

## The Food and Drug Administration Safety and Innovation Act of 2012: Assessing the Impact on the Pharmaceutical and Biotechnology Industries



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**O**n July 9, 2012, President Obama signed into law the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA).<sup>1</sup> The legislation, which stemmed from separate bills that made their way through both houses of Congress over the past several months, amends the Federal Food, Drug, and Cosmetic Act (FDCA) to reauthorize the Food and Drug Administration (FDA) user fee programs for drugs and medical devices through September 30, 2017. The law also creates new user fee programs for generic drugs and biosimilars and permanently reauthorizes the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. In addition to its user fee provisions, FDASIA contains measures that enhance drug supply chain

safety requirements, expand antibiotic development incentives, augment expedited drug development programs, and strengthen FDA's authority to address drug shortages. The law also includes several "Miscellaneous Provisions" that will further affect FDA's regulation of pharmaceuticals.

FDASIA was developed through an extensive two-year collaboration between FDA, industry, and the public, and the legislation generally enjoyed widespread support throughout the process, including bipartisan congressional sponsorship and consistent backing from the White House. This article provides an overview of the statute's major drug provisions and their impact on the pharmaceutical and biotechnology industries.

### Prescription Drug User Fees

The Prescription Drug User Fee Act of 1992 (PDUFA)<sup>2</sup> was enacted to enable user fee payments by the drug and biologic industries to supplement congressional appropriations to FDA in return for Agency commitments to outlined performance goals. The PDUFA framework includes three types of fees—application fees, establishment fees, and product fees—each amounting to an equal third of the overall PDUFA fee revenue, which have resulted in reduced review times for new drug applications (NDAs) and biologics license applications (BLAs) over the past 20 years. PDUFA has

<sup>1</sup> Pub. L. No. 112-144, 126 Stat. 993. (10 PLIR 891, 7/13/12)

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<sup>2</sup> Pub. L. No. 102-571, 106 Stat. 4491.

also generated other regulatory improvements, including increased FDA communication with applicants and guidance to drug developers.

PDUFA legislation must be renewed every five years, and the fifth iteration of PDUFA enacted in FDASIA reauthorizes the program through fiscal year 2017. Under PDUFA V, which was negotiated between FDA and industry with input from a public meeting and docket, the drug industry will pay a base fee of \$693 million each year plus additional amounts after adjustments for inflation and workload. FDA must apply the statutory adjustment factors to calculate the user fee rates for promulgation in the Federal Register at least 60 days before the start of each fiscal year. FDA published its fiscal year 2013 rates on August 1.<sup>3</sup>

**Application Fees.** Under the PDUFA framework, different types of applications are associated with different fee amounts as calculated from a base amount—the full application fee. A full application fee is assessed for human drug applications in which FDA requires clinical data with respect to safety or effectiveness (excluding bioavailability and bioequivalence studies). Half of a full application fee is assessed for applications in which FDA does not require such data, as well as for supplements in which FDA requires such data. The new full application fee amount is \$1,958,800 for fiscal year 2013, up from \$1,841,500 for fiscal year 2012.

**Establishment Fees.** PDUFA requires applicants to pay annual establishment fees for each manufacturing establishment listed in their applications. Establishments are assessed only one fee per year, notwithstanding the number of prescription drugs manufactured at the facility, and if more than one applicant lists an establishment in its application, the annual fee is divided equally among them. The new establishment fee is \$526,500 for fiscal year 2013, up from \$520,100 for fiscal year 2012.

**Product Fees.** PDUFA requires applicants to pay annual product fees for each prescription drug product named in their applications. The new product fee for fiscal year 2013 is \$98,380, compared to \$98,970 for fiscal year 2012.

The PDUFA legislation permits waivers and reductions in certain circumstances, including for small businesses and orphan drugs, but overall, user fees fund over half of the total human drug application review cost, with the remainder funded through appropriations.<sup>4</sup> In return, FDA must issue annual performance reports to Congress detailing the Agency's performance

in meeting its PDUFA goals each year. Every five years upon reauthorization, FDA's PDUFA commitments contain review performance goals where FDA specifies the number of submissions on which it aims to take action within a certain specified timeframe. Under PDUFA V, FDA has committed to taking action on 90% of original NDAs and BLAs within 10 months for standard reviews, and within six months for priority reviews, among other performance goal commitments.<sup>5</sup>

FDA's PDUFA V commitment letter contains much more than performance goal timeframes. Some of the key FDA commitments include a new review model aimed at improving review transparency and communication; new staff dedicated to drug development communication; a new dedicated review team with meta-analysis expertise; new staff with capacity to review submissions containing biomarkers, pharmacogenomics, patient-reported outcomes, and other complex endpoint assessments; new staff in drug and biologic rare disease programs; and a structured benefit-risk assessment in the new drug approval process. In addition, under its commitments to modernize the drug safety system, FDA has agreed to evaluate standardize, and better integrate required risk evaluation and mitigation strategies (REMS); continue development of its Sentinel postmarket safety monitoring system; modernize the process of pharmacovigilance; improve its information systems and infrastructure; and issue draft guidance on required electronic applications by the end of 2012. Finally, FDA agreed to certain automated, standards-based information technology goals, and it agreed to participate in independent contractor assessments of various aspects of its drug and biologic review programs.

