fees may be adjusted by Secretary.)

²¹ *Id.*

²² *Id.*

²³ *Id.*

²⁴ *Id.*

²⁵ *Id.*

²⁶ See “Draft MDUFA Performance Goals and Procedures,” dated February 17, 2012, available at <http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf>.

²⁷ FDASIA §§ 203, 207.

²⁸ *Id.* § 301.

manufacturers, FDA has committed to specific goals and deliverables, including review timelines for original applications, application resubmittals, and supplements. For FY2013, FDA will review 70% of original applications within 10 months and 70% of resubmittals within 6 months. These percentages are to rise to 90% by FY2017. In addition, FDA committed to reviewing 90% of original supplements within 10 months and 90% of manufacturing and resubmitted supplements within 6 months during each year. FDA also agreed to other duties such as review of proprietary names for biosimilars, specific dispute resolution procedures, and timelines for responding to a sponsor's response to a clinical hold.

The amendments made by Title III and IV will also take effect on October 1, 2012 and sunset on October 1, 2017 if not renewed.

III. NON-USER FEE AMENDMENTS

TITLE V-PEDIATRIC DRUGS AND DEVICES

Permanent Authorization; Written Requests; Pediatric Rare Diseases (FDASIA §§ 501-502, 510)

FDASIA reauthorizes the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), statutes that work to increase pediatric-focused drug research to support the safe use of medicines in children.²⁹ The Act also requires the Secretary to hold a public meeting within 18 months of enactment, encouraging and accelerating new therapies for rare pediatric diseases.³⁰ FDASIA clarifies that FDA will grant pediatric exclusivity only for requested and accepted studies under a written BPCA request, eliminating the opportunity for exclusivity grants for studies completed under other parts of FFDCA that meet the criteria in this section.³¹

Pediatric Study Plans (FDASIA § 506)

Section 506 of FDASIA requires the submission of an initial pediatric study plan, including study objectives, study design, population information, endpoints, and deferrals or waiver requests, prior to submission of required assessments and within 60 days of the end-of-Phase 2 meeting or other time as agreed to by the Secretary.³² Following submission of the initial plan, the Secretary must either meet with the applicant regarding the plan or supply comments to the applicant within 90 days.³³ The Secretary will consult with the internal pediatric review committee regarding the plan and any significant plan amendments. Once agreed upon, the applicant will document and submit the final plan and the Secretary will acknowledge the documentation by the applicant in writing within 30 days. The acknowledgement from the Secretary will address any requests made by the applicant for a "deferral, partial waiver, or waiver."³⁴ The Secretary or applicant may request an amendment to the plan at any time. Under the Act the

Secretary must promulgate proposed regulations and draft guidance to govern this process as amended.³⁵ Amendments under this section take effect 180 calendar days after the enactment of FDASIA whether or not the Secretary promulgates the regulations under this section.

Communication with Pediatric Review Committee; Access to Data; Ensuring the Completion of Pediatric Studies (FDASIA §§ 503-505)

In addition, the Act amends Section 505 to permit FDA to extend deferrals of submissions in specific circumstances. Requests for a deferral must include a revised timeline for completion in the annual review report of the applicant.³⁶ Additionally, applicants must include in the annual review report the reasoning for a requested deferral or deferral extension. This provision will increase accountability for completion of pediatric studies, as information from annual review reports (e.g., applicant name, product approval date and date of each deferral or deferral extension) will be publicly available within 90 days of submission to FDA. Furthermore, FDASIA provides that the Secretary must maintain an aggregate accounting of all deferrals and extensions, completion timelines, pending assessments, and completed assessments.

Applicants must submit extension requests at least 90 days prior to the expiration of a deferral. The Secretary must respond to the deferral extension request within 45 days. Deferral extensions will apply to deferrals that expire prior to enactment of FDASIA or those that will expire prior to 270 days after the enactment of FDASIA. For such deferrals an applicant may request an extension within 180 days of FDASIA's enactment.³⁷ Should an applicant not provide a requested assessment, fail to meet the requirements above, or fail to submit pediatric formulation approval under this section 270 days after the enactment of FDASIA, the Secretary may issue a non-compliance letter to applicants requiring a written response within 45 days.³⁸ The written response can include a request for a deferral extension. Both the letter and the response will be available to the public for review on FDA's website 60 days after issuance. In addition, FDA may consider the drug product at issue in the non-compliance letters misbranded due to the pediatric study related failures, subjecting these products to potential enforcement action.

FDASIA also amends the FFDCA, to include a requirement for the Secretary to issue internal standard operating procedures to govern the review of any significant modifications to pediatric study plans by the internal pediatric review committee.³⁹ In addition, the Act amends Section 505 such that the Secretary must provide on the FDA website the clinical pharmacology reviews and corresponding written requests of pediatric studies submitted to FDA between January 4, 2002 and September 27, 2007 that received 6 months of exclusiv-

²⁹ *Id.* § 501.

³⁰ *Id.* § 510.

³¹ *Id.* § 502.

³² *Id.* § 506.

³³ *Id.*

³⁴ *Id.*

³⁵ *Id.*

³⁶ *Id.* § 505.

³⁷ *Id.*

³⁸ *Id.*

³⁹ *Id.* § 503.

ity and resulted in the label of the drug product being changed.⁴⁰

Reauthorizations; Report; Technical Amendments; Staff of Office of Pediatric Therapeutics (FDASIA §§ 507-509, 511)

FDASIA permanently authorizes the Pediatric Advisory Committee, reauthorizes the Pediatric Subcommittee of the Oncologic Drug Advisory Committee and extends the Humanitarian Device Exemption.⁴¹ Furthermore, FDASIA will require that the Secretary report on the effectiveness of BPCA and PREA to Congress not more than 4 years after the enactment of FDASIA and every 5 years after the initial report. The Secretary is also required to consult stakeholders at least 180 days before the report is due to Congress for recommendations and suggestions.⁴²

FDASIA amends the time for adverse event reporting to the Pediatric Advisory Committee from one year to 18 months.⁴³ The Act preserves the authority of the Office of Pediatric Therapeutics to allow for review of adverse event reports by the Pediatric Advisory Committee prior to the 18 months if necessary to ensure the continued safety of the pediatric population and provides additional personnel with pediatric expertise as recommended by the Institutes of Medicine and the U.S. Comptroller General.⁴⁴

TITLE VI—MEDICAL DEVICE REGULATORY IMPROVEMENTS

Investigational Device Exemptions (FDASIA § 601)

Under FDASIA, the Secretary may not hold up an investigational device exemption due to a judgment that the investigation does not support substantial equivalence, *de novo* classification or approval, or if the investigation lacks support of a data requirement for approval.⁴⁵ In addition, the Secretary may not disapprove an IDE application if it needs an additional investigation to support approval of the device.

Clarification of Least Burdensome Standard (FDASIA § 602)

FDASIA also clarifies the least burdensome standard for device applications.⁴⁶ Under this section, at a minimum, a PMA applicant must provide evidence demonstrating that the device is effective for the conditions of use and a 510(k) applicant must support that devices with differing technological characteristics are substantially equivalent.⁴⁷

Agency Documentation and Review of Significant Decisions (FDASIA § 603)

FDASIA amends the FFDCA by adding Section 517A, “Agency Documentation and Review of Significant De-

cisions Regarding Devices.”⁴⁸ The Secretary must accompany any significant decision made regarding a 510(k) application or an application for exemption with a summary of the rationale.⁴⁹ An applicant may request review of the significant decision by the individual who made the determination or an individual above that individual. An applicant must make the request for supervisory review within 30 days of the significant decision and include whether the request is for an in-person meeting or a teleconference.⁵⁰ The Secretary must respond to a request for supervisory review by scheduling an in-person or teleconference review meeting within 30 days of the request. The Secretary must respond to applicants with a decision within 45 days of the request or 30 days following the scheduled review meeting.⁵¹ These timeframes do not apply to requests requiring an outside expert.

Device Modifications Requiring Premarket Notification Prior to Marketing

(FDASIA § 604)

FDASIA § 604 requires the Secretary to submit a report to Congress regarding when a sponsor should submit a 510(k) notification due to a modification to a device previously cleared for marketing.⁵² FDA must consider input from stakeholders in compiling this report. Additionally, the Secretary must withdraw the July 27, 2011 guidance on 510(k) device modifications and must not use this guidance to support any enforcement actions. The Act prohibits the Secretary from issuing any draft guidance or proposed regulations on this topic prior to the submission of the report to Congress, or any final guidance or regulation one year after submission of the Congressional report on device modification.⁵³ In the interim, the January 10, 1997 guidance on 510(k) modifications will govern FDA’s actions.

Program to Improve the Device Recall System (FDASIA § 605)

Under new FFDCA Section 518A, FDA must create a system that will assess device recall information.⁵⁴ The program will identify trends (i.e., types of devices most frequently recalled and underlying causes of recalls) and assist FDA in mitigating health risks related to defective or unsafe medical devices.⁵⁵ In addition, the program must clarify the process for audit checks, provide criteria for a sponsor to determine whether a correction plan is effective for a particular recall, and document FDA’s support for terminating a recall.