At bottom, the new fee amount represents a 6% increase from PDUFA IV in exchange for FDA's detailed performance commitments. FDA lobbied for the increase in order to better address the challenges posed by added drug safety regulatory requirements and the growth of overseas clinical trials and drug manufacturing.<sup>6</sup> With this in mind, industry remains optimistic that the Agency will follow through with its stated commitments to utilizing user fee revenue in furtherance of a more streamlined, predictable, and transparent drug and biologic development and approval process.

## Generic Drug User Fees

The number of abbreviated new drug applications (ANDAs) submitted to FDA has consistently increased since the enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Amendments),<sup>7</sup> which estab-

<sup>3</sup> See Prescription Drug User Fee Rates for FY 2013, 77 Fed. Reg. 45,639 (Aug. 1, 2012) (10 PLIR 1006, 8/3/12).

<sup>4</sup> PDUFA fees funded 62% of the human drug review cost in 2010. See *FDA User Fees 2012: How Innovation Helps Patients and Jobs: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 112th Cong. 3 (2012) (statement of Janet Woodcock, M.D. Director, FDA Center for Drug Evaluation and Research) [hereinafter *FDA User Fees*], available at <http://republicans.energycommerce.house.gov/Media/file/Hearings/Health/20120418/HHRG-112-IF14-WState-WoodcockJ-20120418.pdf>.

<sup>5</sup> FDA, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017*, <http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf>.

<sup>6</sup> *FDA User Fees*, *supra* note 4, at 10–11.

<sup>7</sup> Pub. Law. No. 98-417, 98 Stat. 1585.

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lished the generic drug approval pathway. FDA received almost 1,000 ANDAs in the past year alone, and drug master file (DMF) submissions—used to provide FDA with manufacturing information about active pharmaceutical ingredients (APIs) without disclosing the information to ANDA applicants—have grown comparably.<sup>8</sup> But generic sponsors and manufacturers have never paid the user fees that their brand-name counterparts do under PDUFA. As a result, FDA is currently experiencing an approximate 2,500 ANDA backlog, and the Agency is at pains to keep up with inspecting the growing overseas generic drug manufacturing industry.<sup>9</sup>

The Generic Drug User Fee Amendments of 2012 (GDUFA) enacted in FDASIA are intended to address these key issues. Similar to PDUFA V, GDUFA was negotiated between FDA, the generic drug industry, and other public stakeholders. Under the new user fee program, the generic drug industry will pay approximately \$1.5 billion over the next five years in return for faster and more predictable ANDA reviews, increased inspections of generic drug facilities, and other FDA efficiency commitments. The legislation includes two types of fees—application fees and facility fees—totaling \$299 million annually, to be adjusted for inflation and workload.

**Application Fees.** The GDUFA application fee structure, which accounts for 30% of overall GDUFA revenue, is divided into three parts: a one-time ANDA backlog fee, DMF fees, and ANDA and prior approval supplement filing fees:

- Under the ANDA backlog fee provisions, \$50 million of the fiscal year 2013 user fee revenue will be generated from applicants who have a pending ANDA as of October 1, 2012 without tentative approval from FDA. Each pending application will be associated with this one-time fee obligation.
- Under the DMF fee provisions, 6% of each fiscal year's fees will be generated from Type II API DMF holders, who will be responsible for a one-time fee the first time a DMF is referenced in a generic drug submission by an initial letter of authorization.
- Under the ANDA and prior approval supplement filing fee provisions (a prior approval supplement being a request for a substantial change in the drug substance, drug product, production process, quality controls, equipment, or facilities covered by an approved ANDA), 24% of each fiscal year's revenue will be generated from application and supplement filers, with the fee for a prior approval supplement amounting to half the ANDA fee. Applicants will be required to submit additional fees to be set by FDA if their submissions contain information regarding API manufacturing that does not reference a Type II API DMF and no DMF fee has previously been paid with respect to the information.

**Facility Fees.** The remaining 70 percent of each year's GDUFA revenue will be generated from facility fees. The GDUFA facility fee structure is divided into two parts: finished drug product manufacturing facility fees

and API manufacturing facility fees. Finished drug establishments will be responsible for 56% of all facility fees, and API establishments will be responsible for the remaining 14%. For both types of fees, the minimum fee for facilities located outside the United States is \$15,000, but the fee cannot be more than \$30,000 higher than the fee for U.S. facilities. Facilities producing both finished generic drug products and APIs will be required to pay both types of fees.

**Penalties.** Under GDUFA, generic drug sponsors and manufacturers will face significant penalties for failure to pay the new user fees.

- Failure to pay the one-time ANDA backlog fee will result in an applicant's placement on an arrears list, with the effect that no new ANDA or supplement filed by the applicant or any of its affiliates may be deemed "received" under Section 505(j)(5)(A) of the FDCA until the fee is paid. Section 505(j)(5)(A) starts FDA's statutory 180-day review clock upon FDA's "receipt" of the submission; thus, failing to pay the fee can prevent or significantly postpone later generic drug approvals.
- Failure to pay a DMF fee will render the DMF at issue not "available for reference" by any generic drug submission, and any generic drug submission that nonetheless references the DMF will likewise not be "received" for purposes of Section 505(j)(5)(A) of the FDCA until the fee is paid.
- Failure to pay an ANDA or prior approval supplement fee will again render the ANDA or supplement not "received" for purposes of Section 505(j)(5)(A). Failure to pay an ANDA fee will also render the ANDA not "substantially complete" for purposes of Section 505(j)(5)(B)(iv)(II)(cc) of the FDCA until the fee is paid. Section 505(j)(5)(B)(iv)(II)(cc) grants a 180-day exclusivity period to "first applicants" who file "substantially complete" ANDAs with Paragraph IV certifications of patent invalidity or non-infringement; thus, failing to pay an ANDA filing fee not only prevents the start of the review clock, but it also prohibits "first applicant" status until the fee is paid, which could be too late to secure the exclusivity period if another ANDA filer has submitted a substantially complete application for the same drug in the interim.
- Failure to pay a facility fee will result in several punishments until the fee is paid, including placement on an arrears list, rendering any generic drug submission referencing the facility not "received" for purposes of Section 505(j)(5)(A), and—most significantly—rendering all drugs or APIs manufactured in the facility misbranded under the FDCA.

As with PDUFA, FDA must report to Congress on its performance goals each year. FDA's GDUFA performance goals include a commitment to completing 60% of ANDA reviews in 15 months in 2013–2015, 75% in 15 months in 2016, and 90% in 10 months in 2017,<sup>10</sup> where the current median approval timeframe is around 31

<sup>8</sup> FDA User Fees, *supra* note 4, at 16.

<sup>9</sup> *Id.*

<sup>10</sup> FDA, *Generic Drug User Fee Act Program Performance Goals and Procedures*, <http://www.fda.gov/downloads/Food/Industry/UserFees/GenericDrugUserFees/UCM282505.pdf>.

months.<sup>11</sup> FDA has also agreed to expedite review of ANDAs containing Paragraph IV certifications that may be eligible for “first applicant” status, as such applicants’ failure to obtain tentative approval within a certain timeframe can result in forfeiture of the 180-day exclusivity period,<sup>12</sup> and FDA has set additional review timeline goals for ANDA amendments, prior approval supplements, and controlled correspondence. The GDUFA goals letter also commits FDA to conducting risk-adjusted biennial current good manufacturing practice (cGMP) surveillance inspections of generic manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms by fiscal year 2017, and to addressing the ANDA backlog by reviewing 90% of ANDAs, ANDA amendments, and ANDA prior approval supplements pending on October 1, 2012 by the end of fiscal year 2017.

Again, similar to PDUFA, the GDUFA goals letter contains a number of regulatory initiatives in addition to its review performance goals, which mainly focus on efficiency and regulatory science enhancements. On the efficiency side, FDA’s commitments include issuing complete response letters rather than discipline-specific letters in both ANDA and DMF reviews; telephone conferences upon request following first-cycle complete response letters; enhanced refusal to receive standards; development of a program to utilize foreign inspection classifications where appropriate; development of facility and chemistry, manufacturing, and controls databases; and issuance of electronic data submission standards. On the regulatory science side, FDA has committed to convening a working group to develop an annual list of regulatory science initiatives each year; the fiscal year 2013 plan focuses on development and improvement of FDA and industry understandings of complex drug development issues and endpoint assessments for specific classes of drugs.

FDA has stated that its overall goal under GDUFA is to increase consumer access to low-cost, high-quality generic drugs, and the user fees will provide FDA with the ability to achieve this by performing critical program functions that could not otherwise occur.<sup>13</sup> FDA and the generic drug industry anticipate a beneficial return from the program, and many hope that costs in the country’s healthcare market benefit as well.