Clinical Holds on Investigational Device Exemptions (FDASIA § 606)

FDASIA amends FFDCA Section 520(g) by adding a provision allowing FDA to issue a clinical hold prohibiting the use of a medical device in an investigation at any time, if it is determined that the device involves an

⁴⁰ *Id.* § 504.

⁴¹ *Id.* § 507.

⁴² *Id.* § 508.

⁴³ *Id.* § 509.

⁴⁴ *Id.* § 511.

⁴⁵ *Id.* § 601.

⁴⁶ *Id.* § 602.

⁴⁷ *Id.*

⁴⁸ *Id.* § 603.

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ *Id.*

⁵² *Id.* § 604.

⁵³ *Id.*

⁵⁴ *Id.* § 605.

⁵⁵ *Id.*

unreasonable health risk to the participants of the study.⁵⁶ The Secretary must provide the sponsor with the specific reasoning for the clinical hold determination. Moreover, a sponsor may make a written request for the removal of a clinical hold and must receive a response from FDA within 30 days.⁵⁷

Modification of De Novo Application Process; Reclassification Procedures (FDASIA §§ 607, 608)

If an applicant determines that there is no device on which to base a substantial equivalence determination, the applicant may request classification by the Secretary in lieu of submitting a 510(k) report.⁵⁸ The Secretary may choose to classify the device or decline to classify the device due to identifying a substantially equivalent device or determining that the device is not a low/moderate risk device controllable with general controls or subject to mitigation with special controls. An applicant may suggest a classification in their request. If the suggestion is for a Class II classification, the request should include proposed special controls that when coupled with general controls will ensure the safety and effectiveness of the device at issue.⁵⁹

FDASIA also amends FFDCA to allow the Secretary to change the classification of a device based on new information.⁶⁰ The determination requires FDA to publish a proposed order for reclassification, allowing for public comment, and then issuance of a final order.⁶¹ For classification changes from Class II to Class III, applicants should include why general and special controls do not ensure the safety of the device or, alternatively, if the request is for a change from a Class III to a Class II classification an applicant must support why the general and special controls are now adequate. The Secretary may delegate authority under this section no lower than the Director of the Center for Devices and Radiological Health in consultation with the FDA Commissioner.

This section will not apply to 513(g) classifications issued prior to the enactment of FDASIA. The Secretary will post the number and type of annual reclassifications on the FDA website.⁶²

Harmonization of Device Premarket Review, Inspection, and Labeling Symbols; Participation in International Forums (FDASIA § 609-610)

The Secretary may engage other nations in an effort to harmonize the regulatory requirements under this Title.⁶³ Section 610 amends the Act to allow the Secretary to participate in International forums such as the International Medical Device Regulators Forum, providing guidance and soliciting comment and review where appropriate. In addition, the Secretary may inform the public of such activities and share documentation on relevant policies and issues.

⁵⁶ *Id.* § 606.

⁵⁷ *Id.*

⁵⁸ *Id.* § 607.

⁵⁹ *Id.*

⁶⁰ *Id.* § 608.

⁶¹ *Id.*

⁶² *Id.*

⁶³ *Id.* § 609.

Reauthorization of Third-Party Review; Reauthorization of Third-Party Inspections (FDASIA § 611, 612)

Title VI of FDASIA also acts to reauthorize accredited third party review and accredited third-party inspections.⁶⁴ Any accreditations under Section 611 are valid for three years from the date of issuance. The Secretary must deny or approve requests for reaccreditation within 60 days. FDA must publish in the *Federal Register* the criteria for reaccreditation under this section and the areas for which the FDA will approve reaccreditation.⁶⁵

Humanitarian Device Exemptions (HDE) (FDASIA § 613)

Section 613 amends the current humanitarian device exemption (HDE).⁶⁶ A humanitarian use device is “intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect” less than 4,000 individuals in the U.S. yearly.⁶⁷ Under the Act a device would qualify for the HDE prohibition on profit exemption if its intended use is for a “disease or condition that does not occur in pediatric patients,” or it occurs in pediatric patients in numbers that result in device development being “impossible, impracticable, or unsafe.”⁶⁸ The number of devices manufactured under this exemption would have to be less than the amount needed to “treat 4,000 individuals in the United States,” although this provision is subject to modification by petitioning the Secretary.⁶⁹ Sponsors with HDEs granted before the enactment of FDASIA may request a determination to see if they may qualify for this exemption.⁷⁰

Unique Device Identifiers (FDASIA § 614)

FDASIA requires that FDA promulgate the regulations for the unique identifier system by December 31, 2012, finalize these regulations within 6 months of the comment period, and implement these regulations no later than 2 years after finalization.⁷¹

Sentinel (FDASIA § 615)

The Secretary must modify the FDA’s post-market risk identification and analysis system, Sentinel, by adding medical devices to the database.⁷² The amendments provide that the Secretary must utilize data from cleared 510(k) devices and devices approved under Section 515. The Secretary is required to involve stakeholders in the development of the Sentinel expansion.⁷³

Post-market Surveillance (FDASIA § 616)

FDASIA clarifies that FDA may order manufacturers to conduct post-market surveillance at the time of approval or at any time after approval. The manufacturer

⁶⁴ *Id.* §§ 611, 612.

⁶⁵ *Id.* § 611.

⁶⁶ *Id.* § 613.

⁶⁷ FFDCA § 520(m).

⁶⁸ *Id.*

⁶⁹ *Id.*

⁷⁰ *Id.*

⁷¹ *Id.* § 614.

⁷² *Id.* § 615.

⁷³ *Id.*

must commence requested post-market surveillance within 15 months of the Secretary's order.⁷⁴

Custom Devices (FDASIA § 617)

The Act adds additional characteristics to receive exemption for a device from the requirements of FFDCA §§ 514 and 515. These characteristics include devices for unique conditions untreatable by current domestic devices; devices manufactured on a case-by-case basis; and devices "with a common design, and composition" that are manufactured as commercially distributed devices.⁷⁵ Section 617 also limits the exemption to devices for rare conditions and those with limited production not exceeding more than 5 units a year. For applicants to receive this exemption they must notify the Secretary annually.⁷⁶ The Secretary will be required to issue guidance on the limited production of devices under this section.⁷⁷

Health Information Technology (FDASIA § 618)

Section 618 of FDASIA requires that the Secretary publish a risk-based strategy for regulating health information technology (Health IT), including mobile medical applications (MMAs), that promote innovation, protects patient safety, and avoids regulatory duplication. The Secretary must convene a working group consisting of diverse stakeholders to assist in the development of the regulatory strategy, and should receive input on the strategy from the National Coordinator for Health IT and the Chairman of the Federal Communications Commission.⁷⁸

Good Guidance Practices Relating to Devices (FDASIA § 619)

FDASIA provides that FDA will treat "notice to industry guidance letters, notice to industry advisory letters, and notices setting forth either initial interpretations of a regulations or policy changes in interpretation or policy," as guidance documents for devices going forward.⁷⁹

Pediatric Device Consortia (FDASIA § 620)

Section 620 requires that FDA implement a final rule on tracking pediatric devices no later than December 31, 2013.

TITLE VII—DRUG SUPPLY CHAIN

Registration of Domestic Drug Establishments; Registration of Foreign Establishments; Identification of Drug Excipient Information with Product Listing; Electronic System for Registration and Listing (FDASIA §§ 701-704)

FDASIA Section 701 amends the FFDCA such that establishment registrants must submit to FDA addi-

tional identifying information, including unique facility identifiers and point-of-contact e-mail addresses. This information will be required of every establishment upon their initial participation in the manufacturing process for drugs and devices. The legislation will alter the timing of annual registration to between October 1 and December 31 of each year. While the legislation provides the Secretary with the discretion to specify the unique facility identifier system that registrants must use, this requirement will not apply to registrants until the Secretary establishes this system.

Under FDASIA any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or device that is imported or offered for import into the United States must register with the Secretary immediately upon engaging in such activity.⁸⁰ The Secretary may deem a drug or device misbranded due to manufacture in foreign establishments that fail to register with the Secretary. Like domestic establishments, foreign establishments must also register between October 1 and December 31 of each year.⁸¹ In general, Section 702 requires foreign establishments to submit certain identifying information to FDA when registering, however, the requirements differ between drug⁸² and device manufacturers.⁸³ The Act also requires establishments to submit certain identifying information for excipient manufacturers when submitting product listing information for drugs.⁸⁴

Section 704 requires FDA to establish and maintain an electronic database, with certain specifications, to collect establishment registration and drug listing information to inform riskbased inspections, within two years of establishing a unique facility identifier system.⁸⁵

Risk-Based Inspection Frequency (FDASIA § 705)

The frequency of inspections established by Section 705 differs for drugs and devices.⁸⁶ FDA will inspect all registered device establishments that process a device or devices classified as Class II or III at least once in the 2-year period beginning with the date of registration of such establishment, and at least once in every successive 2-year period thereafter.⁸⁷ The Secretary will in-

⁸⁰ *Id.* § 702.

⁸¹ *Id.*

⁸² Foreign drug manufacturers must submit to the Secretary, the name and place of business of such person, all such establishments, the unique facility identifier of each such establishment, a point of contact e-mail address, the name of the United States agent of each such establishment, the name of each importer of such drug in the United States that is known to the establishment and the name of each person who imports or offers for import such drugs into the United States, for purposes of importation.