### **Biosimilar User Fees**

The Biologics Price Competition and Innovation Act of 2009, enacted as part of the Patient Protection and Affordable Care Act of 2010, established a new abbreviated approval pathway for biologics shown to be “biosimilar to” or “interchangeable with” an FDA-licensed

biological product.<sup>14</sup> Although biosimilars are intended to be for biologics what generic drugs are for brand-name drugs, the molecular complexity of biologics poses many new challenges for both FDA and the burgeoning biosimilars industry.<sup>15</sup>

The new Biosimilars User Fee Act of 2012 (BSUFA) enacted in FDASIA was developed by FDA with required consultation from patient and consumer advocates, healthcare professionals, and scientific and academic experts, and is intended to address the top priorities and challenges identified by FDA and public stakeholders.<sup>16</sup> Under BSUFA, the biosimilars industry will pay four types of fees—product development fees, application fees, establishment fees, and product fees—based on the PDUFA fees to be set annually by FDA. FDA published its biosimilar user fee rates for fiscal year 2013 on August 1 in conjunction with its PDUFA fee rate notice.<sup>17</sup>

**Product Development Fees.** Because there are currently no marketed biosimilar products, BSUFA’s product development fee provisions are intended to generate revenue in the short-term to enable sponsors to have meetings with FDA early in development, and facilitate the process of bringing the first biosimilars to market.<sup>18</sup> Unlike other user fees, they cannot be waived, reduced, or refunded. The product development fee provisions contemplate three different sub-types of fees: initial product development fees, annual product development fees, and reactivation fees:

- An initial product development fee of 10% of the PDUFA application fee rate is required upon a developer’s first meeting request or biosimilar investigational new drug application (IND) submitted to FDA.
- An annual product development fee of 10% of the PDUFA application fee rate is required for each subsequent fiscal year in which the product is being developed. A biosimilar sponsor may discontinue its fee obligation by submitting a declaration that it no longer intends to develop the product or by withdrawing its IND.

<sup>14</sup> Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804. See generally Carolyne R. Hathaway, John R. Manthei & Elizabeth D. Meltzer, *A Brave New World: The U.S. Food and Drug Administration’s Newfound Authority for Regulation of Follow-on Biologics*, 3 BLOOMBERG L. REP. – HEALTH L. (2010). The Patient Protection and Affordable Care Act was recently upheld by the U.S. Supreme Court in *National Federation of Independent Business v. Sebelius*, slip op. (June 28, 2012). The Court’s decision makes no particular mention of the biosimilar provisions of the law, but the overall upholding of the legislation leaves intact FDA’s developing framework for the abbreviated pathway, and thereby clears the way for the new user fee program.

<sup>15</sup> FDA recently released three draft guidance documents intended to implement the abbreviated biosimilars pathway, but many questions remain as to how biosimilars will be developed and approved. See generally John Manthei & Carolyne Hathaway, *Opening the Door for Generic Biologics: FDA Releases the First Guidance Documents Implementing the Biosimilar Approval Pathway*, 10 BLOOMBERG BNA PHARMACEUTICAL L. & INDUSTRY REP. 300 (Mar. 3, 2012) (10 PLIR 300, 3/2/12).

<sup>16</sup> FDA User Fees, *supra* note 4, at 19.

<sup>17</sup> See Biosimilar User Fee Rates for Fiscal year 2013, 77 Fed. Reg. 45,634 (Aug. 1, 2012).

<sup>18</sup> See FDA User Fees, *supra* note 4, at 20.

<sup>11</sup> FDA User Fees, *supra* note 4, at 16.

<sup>12</sup> Pre-FDASIA, applicants holding ANDAs with first-applicant status forfeited their generic exclusivity period if they failed to obtain tentative ANDA approval within 30 months of submission. This provision of the FDCA was amended by FDASIA to extend the 30-month timeframe to 40 months initially, and 36 months starting in 2015. The extension, combined with FDA’s commitment to expedited reviews of first-applicant ANDAs, is likely to result in fewer exclusivity period forfeitures and greater incentives for generic drug development.

<sup>13</sup> FDA, *supra* note 10.

- A reactivation fee of 20% of the PDUFA application fee rate is required if an applicant subsequently requests a new meeting or submits and IND for a product for which it previously discontinued its annual product development fee obligations.

**Application Fees.** BSUFA application fees are equal to the PDUFA application fee rates, but are reduced by the cumulative amount paid by the sponsor in product development fees for the particular product. Half of the PDUFA application fee rate will be assessed for applications for which clinical safety or effectiveness data are not required, in addition to the cumulative development fee reduction. Half of the PDUFA application fee rate will also be assessed for supplements for which such clinical data are required (other than comparative bioavailability studies).