⁸³ Foreign device manufacturers must submit to the Secretary, the name and place of business of the establishment, the name of the United States agent for the establishment, the name of each importer of such device in the United States that is known to the establishment, the name of each person who imports or offers for import such device to the United States for purpose of importation.

⁸⁴ *Id.* § 703.

⁸⁵ *Id.* § 704.

⁸⁶ *Id.* § 705.

⁸⁷ *Id.*

⁷⁴ *Id.*

⁷⁵ *Id.* § 609.

⁷⁶ *Id.*

⁷⁷ *Id.*

⁷⁸ *Id.*

⁷⁹ *Id.* § 619.

spect drug establishments, both foreign and domestic, in accordance with a “risk-based schedule,” which FDA will establish using the following factors:

- A. The compliance history of the establishment;
- B. The record, history, and nature of recalls linked to the establishment;
- C. The inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment;
- D. The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years;
- E. Whether the establishment has been inspected by a foreign government or an agency of a foreign government recognized under section 809⁸⁸; and
- F. Any other criteria deemed necessary and appropriate by the Secretary for purposes of allocating inspection resources.

In this analysis FDA will not consider whether the drugs manufactured, prepared, propagated, compounded, or processed by such establishment are prescription drugs. Finally, beginning in 2014, the Secretary must submit a report to Congress by February 1 of each year, regarding (i) the number of domestic and foreign establishments registered in the previous fiscal year; (ii) the number of domestic and foreign establishments the Secretary inspected in the previous fiscal year; (iii) the number and type of excipient establishments; and (iv) the percentage of the FDA budget used to fund such inspections. This report will be publicly available on FDA’s website.

Records for Inspection (FDASIA § 706)

Upon request, establishments must provide to FDA, in advance of or in lieu of an inspection, sufficiently described records either electronically or in physical form. FDA must include a “sufficient description of the records requested.”⁸⁹ Establishments must provide such records “within a reasonable time frame, within reasonable limits and in a reasonable manner.”⁹⁰ Establishments are responsible for the costs of producing such records but may challenge record requests that they deem to be overly broad or vague that would not meet the “sufficient description” requirement under this section.⁹¹

Prohibition Against Delaying, Denying, Limiting or Refusing Inspection (FDASIA § 707)

Section 707 would amend Section 501 (21 U.S.C. § 351) by rendering a drug adulterated if the drug “has been manufactured, processed, packed, or held in any factory, warehouse or establishment, and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection.”⁹² Within a year after the enactment of FDASIA, FDA must issue guidance

that defines the circumstances that would constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection for purposes of section 501(j) of the FFDCA.⁹³

Destruction of Adulterated, Misbranded, or Counterfeit Drugs Offered For Import

(FDASIA § 708)

This section amends FFDCA Section 801(a) (21 U.S.C. § 381(a)) by giving FDA the discretion to destroy, without the opportunity for export, any drug refused admission under this section, “if such drug is valued at an amount that is \$2,500 or less (or such higher amount as the Secretary of the Treasury may set by regulation)” and was not brought into compliance as described in section 801(b). FDA must issue regulations providing for notice and an opportunity to appear before FDA and introduce testimony on the destruction of the drug. The regulations must provide that “prior to the destruction, appropriate due process is available to the owner or consignee seeking to challenge the decision to destroy the drug.”⁹⁴ When there is a notice and appearance, FDA must “store and, as applicable, dispose of the drug after the issuance of the notice.”⁹⁵ The owner and consignee will remain liable for the destruction costs. The Secretary must promulgate regulations implementing this amendment within 2 years of enactment of FDASIA, and this section will not take effect until the promulgation of these regulations.

Administrative Detention (FDASIA § 709)

This section amends FFDCA Section 304(g) (21 U.S.C. 334(g)) by authorizing FDA to detain a drug found in a facility being inspected, if during the inspection the inspector has reason to believe that the drug is adulterated or misbranded. FDA must promulgate regulations to implement administrative detention authority with respect to drugs within two years of enactment of FDASIA. Before promulgating such regulations, FDA must consult with stakeholders. Once FDA promulgates these regulations this section will take effect.

Exchange of Information (FDASIA § 710)

Under section 710, FDA is not required to disclose under 5 U.S.C. § 552 (the ‘Freedom of Information Act’) or any other provision of law, any drug-related information 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.”⁹⁶ If the written agreement does not include a specified time for protection of the disclosed informa-

⁸⁸ Section 712 amends Chapter VIII (21 U.S.C. 381 et seq.) by adding Section 809 “Recognition of Foreign Government Inspections.”

⁸⁹ FDASIA § 706.

⁹⁰ *Id.*

⁹¹ *Id.*

⁹² *Id.* § 707.

⁹³ *Id.*

⁹⁴ *Id.* § 708.

⁹⁵ *Id.*

⁹⁶ *Id.* § 710.

tion, this section will cover the information for up to 36 months.

This section also provides FDA with the authority to enter into written agreements to provide trade secret information to foreign governments. First, FDA may only enter into written agreements with foreign governments certified “as having the authority and demonstrated ability to protect trade secret information from disclosure.”⁹⁷ Second, the written agreement must “include a commitment by the foreign government to protect information exchanged during disclosure,” unless the sponsor allows for disclosure through written permission or until the Secretary makes a Section 319 public health emergency declaration under the Public Health Service Act (PHS), relevant to the disclosed information.⁹⁸

If the foreign government has been certified and a written agreement executed, the Secretary is still limited to providing information only if “the Secretary reasonably believes or the written agreement establishes that the government has authority to otherwise obtain such information; and (ii) the written agreement limits the recipient’s use of the information to the recipient’s civil regulatory purposes,” or “to alert the foreign government to the potential need for an investigation, 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.”⁹⁹

Enhancing the Safety and Quality of the Drug Supply Chain (FDASIA § 711)

Section 711 amends Section 501 (21 U.S.C. § 351) by clarifying that ‘current good manufacturing practices’ for the purposes of subsection (a)(2)(B), include “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.”¹⁰⁰

Recognition of Foreign Government Inspections (FDASIA § 712)

This section amends Chapter VIII (21 U.S.C. 381 et seq.) by authorizing the Secretary to enter into agreements with foreign governments to recognize foreign inspections. FDA is restricted to only entering into such agreements after making a determination that the foreign government has the capability to conduct inspections in accord with the FFDCA. This determination will be based on “reviews and audits of drug safety programs, systems, and standards” of a given foreign government. FDA may utilize the results of foreign government inspections as “evidence of compliance with Section 501(a)(2)(B) or Section 801(r)” or for any other purposes the Secretary deems appropriate.¹⁰¹

Standards for Admission of Imported Drugs (FDASIA § 713)

As a condition of granting admission to a drug imported or offered for import into the United States, FDA

may require importers to submit electronically certain information demonstrating that the drug is not violative of the FFDCA.¹⁰² Importers can meet this requirement through verification by a foreign government that inspections were conducted using standards and practices FDA has deemed appropriate; “through representation by a foreign government or an agency of a foreign government recognized under Section 809” or other support as provided by the Secretary.¹⁰³ Any regulations must take into account factors such as the type of import and whether the import is for investigational use. FDA may also consider differences among importers and types of imports. Based on the level of risk posed by the imported drug, FDA may provide for expedited clearance for those importers that volunteer to participate in partnership programs for highly compliant companies.

Registration of Commercial Importers (FDASIA § 714)

This section amends Section 713 of the FFDCA by requiring a commercial drug importer to register with FDA and to include with their registration a unique identifier for the associated registered establishment. Failure to register is a prohibited act under this section. These requirements will not take effect until the system is established. FDA and Homeland Security, acting through U.S. Customs and Border Protection, will promulgate these regulations. The regulations must establish specific directives for importers to follow to avoid importing products violative of the FFDCA and Public Health Service Act. Commercial importers that do not comply with the regulations for this section will jeopardize their importer registration. FDA may establish exemptions from the requirements of this subsection by notice in the *Federal Register*. Section 714 also amends Section 502(o) (21 U.S.C. 352) by deeming a drug misbranded if it was imported or offered for import into the United States by an unregistered commercial importer.

FDA must promulgate these regulations within three years, and provide a “reasonable period of time” for an importer of a drug to comply with good importer practices, taking into account differences among importers including types of imports and level of risk posed by a specific imported product.¹⁰⁴

Notification (FDASIA § 715)

Under Section 712, FDA may require a “regulated person”¹⁰⁵ to notify the agency under certain circumstances. First, a regulated person must notify FDA if they know “that the use of a drug in the United States may result in serious injury or death.” Second, a regulated person must notify FDA if they know of a “significant loss or known theft” of such drug intended for use in the United States. Finally, a regulated person must notify FDA if they know that “(A) a drug has been or is

¹⁰² *Id.* § 713.

¹⁰³ Section 712 amends Chapter VIII (21 U.S.C. 381 et seq.) by adding Section 809 “Recognition of Foreign Government Inspections.”

¹⁰⁴ *Id.* § 714.

¹⁰⁵ A regulated person means 1) a person who is required to register under FFDCA sections 510 or 801(s); 2) a wholesale distributor of a drug product; or 3) any other person that distributes drugs except a person that distributes drugs exclusively for retail sale.

⁹⁷ *Id.*

⁹⁸ *Id.*

⁹⁹ *Id.*

¹⁰⁰ *Id.* § 711.

¹⁰¹ *Id.* § 712.

being counterfeited; and (B)(i) the counterfeit product is in commerce in the United States or could be reasonably expected to be introduced into commerce in the United States; or (ii) such drug has been or is being imported in the United States or may reasonably be expected to be offered for import into the United States.”¹⁰⁶ FDA will specify by regulation or guidance the manner and means of notification for this section.

Protection against Intentional Adulteration; Penalties for Counterfeiting Drugs; (FDASIA §§ 716-717)

Sections 716 and 717 enhance criminal penalties for an individual or entity that knowingly and intentionally “traffics in a counterfeit drug.”¹⁰⁷ The term ‘counterfeit drug’ means “a drug as defined by Section 201 of the FFDCA that uses a counterfeit mark on or in connection with the drug.”¹⁰⁸ This section authorizes the Attorney General to give increased priority to efforts to investigate and prosecute offenses under 18 U.S.C. § 2320 involving counterfeit drugs. Enhanced penalties for individuals include up to 20 years in prison and fines up to \$5,000,000, or both. Penalties for entities include fines up to \$15,000,000. For second or subsequent offenses by individuals, penalties include up to 30 years in prison and fines up to \$15,000,000 or both; penalties for subsequent offenses by entities include fines up to \$30,000,000. This section also requires enhanced sentencing guidelines and policy statements from the United States Sentencing Commission.

Extraterritorial Jurisdiction (FDASIA § 718)

Section 718 authorizes extraterritorial jurisdiction over any violation of the FFDCA for regulated articles “intended for import into the United States or if any act in furtherance of the violations was committed in the United States.”¹⁰⁹

TITLE VIII-GENERATING ANTIBIOTIC INCENTIVES NOW

Extension of Exclusivity Period for Drugs (FDASIA § 801)

The Generating Antibiotic Incentives Now Act (GAIN Act) provides an additional five years of exclusivity to incentivize the development of new qualified infectious disease products.¹¹⁰ Under this section a QIDP is “an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens” or caused by qualifying pathogens listed by FDA.¹¹¹ The additional exclusivity applies to QIDPs approved under NDAs, ANDAs, supplements to NDAs and ANDAs, and orphan drugs.¹¹² These GAIN Act ex-

tensions apply in addition to any pediatric exclusivity.¹¹³

Notwithstanding the above, a GAIN Act extension does not apply to a supplement to an NDA for any QIDP for which a GAIN Act extension is already in effect or has expired.¹¹⁴ A GAIN Act extension also does not apply for “a subsequent application filed for an approved drug for “a change that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength,” or for an unapproved use that was not included in the QIDP designation.”¹¹⁵

For purposes of QIDP designation, FDA will identify and list “qualifying pathogens” that have “the potential to pose a serious threat to public health.”¹¹⁶ FDA must publicize the methodology for developing the list and 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;
- the morbidity and mortality in humans; and
- the opinions of experts in infectious diseases and antibiotic resistance.¹¹⁷

Every five years, or as often as needed, FDA must review and revise the list by regulation, as necessary.

A sponsor may request FDA to designate a drug as a QIDP at any time before submitting an NDA, and FDA must make a QIDP determination no later than 60 days after the request.¹¹⁸ FDA may not revoke a QIDP designation because of a change to the list of qualifying pathogens and may only revoke a QIDP designation if the QIDP request contained an untrue statement of material fact.

FDA must promulgate final regulations implementing the GAIN Act, including developing the list of qualified pathogens, within two years of the enactment of FDASIA.¹¹⁹ In the interim, FDA may still designate drugs as QIDPs, if such drugs meet the definition of a QIDP, and issue draft guidance for sponsors seeking QIDP designation prior to the promulgation of the final rules.

If FDA designates a drug as a QIDP, then FDA must give priority review to any NDA submitted for such drug.¹²⁰ The sponsor of a QIDP designated drug may

¹¹³ FDASIA § 801; FFDCA § 505A(b)(1), 21 U.S.C. § 355a(b)(1).

¹¹⁴ FDASIA § 801.

¹¹⁵ *Id.*

¹¹⁶ *Id.* FDASIA provides an initial list of examples of qualifying pathogens that have the potential to pose a serious threat to public health that includes: resistant gram positive pathogens, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococcus; multi-drug resistant gram negative bacteria, including *Acinetobacter*, *Klebsiella*, *Pseudomonas*, and *E. coli* species; multi-drug resistant tuberculosis; and *Clostridium difficile*. *Id.*

¹¹⁷ *Id.*

¹¹⁸ *Id.*

¹¹⁹ *Id.*

¹²⁰ *Id.* § 802.

¹⁰⁶ FDASIA § 715.

¹⁰⁷ *Id.* § 716. This section amends 18 U.S.C. § 2320(a).

¹⁰⁸ FDASIA § 717.

¹⁰⁹ *Id.* § 718.

¹¹⁰ *Id.* § 801.

¹¹¹ *Id.*

¹¹² *Id.*; FFDCA § 505(c)(3)(E)(ii)-(iv), 21 U.S.C. § 355(c)(3)(E)(ii)-(iv); FFDCA § 505(j)(5)(F)(ii)-(iv), 21 U.S.C. § 355(j)(5)(F)(ii)-(iv); FFDCA § 527(a), 21 U.S.C. § 360cc(a).

also request that FDA designate the drug as a fast track product for expedited review.¹²¹

FDA must review and revise as necessary, for clarity and the latest scientific and medical information, at least three of its guidance documents per year related to clinical trials for antibacterial and antifungal drugs.¹²² A sponsor seeking QIDP designation for a drug may request that FDA provide written recommendations for clinical and nonclinical investigations which FDA believes may be necessary to gain QIDP designation.¹²³

Reassessment of Qualified Infectious Disease Product Incentives in Five Years (FDASIA § 805)

Within five years of the enactment of the GAIN Act, FDA must, in consultation with the Centers for Disease Control and Prevention, and other appropriate agencies, submit to Congress a report containing a review of QIDP designations and the effectiveness of the approval process, recommendations on changes to the list of qualifying pathogens or changes to the QIDP program, and an examination of antibacterial programs in health-care settings.¹²⁴

Guidance on Pathogen-Focused Antibacterial Drug Development (FDASIA § 806)

By June 30, 2013, FDA shall publish draft guidance that:

- specifies how preclinical and clinical data can be utilized to inform an efficient and streamlined pathogen-focused antibacterial drug development program that meets the approval standards of FDA; and

¹²¹ *Id.* § 803; FFDCA § 506(a)(1), 21 U.S.C. § 356(a)(1).

¹²² FDASIA § 804(a)(1). At a minimum, the review must address “the appropriate animal models of infection, in vitro techniques, valid micro-biological surrogate markers, the use of non-inferiority versus superiority trials, trial enrollment, data requirements, and appropriate delta values for non-inferiority trials.” *Id.* § 805(a)(2).

¹²³ *Id.* § 804(b).

¹²⁴ See *id.* § 805(a) requiring the report to include: the number of initial designations of drugs as QIDPs; the number of QIDPs approved; whether such products address the need for antibacterial and antifungal drugs to treat serious and life-threatening infections; a list of QIDPs with information on the types of exclusivity granted for each product; the progress made on reviewing and revising the clinical trial guidance documents under section 804 and its impact on the review and approval of QIDPs; the Federal contribution, if any, to funding of the clinical trials for each QIDP for each phase; recommendations based on the above information, and any other relevant data, on any changes that should be made to the list of qualifying pathogens; recommendations on whether any additional program (such as public-private collaborations) or changes to the incentives under the GAIN Act may be needed to promote the development of antibacterial drugs; an examination of the adoption of programs to measure the use of antibacterial drugs in health care settings; an examination of the implementation and effectiveness of antimicrobial stewardship protocols across all health care settings; any recommendations for ways to encourage further development and establishment of stewardship programs; and a description of the regulatory challenges and impediments to clinical development, approval, and licensure of QIDPs, and the steps FDA has taken and will take to address such challenges and ensure regulatory certainty and predictability with respect to QIDPs.

- provides advice on approaches for the development of antibacterial drugs that target a more limited spectrum of pathogens.¹²⁵

FDA must publish final guidance by December 31, 2014.¹²⁶

TITLE IX-DRUG APPROVAL and PATIENT ACCESS

Enhancement of Accelerated Patient Access to New Medical Treatments (FDASIA § 901)

Under FDASIA, the definition of a fast track product is somewhat broadened to include a drug that, “whether alone or in combination with one or more drugs,” is intended for the treatment of a serious or life-threatening disease or condition.¹²⁷ Previously, a fast track product did not explicitly include a drug working in combination with another drug to treat a serious or life-threatening disease or condition.