**Establishment Fees.** Establishment fees under BSUFA are equal to PDUFA establishment fees, and similar rules apply, such as the assessment of a single fee per establishment regardless of the number of biosimilar products manufactured at the facility.

**Product Fees.** Product fees under BSUFA are equal to PDUFA product fees, and again, similar rules apply.

**Penalties.** BSUFA imposes several penalties for failure to pay user fees. Failure to pay any of the product development fees may result in FDA refusal to grant any product development meetings relating to the product for which fees are owed; FDA deeming a biosimilar IND for the product not “received” under Section 505(i)(2), which results in a halt or delay of the review clock start; FDA institution of a financial hold, prohibiting the sponsor of a biosimilar clinical investigation from continuing the investigation; and FDA refusal to accept any biosimilar application or supplement for filing until the fees are paid. Failure to pay any other fees—application fees, establishment fees, or product fees—will result in an application or supplement being treated as incomplete and refused for filing until all fees owed by the applicant have been paid.

As with other user fee programs, FDA must report to Congress on its BSUFA performance goals, and FDA’s goals for biosimilars likewise include review timeline goals. Specifically, in fiscal years 2013 and 2014, FDA has agreed to review and act on 70% of original biosimilar applications within 10 months, and resubmitted applications within six months; this percentage increases each subsequent year to reach 90% in fiscal year 2017.<sup>19</sup> Again in congruence with the standard PDUFA goals in each reauthorization, the BSUFA goals also include review and response performance goals for first-cycle reviews, proprietary names, major dispute resolutions, clinical holds, special protocol assessments, and meeting management. The BSUFA goals do not contain detailed provisions on program enhancements and regulatory science initiatives, likely due to the novelty associated with biosimilars themselves, let alone biosimilar reviews and approvals at FDA. Regardless, the fast-growing biosimilars industry will benefit from the

<sup>19</sup> FDA, *Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2013 Through 2017*, <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicalApplications/Biosimilars/UCM281991.pdf>.

new user fee program that will enable these novel products to reach the market.

## Pediatric Drugs

The Best Pharmaceuticals for Children Act (BPCA) was enacted as part of the Food and Drug Administration Modernization Act of 1997 to provide FDA with authority to grant a six-month period of marketing exclusivity for a drug (active moiety) in return for the sponsor conducting FDA-requested studies in pediatric populations.<sup>20</sup> The Pediatric Research Equity Act of 2003 (PREA) was enacted in 2003 to provide FDA with authority to require pediatric assessments in approved drugs (subject to waiver or deferral) when a sponsor submits an application seeking a new indication, active ingredient, dosage form, dosing regimen, or route of administration.<sup>21</sup> Both BPCA and PREA work together to spur more pediatric drug studies to provide accurate safety, effectiveness, and dosing information for pediatric treatments where little was known before. However, FDA has stated that more long-term pediatric studies on the effects of drugs on growth, learning, and behavior are badly needed, along with more studies in neonates (age birth to one month).<sup>22</sup>

Until now, both laws had to be reauthorized every five years to avoid their sunset provisions, akin to the user fee programs. FDASIA permanently reauthorizes both BPCA and PREA and enacts several provisions intended to enhance the development of pediatric data. Specifically, among other reforms, the legislation encourages more studies in neonates by requiring FDA to explain its reasoning when it does not include neonatal studies in BPCA written requests, and it fosters more study completions by permitting FDA to extend PREA assessment deferrals to allow for later deadlines for completion under certain circumstances. As a change to existing procedure in an effort to obtain better pediatric data, FDASIA also requires applicants to submit an initial pediatric plan to FDA no later than 60 days after an End-of-Phase 2 Meeting, after which FDA and applicants must follow specified processes to reach an agreement on the plan. FDA is also required to consult with the Pediatric Review Committee on initial pediatric plans and amendments, and it must issue internal standard operating procedures for Pediatric Review Committee review of significant modifications to initial study plans.

Despite some increased burdens on industry, one provision is highly industry-friendly: FDA is now required to issue a noncompliance letter and follow a process for resolving a sponsor’s failure to submit a PREA assessment before it considers a product misbranded for this reason.

## Drug Supply Chain Safety

FDASIA includes several changes to Agency authorities, policies, and procedures in order to enhance the

<sup>20</sup> Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305. The law received its current name when it was reauthorized in its own title legislation in 2002. See Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002). The Patient Protection and Affordable Care Act of 2010 extended BPCA exclusivity to biologics.