FDASIA also sets forth criteria for drug accelerated approval that includes approval of fast track products.¹²⁸ As a codification of the accelerated approval regulations¹²⁹ FDA may grant accelerated approval based “upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.”¹³⁰ With FDASIA, FDA may additionally grant accelerated approval based “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.”¹³¹

Evidence to support a finding that an endpoint is reasonably likely to predict clinical benefit “may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools.”¹³² Previously, FDA did not list types of acceptable evidence. In addition, FDASIA expands FDA’s efforts to encourage the development of clinical endpoints, including biomarkers, and other scientific methods and tools to assist FDA in evaluating evidence of predictive clinical benefit in accelerated approval applications. However, the new law provides that nothing in Title IX changes the existing FFDCA standards of evidence for safety and effectiveness.

Within one year of the enactment of FDASIA, FDA must issue draft guidance on the accelerated approval and fast track processes, including consideration of rare disease issues.¹³³ In developing the guidance, FDA must consider how to incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data un-

¹²⁵ *Id.* § 806(a).

¹²⁶ *Id.* § 806(b).

¹²⁷ *Id.* § 901(b).

¹²⁸ *Id.*

¹²⁹ 21 C.F.R. § 314, Subpart H.

¹³⁰ FDASIA § 901(b).

¹³¹ *Id.*

¹³² *Id.*

¹³³ *Id.* § 901(c)(1).

likely or impractical.¹³⁴ FDA must issue final guidance within one year of issuing the draft guidance.¹³⁵

Breakthrough Therapies (FDASIA § 902)

FDASIA creates a new “breakthrough therapy” designation to expedite the development and review of a drug intended “to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.”¹³⁶ A drug sponsor may request designation as a breakthrough therapy concurrently with, or any time after submission of an Investigational New Drug (IND) application.¹³⁷ Within 60 calendar days of receiving such a request, FDA must make a determination as to whether the drug qualifies as a breakthrough therapy.¹³⁸

Actions to expedite development and review of a breakthrough therapy application may include:

- holding meetings with the sponsor and the review team throughout the development of the drug;
- providing timely advice to, and interactive communication with the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable;
- involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review;
- assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and
- taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment.¹³⁹

Within 18 months of the enactment of FDASIA, FDA must issue draft guidance on implementing the requirements for breakthrough therapies.¹⁴⁰ FDA must then issue final guidance within one year of the close of the comment period for the draft guidance.¹⁴¹ The guidance must specify the process and criteria by which FDA makes a breakthrough therapy designation and specify the actions that FDA will take to expedite the development and review of a breakthrough therapy.¹⁴²

Breakthrough designation, fast track designation, and the accelerated approval process are expedited review programs that primarily differ in the effectiveness that the product must demonstrate against a serious or life-threatening disease or condition.¹⁴³ For designation as a breakthrough therapy, preliminary clinical evidence must indicate that the drug may demonstrate substantial improvement over existing therapies on one

or more clinically significant endpoints.¹⁴⁴ A fast track product must demonstrate the potential to address unmet medical needs.¹⁴⁵ For accelerated approval, there must be evidence that the product has an effect on an endpoint that is reasonably likely to predict clinical benefit.¹⁴⁶ Accelerated approval includes fast track products indicated for a serious or life-threatening disease or condition.¹⁴⁷

Consultation with External Experts on Rare Diseases, Targeted Therapies, and Genetic Targeting of Treatments (FDASIA § 903)

To inform and promote the efficiency of FDA review of new drugs and biological products for rare diseases and genetically targeted drugs and biological products, FDASIA provides that FDA may consult with external experts as necessary and must develop and maintain a list of qualified experts.¹⁴⁸ For this purpose, external experts are “individuals who possess scientific or medical training that [FDA] lacks with respect to one or more rare diseases.”¹⁴⁹ Prior to consulting with an external expert, FDA must determine that such consultation will not delay a product’s review but will facilitate completion of the review and address outstanding deficiencies in the application.¹⁵⁰ Otherwise, FDA must have authorization from the sponsor for such consultation.¹⁵¹

Accessibility of Information on Prescription Drug Container Labels by Visually-Impaired and Blind Consumers (FDASIA § 904)

To develop best practices on access to information on prescription drug container labels by visually-impaired and blind consumers, FDASIA requires the Architectural and Transportation Barriers Compliance Board to convene a stakeholder working group.¹⁵² The working group must be comprised of equal numbers of consumer advocates, such as national organizations for blind and visually-impaired individuals, and industry advocates, such as retail, mail order, and independent community pharmacies.¹⁵³ Within one year of the enactment of FDASIA, the working group must develop “best practices for pharmacies to ensure that blind and visually-impaired individuals have safe, consistent, reliable, and independent access to the information on prescription drug container labels.”¹⁵⁴ Beginning 18 months after the completion of the best practices, GAO must conduct a review of the extent to which pharmacies are implementing the best practices and review the extent to which barriers to accessible information still exist.¹⁵⁵ By September 30, 2016, GAO must submit a re-

¹³⁴ *Id.* § 901(c)(3).

¹³⁵ *Id.* § 901(c)(2).

¹³⁶ *Id.* § 902(a)(3).

¹³⁷ *Id.*

¹³⁸ *Id.*

¹³⁹ *Id.*

¹⁴⁰ *Id.* § 902(b)(1)(A).

¹⁴¹ *Id.*

¹⁴² *Id.* § 902(b)(2).

¹⁴³ See Appendix D for a detailed chart comparing the three provisions.

¹⁴⁴ FDASIA § 902(a)(3).

¹⁴⁵ *Id.* § 901(b).

¹⁴⁶ *Id.*

¹⁴⁷ *Id.*

¹⁴⁸ *Id.* § 903.

¹⁴⁹ *Id.*

¹⁵⁰ *Id.*

¹⁵¹ *Id.*

¹⁵² *Id.* § 904(a)(1).

¹⁵³ *Id.* § 904(a)(2).

¹⁵⁴ *Id.* § 904(a)(3)(A).

¹⁵⁵ *Id.* § 904(b)(1).

port to Congress on this review and include recommendations on how to reduce remaining barriers.¹⁵⁶

Risk-Benefit Framework (FDASIA § 905)

In considering approval of a new drug, FDA “shall 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.”¹⁵⁷ Consideration of this risk-benefit framework does not change the existing criteria for approving a drug.¹⁵⁸

Grants and Contracts for the Development of Orphan Drugs (FDASIA § 906)

FDASIA changes the timeframe for “qualified testing” that is eligible for coverage by orphan drug grants.¹⁵⁹ The new timeframe includes all human clinical testing that occurs before the date of filing a New Drug Application (NDA) or a Biologics License Application (BLA).¹⁶⁰ Previously, “qualified testing” only included testing after the date FDA designated the product an orphan drug and before the date of filing an NDA or BLA.¹⁶¹ In addition, FDASIA reauthorizes the orphan product grants program for another five years from 2013 through 2017.¹⁶² The annual appropriation for the program remains the same at \$30 million.¹⁶³

Reporting of Inclusion of Demographic Subgroups in Clinical Trials and Data Analysis in Applications for Drugs, Biologics, and Devices (FDASIA § 907)

Within one year of the enactment of FDASIA, FDA must publish a report on its website “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.¹⁶⁴ Within one year of the publication of the report, FDA must publish an action plan on its website with recommendations on improving the analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling, and recommendations on improving the public availability of such data.¹⁶⁵

Rare Pediatric Disease Priority Review Voucher Incentive Program (FDASIA § 908)

A sponsor can obtain a priority review voucher for a rare pediatric disease product application that:

- is for a drug or biological product that is for the prevention or treatment of a rare pediatric disease and that contains no active ingredient that has been previously approved in any other application;

- FDA deems eligible for priority review;
- relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population;
- does not seek approval for an adult indication in the original rare pediatric disease product application; and
- approved after the date of the enactment of FDASIA.¹⁶⁶

Priority review means review and action on the application no later than six months after FDA’s receipt of the application.¹⁶⁷ A priority review voucher entitles the holder to priority review of one human drug or biologic application after the date of approval of the rare pediatric disease product application. A rare pediatric disease means a disease that primarily affects people from birth to 18 years, and the disease is a rare disease or condition within the meaning of the Orphan Drug Act. Within 60 days of receiving a request, FDA must determine whether the disease or condition in the request is a rare pediatric disease and whether the application is a valid rare pediatric disease product application. If the sponsor does not market the product that received the voucher within 365 days of the product’s approval, FDA may revoke the voucher.

Additionally, if a sponsor submitted a rare pediatric disease product application prior to 90 days after the enactment of FDASIA, they may not receive a voucher.¹⁶⁸ At least 90 days prior to using a voucher, a sponsor must notify FDA of their intent to submit an application that is the subject of the voucher and commit to paying the associated user fee. FDA must set the user fee each fiscal year based on the difference between the average cost of a priority review in the previous fiscal year and the average cost of a non-priority review in the previous fiscal year. FDA’s authority to award vouchers terminates after the last day of the one-year period that begins on the date that FDA awards the third voucher.

A sponsor who receives a priority review voucher may transfer (including by sale) the entitlement to the voucher.¹⁶⁹ After submitting notice of the intent to use a voucher, a sponsor may still transfer the voucher if the sponsor has not yet submitted the application. There is no limit on transferring the voucher prior to its use. The person who receives the voucher due to a transfer must notify FDA of the change of ownership within 30 days of the transfer.

Within five years of approval, the sponsor of a rare pediatric disease product must submit a report to FDA providing the following information, with respect to the first four years after approval:

- the estimated population in the United States suffering from the rare pediatric disease;
- the estimated demand in the United States for such rare pediatric disease product; and
- the actual amount of such rare pediatric disease product distributed in the United States.¹⁷⁰

Within one year of FDA’s awarding a third voucher, GAO must submit a report to Congress on the effectiveness of awarding rare pediatric disease priority vouchers.

¹⁵⁶ *Id.* § 904(b)(2).

¹⁵⁷ *Id.* § 905.

¹⁵⁸ *Id.*

¹⁵⁹ *Id.* § 906(a).

¹⁶⁰ *Id.*

¹⁶¹ *Id.*

¹⁶² *Id.* § 906(b).

¹⁶³ *Id.*

¹⁶⁴ *Id.* § 907(a)(1).

¹⁶⁵ *Id.* § 907(b).

¹⁶⁶ *Id.* § 908.

¹⁶⁷ *Id.*

¹⁶⁸ *Id.*

¹⁶⁹ *Id.*

¹⁷⁰ *Id.*

ers in the development of human drug products that treat or prevents such diseases.¹⁷¹

TITLE X-DRUG SHORTAGES

Discontinuance or Interruption in the Production of Life-Saving Drugs (FDASIA § 1001)

In light of the rising number of drug shortages in recent years, Title X of FDASIA substantially amends the existing FFDCA drug shortage provisions. FDASIA eliminates the requirement that a manufacturer be the sole manufacturer of a drug to be subject to the drug shortage notice requirements.¹⁷² Additionally, FDASIA explicitly makes drugs used in emergency medical care or during surgery subject to drug shortage notice requirements.¹⁷³ Previously, only drugs that were lifesupporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition were subject to these requirements.¹⁷⁴ New exclusions from the notice requirements include radiopharmaceutical drug products or any other product as designated by FDA.¹⁷⁵ Prior to these amendments, the exclusion only applied to products originally derived from human tissue and replaced by a recombinant product.

Manufacturers covered by the FDASIA notice requirements must notify FDA of either “a permanent discontinuance in the manufacture of the drug or an interruption of the manufacture of the drug that is likely to lead to a meaningful disruption in the supply of that drug in the United States, and the reasons for such discontinuance or interruption.”¹⁷⁶ Previously, the FFDCA only required notification for discontinuance in the manufacture of a drug. Under FDASIA, manufacturers must notify FDA at least six months before the date of the discontinuance or interruption, or as soon as practicable if the six-month minimum is not possible. Previously, the FFDCA only specified that manufacturers must notify FDA at least six months prior to the date of discontinuance. To the maximum extent practicable, FDA must inform appropriate organizations — including physician, health provider, and patient organizations — of drug shortages. Within 30 days of receiving notice of a drug shortage pertaining to a controlled substance subject to a production quota, FDA will notify the Attorney General and request that the Attorney General increase the production quotas if FDA deems it necessary to address the shortage.

If a manufacturer fails to submit information about a drug shortage as required, FDA must issue a letter informing it of the failure. Within 30 days of the issuance of the letter, the manufacturer must submit to FDA a written response setting forth the basis for noncompliance and providing the required drug shortage information. Within 45 days of the issuance of the letter, FDA must publish the letter and any response on the FDA’s website, unless FDA issued the letter in error or the manufacturer’s response shows that there was a reasonable basis for not notifying as required.

FDASIA authorizes FDA to respond to a drug shortage by expediting the review of an ANDA or a supplement to an ANDA or NDA that could help mitigate or prevent the shortage. FDA may also expedite an inspection or re-inspection of an establishment that could help mitigate or prevent the shortage.

Within 18 months of the enactment of FDASIA, FDA must adopt a final regulation implementing these drug shortage requirements.¹⁷⁷ FDA may also apply these requirements by regulation to biological products if FDA “determines such inclusion would benefit the public health.”¹⁷⁸

Annual Reporting on Drug Shortages (FDASIA § 1002)

By the end of calendar year 2013, and no later than the end of each calendar year thereafter, FDA must submit a report to Congress on drug shortage statistics, communication within FDA on addressing shortages, and actions taken by FDA to prevent or mitigate shortages.¹⁷⁹

Coordination; Task Force and Strategic Plan (FDASIA § 1003)

As soon as practicable after the enactment of FDASIA, FDA must establish a task force to develop and implement a strategic plan for enhancing FDA’s response to preventing and mitigating drug shortages.¹⁸⁰ Among other issues, the plan must examine whether to establish a “qualified manufacturing partner program.”¹⁸¹ A qualified manufacturer would need to have the capability and capacity to supply products determined or anticipated to be in shortage within a rapid timeframe. FDA must also consider whether incentives are necessary to encourage participation in a qualified manufacturing program. Within one year of the enactment of FDASIA, the task force must publish the strategic plan and submit it to Congress.

Prior to any enforcement action or issuance of a warning letter that could reasonably lead to a meaningful disruption in the supply of a drug as described above, FDA must ensure that there is communication with the appropriate FDA office with expertise in drug shortages.¹⁸² If after the communication, FDA determines that an enforcement action or warning letter “could reasonably cause or exacerbate a shortage of a drug,” then FDA 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.”¹⁸³

The task force, strategic plan, communication, and risk evaluation requirements of section 1003 described above expire five years after the enactment of FDASIA. To allow healthcare providers and other third-party organizations an opportunity to report evidence of drug shortages, FDA must identify or establish a reporting mechanism.

¹⁷¹ *Id.*

¹⁷² FDASIA § 1001(a).

¹⁷³ *Id.*

¹⁷⁴ FFDCA § 506C(a)(1).

¹⁷⁵ FDASIA § 1001(a).

¹⁷⁶ *Id.*

¹⁷⁷ *Id.*

¹⁷⁸ *Id.*

¹⁷⁹ *Id.* § 1002.

¹⁸⁰ *Id.* § 1003.

¹⁸¹ *Id.*

¹⁸² *Id.*

¹⁸³ *Id.*

Drug Shortage List (FDASIA § 1004)

FDA must maintain an up-to-date list of drugs determined by FDA to be in shortage in the United States.¹⁸⁴ For each drug on the list, FDA must include the following: the name of the drug, the name of the manufacturer, the reason for the shortage, and the estimated duration of the shortage as determined by FDA.¹⁸⁵ The information in the list must be publicly available, unless the information involves trade secrets or confidential information, or if FDA “determines that disclosure of such information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption of the availability of drug products to patients).”¹⁸⁶

Quotas Applicable to Drugs in Shortage (FDASIA § 1005)

Section 1005 amends the Controlled Substances Act to allow manufacturers of a schedule II controlled substance that is on FDA’s list of drugs in shortage to request an increase in production quotas from the Attorney General.¹⁸⁷ Within 30 days of such a request, the Attorney General must review the request and decide whether increasing production quotas is necessary to address a shortage of a controlled substance.¹⁸⁸ If the Attorney General determines that the level requested is not necessary to address a shortage of a controlled substance, the Attorney General must provide a written response detailing the basis for the determination and publish the response on FDA’s website.¹⁸⁹

Attorney General Report on Drug Shortages (FDASIA § 1006)

Within six months of the enactment of FDASIA, the Attorney General must submit to Congress a report on drug shortages that:

- identifies the number of requests received under section 1005, the average review time for such requests, the number of requests granted and denied, and, for each of the requests denied, the basis for such denial;
- describes the coordination between the Drug Enforcement Administration and FDA on efforts to prevent or alleviate drug shortages; and
- identifies drugs containing a controlled substance subject to section 1005 when FDA determines such a drug is in shortage.¹⁹⁰

Hospital Repackaging of Drugs in Shortage (FDASIA § 1007)

A hospital may repackage a drug (excluding controlled substances) for transfer to another hospital within the same health system and need not register as a repackager if:

- the drug is listed on FDA’s drug shortage list, or it is during the 60-day period following a period when the drug was on the list;

- the 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 such health system; and

- repackaging completed in compliance with applicable State requirements.¹⁹¹

This exception does not apply starting on the date on which FDA “issues final guidance that clarifies the policy of the Food and Drug Administration regarding hospital pharmacies repackaging and safely transferring repackaged drugs to other hospitals within the same health system during a drug shortage.”¹⁹²

Study on Drug Shortages (FDASIA § 1008)

Within 18 months of the enactment of FDASIA, GAO must submit a report to Congress on the cause of drug shortages and on recommendations on how to prevent or alleviate shortages.¹⁹³

TITLE XI - OTHER PROVISIONS¹⁹⁴

Reauthorization of Provision Relating to Exclusivity of Certain Drugs Containing Single Enantiomers (FDASIA § 1101)

FDASIA extends to October 1, 2017 the opportunity for manufacturers to take advantage of the ability for FDA to consider single enantiomer drugs as new chemical entities under FFDCA § 505(u) for exclusivity purposes, and clarifies that for new chemical entity determination the new single enantiomer may not rely on clinical investigations from the racemic product’s approval.¹⁹⁵

Reauthorization of the Critical Path Public-Private Partnerships (FDASIA § 1102)

The bill renews, through fiscal year 2017, the authorization of \$6M per year toward Critical Path public-private partnerships under FFDCA § 566.¹⁹⁶

Regulation of Medical Gases (FDASIA § 1111)

FDASIA establishes a new regulatory review process for certain designated medical gases (e.g., oxygen),¹⁹⁷ whereby sponsors, upon certification, are deemed to have an approved drug application provided they only market the medical gas for specified indications and include specific labeling. Sponsors are subject to all other post-approval requirements. The specific labeling requirements for designated medical gases will be determined via rulemaking. To be certified, a sponsor must submit a description of the medical gas and identify the manufacturer and sponsor; FDA has 60 days to object

¹⁸⁴ *Id.* § 1004.