<sup>21</sup> Pub. L. No. 108-155, 117 Stat. 1935.

<sup>22</sup> *FDA User Fees*, supra note 4, at 24.

FDA safety network for an ever-growing and increasingly globalized drug supply chain. One major reform is the legislation's requirement for FDA to implement a new risk-based schedule for drug facility inspections. To do so, FDA must implement a new facility identifier system into its establishment registration structure for both domestic and foreign establishments engaged in the manufacture, preparation, proposition, compounding, or processing of drugs, and require more detailed information in establishment registrations. FDA must then link the unique facility identifier system with other relevant databases and use the information to identify and inform its risk-based inspections. FDASIA also enhances FDA's authorities with regard to inspections generally: a drug is now deemed adulterated if it was manufactured, processed, packed, or held in any facility where an inspection was delayed, denied, limited, or refused; FDA may detain drugs during an inspection that it believes may be adulterated or misbranded; and FDA may require drug manufacturers to provide records for inspection in advance of physical facility inspections. FDA also has authority to enter into agreements with foreign governments to recognize inspections of FDA-registered foreign establishments.

Other major supply chain regulation changes focus on import safety and illegal drug products. Congruent with the new facility identifier system, commercial drug importers must now register with FDA and obtain a unique identifier, permitting FDA to deem noncompliant importers' products misbranded and implement a new system for screening imported drugs through a risk-based approach. FDASIA also grants FDA explicit extraterritorial jurisdiction over any violation of the FDCA with regard to any article intended for import into the United States. With regard to illegal drug products, FDA is now permitted to destroy up to a specified amount of counterfeit or adulterated drugs that are refused for import, and FDASIA increases the penalties for intentional adulteration and selling or dispensing counterfeit drugs, including criminal penalties for counterfeit drug trafficking.

### **Generating Antibiotic Incentives**

The medical community has strongly expressed the need for new strategies to combat the rise of antibiotic resistance, and legislators have been listening. The Generating Antibiotic Incentives Now (GAIN) Act enacted in FDASIA takes aim at the problem by incentivizing the development of antibacterial or antifungal drugs intended to treat serious or life-threatening infections, including those caused by antibacterial or antifungal resistant pathogens, such as the deadly methicillin-resistant *Staphylococcus aureus* (MRSA) pathogen. Applications for such "qualified infectious disease products" that are able to treat "qualifying pathogens" are eligible to receive priority review and fast-track status, in addition to five years of marketing exclusivity on top of other exclusivity periods. The legislation also requires FDA to provide additional guidance on antibacterial and antifungal drug development and the conduct of clinical trials for such drugs. FDA has expressed that although the development of new antibiotic drugs is not the entire solution to the problem of drug resistance, it is an important part, and the new legislation is aimed at helping developers overcome the

growing challenges of new antibiotic drug development.<sup>23</sup>

### **Drug Approval and Patient Access**

One of the popular initiatives of Congress's user fee reauthorization effort was to encourage expedited development of innovative new medicines intended to treat serious, life-threatening, or rare diseases and conditions, including those associated with unmet medical needs. To that end, FDASIA contains several provisions that expand the scope of FDA's current fast-track and accelerated approval programs, permitting more surrogate and clinical endpoints to be used in clinical trials to obtain faster drug approvals. In return, these provisions require enhanced postapproval studies. FDASIA also contains a section that establishes a new "breakthrough therapy" expedited development and review program for drugs that show potential as a substantial improvement over existing therapies for serious or life-threatening diseases, and the law creates a new demonstration project that provides transferable priority review vouchers to companies that develop drugs for pediatric rare diseases. In an effort to streamline drug approvals, FDASIA also requires FDA to implement a structured risk-benefit assessment framework in the new drug approval process.

In addition to the accelerated approval provisions, FDASIA establishes regulatory reforms for new rare-disease drugs and genetically targeted therapies, under which FDA must consult with external experts on specified topics when the Agency lacks the requisite expertise to review and approve such products. FDASIA also reauthorizes the grant and contract program for orphan drugs intended to treat rare diseases and conditions. Finally, in an effort to improve prescribing information for demographic subgroups, FDA is required publish a report and action plan regarding the extent to which clinical trials and drug applications address demographic subgroups, including sex, age, race, and ethnicity.

### **Drug Shortages**

Last fall, President Obama issued an executive order requiring FDA to utilize its administrative resources to seek broader reporting for drug shortages and implement expedited regulatory review processes for products that could alleviate shortages.<sup>24</sup> FDA in turn promulgated an interim final rule regarding advanced anticipated drug shortage reporting,<sup>25</sup> stating that while many of the root causes of drug shortages are beyond the Agency's control, notification procedures can help alleviate the impact of shortages when they occur.<sup>26</sup>

FDASIA goes one step further, echoing these recent policy initiatives to statutorily address drug shortages in the United States. The legislation modifies existing reporting requirements for manufacturers of certain

<sup>23</sup> *FDA User Fees*, *supra* note 4, at 27–8.