¹⁸⁵ *Id.*

¹⁸⁶ *Id.*

¹⁸⁷ *Id.* § 1005.

¹⁸⁸ *Id.*

¹⁸⁹ *Id.*

¹⁹⁰ *Id.* § 1006.

¹⁹¹ *Id.* § 1007.

¹⁹² *Id.*

¹⁹³ *Id.* § 1008.

¹⁹⁴ See Appendix E.

¹⁹⁵ FDASIA § 1101.

¹⁹⁶ *Id.* § 1102.

¹⁹⁷ *Id.* § 1111. The specified medical gases are: oxygen, nitrogen, nitrous oxide, helium, carbon monoxide, carbon dioxide, medical air, and any other medical gas product FDA deems appropriate.

to the certification, otherwise the sponsor may consider the request for certification granted.

Guidance Document Regarding Product Promotion Using the Internet (FDASIA § 1121)

Within 2 years of FDASIA's enactment the Secretary must issue guidance on internet promotion of FDA regulated products including the use of social media.

Combating Prescription Drug Abuse (FDASIA § 1122)

In an effort to combat the rise in prescription drug abuse, FDASIA requires that the Secretary in coordination with other Federal agencies identify initiatives regarding safe use of potentially abused prescription drug products and treatments for prescription drug abuse. Within one year the Secretary must post a report on the findings including how to leverage current Federal data source on these issues, how to disseminate best practices and how best to formulate effective education tools for healthcare providers and patients.

Optimizing Global Clinical Trials (FDASIA § 1123)

Without changing FDA's standards for clinical trials, FDA is required to work with foreign regulatory bodies to harmonize standards in order to avoid duplicative studies. Going forward, FDA must explain in writing why it will not accept any foreign clinical studies submitted for drugs and devices.¹⁹⁸

Advancing Regulatory Science to Promote Public Health Innovation; Information Technology (FDASIA § 1124, 1125)

Under FDASIA Section 1124 the Secretary must develop and implement a plan that identifies FDA's regulatory science gaps that impede review, priorities for allocating resources, and metrics on how to move forward. The Secretary must submit reports on this plan as part of the performance reports that FDA submits to Congress annually. In addition, the Secretary must report to Congress within a year on the progress made by FDA in implementing a comprehensive information technology modernization project including goals and milestones.¹⁹⁹

Nanotechnology (FDASIA § 1126)

FDA must establish activities with the express charge of expanding scientific knowledge on nanotech related products and potential regulatory issues with such products. FDA will achieve these goals by working with other Federal agencies, participating in national and international standards setting activities, and building scientific expertise in nanotech within FDA.

Online Pharmacy Report to Congress (FDASIA § 1127)

FDASIA establishes that within one year the U.S. Comptroller General must submit to Congress a report

on the issues raised by internet pharmacy websites.²⁰⁰ In particular, the report must address websites violating Federal or State laws, patient harm associated with such websites, investigation efforts and successes, and whether there is enough authority available to address these issues.

Report on Small Businesses; Protections for the Commissioned Corps of the Public Health Service Act; Compliance Date for the Rule Relating to Sunscreen Drug Products; Strategic Integrated Management Plan (FDASIA §§ 1128-1131)

The Act requires that the FDA Commissioner report to Congress on the status of relationships and outreach efforts between FDA and small business within a year of FDASIA's enactment.²⁰¹ Section 1129 of FDASIA, amends the PHS such that the reference to Inspector General in Section 1034 specifies that it refers to the Inspector General of HHS. In addition, the Act requires that sunscreen drug products comply with the labeling and testing rule established in May 2012 by December 17, 2013 for all products with less than \$25,000 in sales and December 17, 2012 for all other products.²⁰² Within one year of enactment the Secretary must submit to Congress strategic integrated management plans for CDER, CDRH and CBER including institutional goals and the actions necessary to achieve such goals.²⁰³

Assessment and Modification of REMS (FDASIA § 1132)

FDASIA requires an assessment strategy to determine whether a risk evaluation and mitigation strategy (REMS) is effective or needs modifications made so that the benefits of the drug continue to outweigh the risks and the associated burden on the health care delivery system is minimized. Applicants may propose modifications at any time. Modification requests may address the "addition, modification, or removal" of any component of the REMS assessment. In addition, the Secretary may request that an applicant submit a modification to a REMS within 120 days of the request or other time as agreed to by the Secretary. The Secretary must review and act on a given strategy within 180 days of the request or within 60 days for minor modifications and modifications based on safety label changes. FDA must provide guidance governing these procedures.

Extension of Period for First Applicant to Obtain Tentative Approval without Forfeiting 180-day-exclusivity Period; Deadline for Determination on Certain Petitions; Final Agency Action Relating to Petitions and Civil Actions (FDASIA §§ 1133- 1135)

Under the Act the time period for an applicant to obtain tentative approval to prevent the loss of the 180-day exclusivity period under FFDCA § 505(j) is extended: (1) if a first applicant files an ANDA within 30 months

¹⁹⁸ *Id.* § 1123.

¹⁹⁹ *Id.* § 1125.

²⁰⁰ *Id.* § 1127.

²⁰¹ *Id.* § 1128.

²⁰² *Id.* § 1130.

²⁰³ *Id.* § 1127.

of FDASIA's enactment and the application includes a certification "that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted"; or (2) the ANDA is amended within 30 months of FDASIA's enactment to contain such certification.²⁰⁴ From the date of enactment until September 30, 2015, the new extension time will be 40 months. However, the Act reduces the extension to 36 months from October 1, 2015, through September 30, 2016. In addition, FDASIA requires that the Secretary issue a substantive final determination for petitions, requesting clarification whether a "listed drug has been voluntarily withdrawn for safety or effectiveness reasons," brought under 21 C.F.R. §§ 10.25(a) and 10.30.²⁰⁵ Section 1135 of FDASIA expands Section 505 of the FFDCA to include applications submitted under PHS among those prohibited from delay of approval. In addition, this section reduced the time FDA has for final agency action on a given petition from 180 days to 150 days from the date of submission. Furthermore, petitions addressing issues related to applications submitted under PHS are not subject to the timelines governing the exhaustion of administrative remedies under Section 505.

Electronic Submission of Applications (FDASIA § 1136)

FDASIA prohibits FDA from requiring only electronic drug and biologic submissions for at least 2 years after the issuance of a final guidance, except for expanded access drugs and biologics, under this section.²⁰⁶ FDA may issue guidance requiring the electronic submission of medical device submissions under this section.

Patient Participation in Medical Product Discussions; Ensuring Adequate Information Regarding Pharmaceuticals for All Populations (FDASIA §§ 1137, 1138)

Under section 1137, FDA must develop and implement strategies to involve patient perspectives, including participation in sponsor and FDA internal meetings regarding medical products. Participating individuals are subject to the Ethics in Government Act. Additionally, in light of the HHS Strategic Action Plan to Reduce Racial and Ethnic Health Disparities, the Commissioner must review and modify the FDA's plan to provide risk and benefit information on medical products to members of underrepresented subpopulations.²⁰⁷

Scheduling of Hydrocodone; Study on Drug Labeling by Electronic Means; Recommendations on Interoperability Standards (FDASIA §§ 1139-1141)

The FDA must hold a public meeting regarding medical and scientific evaluations that FDA must conduct to prepare a recommendation regarding the scheduling of hydrocodone for the Drug Enforcement Administration

(DEA).²⁰⁸ Any such meeting will have input from stakeholders and FDA must make the transcript of the meeting publicly available. FDASIA also requires that the Comptroller General conduct a study on the use of electronic prescription drug labeling for patients.²⁰⁹ The study will cover both implementation of such a system and associated costs. Within a year of the enactment, the Comptroller General must submit a report to Congress on the study results. Additionally, the Act will require the Secretary to work with the Attorney General to create recommendations regarding interoperability standards for exchanging prescription drug monitoring information across State lines.²¹⁰ The Secretary will submit a report on these recommendations to Congress within a year of FDASIA's enactment.

Conflicts of Interest (FDASIA § 1142)

Section 1142 alters the review of FDA advisory committee members by removing the requirement that committee members be subject to the Ethics in Government Act, and replacing the conflict waiver provisions with a process whereby FDA determines whether a potential member's interests are of the type, nature, and magnitude such that the public health interest in having the expertise on the panel does not outweigh the conflict. FDA is to issue a guidance document that details the specific information and methods for making conflict determinations. Reports to Congress must be public, and FDA is required to seek referrals for new committee members from a wide range of various stakeholders, including, professional societies, academia, and medical societies.

Notification of FDA Intent to Regulate Laboratory-Developed Tests (FDASIA § 1143)

The FDA may not issue any draft or final guidance on the regulation of laboratory-developed tests without providing 60 days notice to Congress. Such notice shall include the details of the guidance.

Synthetic Drug Abuse Prevention Act; Addition of Synthetic Drugs to Schedule I of the Controlled Substances Act; Temporary Scheduling to Avoid Imminent Hazards to Public Safety Expansion (FDASIA §§ 1151-1153)

FDASIA amends the Controlled Drug Substances Act to include synthetic drug products that may be subject to abuse, including Cannabimimetic agents.²¹¹ The Act also increases the time that a drug may be temporarily scheduled to avoid imminent hazards from one year to two years and provides the Attorney General to extend such scheduling by one year increments.²¹² Prior to the Act the Attorney General could only extend such scheduling in six month increments.

²⁰⁴ *Id.* § 1133, see also FFDCA Section 505(j).

²⁰⁵ 21 C.F.R. § 314.161.

²⁰⁶ *Id.* § 1136.

²⁰⁷ *Id.* § 1138.

²⁰⁸ *Id.* § 1139.

²⁰⁹ *Id.* § 1140.

²¹⁰ *Id.* § 1141.

²¹¹ *Id.* § 1152.

²¹² *Id.* § 1153.

* * *

Appendix A

Performance Goals for Original Applications and Supplements²¹³

Submission Cohort	Standard	Priority
NME NDAs and Original BLAs	90% in 10 months of the 60 day filing date	90% in 6 months of the 60 day filing date
Non NME NDAs	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Original Efficacy Supplements	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Manufacturing Supplements	90% in 4 months of the receipt date	90% in 6 months of the receipt date

Appendix B

Timelines for PDUFA Reauthorization Procedures and Performance Goals²¹⁴

REAUTHORIZATION PROCEDURES	PERFORMANCE GOALS
New Molecular Entity NDA and Original BLA Performance	<ul style="list-style-type: none"> ■ Less than 2 Months Prior to application submission - Pre-Submission Meeting ■ 10 month review goals for priority and standard applications for Refuse-to-File Applications submitted over protest ■ 74 Days from Original Application Submission- Review Timeline ■ 2 weeks after mid-cycle review of application- Status Update for Applicant ■ Before Late Cycle Review Meeting- Discipline Review Letters Issued Unless Substantive Issues Exist ■ 12 Calendar days before Advisory Committee meeting- Late Cycle Meeting for Applications ■ FDA will conduct Advisory Committee meetings 3 months before PDUFA goal for (standard review) and 2 months before PDUFA goal for (priority review) ■ 3 months before PDUFA goal date- Late Cycle Meetings for non-Advisory Committee Meeting Applications (standard review)

²¹³ See “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,” available at <http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf>.

²¹⁴ See “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,” available at <http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf>.

REAUTHORIZATION PROCEDURES	PERFORMANCE GOALS
	<ul style="list-style-type: none"> ■ 2 months before PDUFA goal date- Late Cycle Meetings for non-Advisory Committee Meeting Applications (priority review) ■ 10 months within submission of original application (standard review) and 6 months within submission of application for (priority review) inspection expected to be complete for GCP, GLP and GMP
Review of Proprietary Names to Reduce Medication Errors	<ul style="list-style-type: none"> ■ Review 90% of proprietary names filed with 180 days of receipt — IND Phase Submissions ■ Review 90% of proprietary names files in 90 days of receipt — NDA/BLA Submissions
Major Dispute Resolution	<ul style="list-style-type: none"> ■ 90% of responses to applicant within 30 calendar days of Center receiving sponsor's written appeal
Clinical Holds	<ul style="list-style-type: none"> ■ 90% of responses to applicant within 30 calendar days of FDA receiving sponsor's response
Special Protocol Question Assessment and Agreement	<ul style="list-style-type: none"> ■ 90% completion of special protocols and agreement requests returned to sponsors within identified timeframes
Meeting Management Goals	<ul style="list-style-type: none"> ■ 90% of Type A meeting requests receive notification within 14 days and meetings should occur within 30 calendar days of request ■ 90% of Type B requests receive notification within 21 days and meetings should occur within 60 calendar days of request ■ 90% of Type C requests receive notification within 21 days and meetings should occur within 75 calendar days of request ■ 90% of meetings held and written responses provided within specified timeframes

Appendix C

MDUFA III USER FEES 2013-2017²¹⁵

	FY2013	FY2014	FY2015	FY2016	FY2017
Fee Type					
Premarket Application	\$248,000	\$252,960	\$258,019	\$263,180	\$268,443
Establishment Registration	\$2,575	\$3,200	\$3,750	\$3,872	\$3,872

²¹⁵ FDASIA § 203.

Appendix D

Title IX

Comparison of Expedited Review Programs²¹⁶

	Fast Track Designation (existing FFDCA § 506)	Fast Track Designation (FDASIA § 901(b))	Accelerated Approval Process (FDASIA § 901(b))	Breakthrough Designation (FDASIA § 902(a))
Covered Conditions	Serious or life-threatening	Serious or life-threatening	Serious or life-threatening, including a fast track product	Serious or life-threatening
Other Pre-Requisites	None	None	Accelerated approval may be conditioned on one or both of the following requirements: 1) post-approval studies to verify and describe the predicted clinical benefit; or 2) submission of promotional materials	None
Scope of Drug Action/ Effectiveness Under Review	The effectiveness of only the product that is the subject of the application	The effectiveness of either the drug alone or in combination with one or more other drugs	The effectiveness of only the product that is the subject of the application, or, if a fast track product, the effectiveness of either the drug alone or in combination with one or more other drugs	The effectiveness of either the drug alone or in combination with one or more other drugs
Demonstration of Effectiveness	<i>Demonstrates the potential to address unmet medical needs</i>	<i>Demonstrates the potential to address unmet medical needs</i>	The product has an effect on a surrogate endpoint that is <i>reasonably likely to predict clinical benefit</i> , 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.	Preliminary clinical evidence indicates that the drug <i>may demonstrate</i> substantial improvement over existing therapies on one or more clinically significant endpoints
Data Required with Request for Designation	None	None	Evidence that the product has an effect on an endpoint that is reasonably likely to predict clinical benefit as described above	Preliminary clinical evidence as described above
Timeline for Agency Decision on Requests	60 Days	60 Days	None stated	60 Days
Required Agency Actions Once Designated	Such actions as are appropriate to expedite the development and review of the application	Such actions as are appropriate to expedite the development and review of the application	Accelerated approval of the application	Such actions as are appropriate to expedite the development and review of the application

²¹⁶ FDASIA §§ 901, 902.

Appendix E
Title XI
Timelines for Required Actions and Reports ²¹⁷
(excluding the User Fee provisions)

Within 6 months	■ Issue guidance regarding the development of abuse-deterrent drug products. (§ 1122)
Within 1 year	<ul style="list-style-type: none"> ■ Issue a public report reviewing current initiatives to combat prescription drug abuse and identify gaps and opportunities to ensuring the safe use of drugs that have a potential for abuse. The report must include findings and recommendations about using and building central data clearinghouses, how to achieve greater coordination among the States' drug monitoring programs, and how to best develop education tools and dissemination methods. (§ 1122) ■ Develop a strategy and implementation plan for advancing regulatory science that includes priorities, gaps that impede timely and efficient reviews, and measurable metrics. Annual reports to Congress must include information regarding FDA's progress with respect to such plans. (§ 1124) ■ Submit a report to Congress regarding its information technology plan, and inventory of FDA IT systems, and develop an enterprise program management plan and a skills inventory. (§ 1125) ■ Submit to Congress a strategic integrated management plan that identifies institutional goals, describes a workforce recruitment and maintenance plan, and identifies outcome-based measures of achieving such goals. (§ 1131) ■ The Comptroller General must submit to Congress a report regarding issues with pharmacy internet websites that violate the FFDCA, including whether FDA and States have sufficient authorities to deal with these issues, and, if not, what authorities are needed. (§ 1127) ■ Submit to Congress a report regarding FDA interactions with small businesses and the partnership between FDA and the Small Business Administration (SBA). (§ 1128) ■ Issue a communication plan focusing on underrepresented populations that informs healthcare providers and patients of risks and benefits for particular medical products. (§ 1138) ■ The Comptroller will submit a report to Congress summarizing results of study on benefits of electronic prescription drug labeling. (§ 1140) ■ Submit a report to Congress regarding recommendations to enhance the interoperability of State prescription drug monitoring programs. (§ 1141)
Within 18 months	■ Submit a report to the House and Senate regarding any necessary changes to regulations in order to implement the medical gas provisions in § 1111. (§ 1112)
Within 2 years	■ Issue a guidance document regarding internet and social media promotion of FDA-regulated products. (§ 1121)
By January 1, 2016	■ The GAO must issue a report regarding FDA's information technology strategic plan. (§ 1125)

²¹⁷ FDASIA §§ 1101-1142.