<sup>24</sup> Exec. Order No. 13588, 76 Fed. Reg. 68, 295 (Nov. 3, 2011) (9 PLIR 1386, 11/4/11).

<sup>25</sup> Applications for Food and Drug Administration Approval to Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance, 76 Fed. Reg. 78,530 (Dec. 19, 2011).

<sup>26</sup> *FDA User Fees*, *supra* note 4, at 28–29.

drugs to require notification to FDA of any permanent drug discontinuance or drug manufacturing interruption that is likely to lead to a meaningful disruption in the drug supply. Under the new law, manufacturers of drugs that are life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including drugs used in emergency medical care or during surgery, must report to FDA no later than six months prior to the discontinuance or interruption (or as soon as practicable thereafter if six-month compliance is not possible) and provide the reasons for such discontinuation or interruption. FDA must widely notify healthcare providers and patient organizations, as well as maintain an up-to-date list of drug shortages.

In addition to the reporting provisions, FDASIA aims to establish a better framework for addressing current drug shortages and obtain information to better prevent them in the future. To alleviate current drug shortages, FDA is required to coordinate with the Attorney General on shortages of controlled substances, and the Agency must provide expedited inspections and reviews of facilities and drug applications that could mitigate a current or impending shortage. Hospitals within the same health system will also now be permitted to repackage drugs into smaller units to alleviate shortages within the system. To inform the process of developing better prevention methods going forward, FDA must create a drug shortage task force to develop a strategic plan for preventing shortages through manufacturing partnerships and other means.

### **Additional Amendments and Provisions Applicable to Drugs**

The final title of FDASIA contains several provisions aimed at miscellaneous Agency reforms. Some of the more significant provisions impacting the pharmaceutical and biotechnology industries include the following:

- Section 1101 reauthorizes provisions granting exclusivity to certain drugs containing single enantiomers.
- Section 1102 reauthorizes \$6 million each year for fiscal years 2013 through 2017 for Critical Path Initiative public-private partnerships, which are aimed at obtaining greater scientific knowledge on the complexities of new product development in order to facilitate more innovative medical products.
- Section 1121 requires FDA to issue a guidance document describing its policy on Internet and social media promotion of regulated medical products by July 2014.
- Section 1122 requires FDA to review and report on current federal initiatives and identify gaps and opportunities with respect to combating prescription drug abuse, and develop guidance on development of abuse-deterrent drugs by January 2013.
- Section 1123 explicitly authorizes FDA to work with foreign regulatory authorities, medical research companies, and international organizations to foster uniform, scientifically driven global clinical trial standards. Under the provision, FDA must

enhance its commitment to providing parallel scientific advice for manufacturers seeking simultaneous global development of medical products by facilitating the use of foreign data in FDA regulatory submissions and minimizing the need for sponsors to conduct duplicative studies. FDA is also now required to accept data from international clinical investigations during its review of medical product applications if the data are adequate to support product approval.<sup>27</sup>

- Section 1124 requires FDA to develop a strategy and implementation plan for advancing regulatory science for medical products by July 2013 and submit annual performance reports on its progress.
- Section 1126 instructs FDA to enhance scientific knowledge regarding nanomaterials in regulated medical products.
- Section 1132 amends the REMS provisions of the FDCA to establish a more streamlined process for FDA review of modifications to approved REMS programs. Under the law, modifications to a REMS need not occur in the context of mandated periodic assessments; rather, sponsors may propose modifications at any time, and FDA has 180 days to respond (60 days for minor modifications). FDA is also required to issue guidance describing minor modifications by July 2013 and must establish a simple notification procedure for certain types of modifications.
- Section 1136 requires electronic submission of drug and biologic applications beginning no earlier than 24 months after issuance of a final guidance, with waivers and exemptions defined in the guidance.
- Section 1137 instructs FDA to solicit the views of patients during the medical product development and review process and consider the perspectives of patients during regulatory decision-making. FDA must utilize a patient representative to serve as a special government employee in appropriate agency meetings and explore ways to identify patient representatives who have little or no financial interests in the medical products industry.
- Section 1138 requires FDA to develop a communication plan to inform and educate healthcare providers and patients on the benefits and risks of medical products, with a particular focus on underrepresented subpopulations, including racial subgroups, by July 2013.
- Section 1139 requires FDA to hold a public meeting to solicit advice and recommendations in connection with a scheduling recommendation to the Drug Enforcement Administration regarding certain hydrocodone products. A public meeting of

<sup>27</sup> FDA has implemented policies accepting foreign clinical trial data under certain circumstances, but the new legislative mandate requiring it to do so is likely to increase instances where FDA will accept such data, and may also increase the requirements foreign clinical trials must meet. See generally Carolyne Hathaway & Anne Hanson, *Client Alert: FDA Offers New Guidance on Acceptance of Foreign Clinical Trials* (Apr. 23, 2012).

the Drug Safety and Risk Management Advisory Committee is scheduled to be held on October 29–30, 2012 to discuss the benefits and risks of these hydrocodone products.

- Section 1140 requires the Comptroller General to conduct a study on the benefits and efficiencies of electronic patient labeling of prescription drugs as a complete or partial substitute for patient labeling in paper form and submit a report to Congress by July 2013.
- Section 1142 provides FDA with greater flexibility under its conflict of interest rules to fill advisory committee vacancies with experts who have a financial interest that could be affected by the advice given to FDA, provided that FDA adequately discloses the nature of the interest and reports annually to Congress regarding advisory committee membership. The provision calls for FDA to develop and implement strategies for effective outreach, advertising, and recruitment efforts, as well as disclose the type, nature, and magnitude of advisory committee members' financial interests at least 15 days before a committee meeting. FDA must also issue a guidance document on FDA's review of financial interests.
- Sections 1151–1153 amend the Controlled Substances Act to schedule 26 synthetic substances as Schedule 1 drugs and increase the timeframe during which a drug may be temporarily scheduled to avoid imminent hazards from one to two years, with authority granted to the Attorney General to extend such scheduling by one-year increments.

Three sequential miscellaneous provisions are specifically aimed at moving generic drugs to market more quickly, and they will result in significant new considerations and consequences for generics and innovators alike. These provisions include the following:

- Section 1133 extends the period of time for an ANDA “first applicant” to obtain tentative approval without forfeiting its 180-day marketing exclusivity from 30 months to 40 months initially, then 36 months starting October 1, 2015. The provision recognizes that FDA's review times should decrease over the next five years with the enactment of GDUFA. This provision, combined with FDA's GDUFA performance goal commitment to review first-applicant ANDAs expeditiously, is aimed at renewing incentives for generic drug sponsors to obtain first-applicant status by developing their generic products early and filing Paragraph IV certifications to challenge existing patents.
- Section 1134 establishes a 270-day timeframe within which FDA must respond to petitions requesting a determination on whether a reference listed drug (RLD) was withdrawn from the market

for reasons of safety or effectiveness. Before FDASIA, no such deadline existed for FDA to respond to these petitions, and FDA's responses govern the all-important determination of whether a sponsor can reference an RLD in its ANDA. This provision is likewise aimed at reducing impediments to generic drug development by encouraging more ANDA applicants to file such petitions to develop new generics based on brand-name drugs that are no longer marketed.

- Section 1135 shortens the timeframe for FDA to respond to Section 505(q) citizen petitions requesting a stay of action on a pending ANDA due to scientific or medical questions with the application. FDA must now respond in 150 days (previously 180 days), a legislative move expected to generate significant savings to the healthcare system (and pay for other costly provisions of the FDASIA legislation) by speeding lower-cost generics to the market.

## **Conclusion**

Several major provisions were excised from the legislation as the House and Senate bills were reconciled and negotiated for final congressional passage. In particular, a national “track-and-trace” system intended to streamline and improve prescription drug safety efforts throughout the supply chain was one of the major items left out of the Act. The track-and-trace language was supported by major pharmaceutical industry groups for its ability to preempt state laws and provide nationwide regulatory consistency, but the language was reportedly dropped for a lack of consensus during final deliberations. In addition, legislators also rejected a provision that would have penalized generics for entering into “pay-for-delay” patent litigation settlements with innovators. Legislators also eliminated language that would have prohibited brand-name drug makers with approved REMS from citing to REMS elements to assure safe use in order to refuse samples of their drugs to generic developers, a provision that was strongly backed by the generic drug industry.

Although there were many controversial proposals associated with the legislation, most of which did not make it into the final statute, the user fee bills nonetheless enjoyed consistent support from the majority of public stakeholders through the development process, as well as backing from the White House, which lauded the bipartisan effort. The bill was considered “must pass” legislation, which likely contributed to the general ease with which the legislation moved through Congress. Many of the legislative reforms and provisions will have wide-ranging impacts on FDA's authority and regulation over pharmaceutical and biologic products. As a result, FDA and industry must now begin the onerous task of understanding, and implementing, those provisions.