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Client Alert

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

On July 9, 2012, President Obama signed the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) into law.[1] 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 enacts several Agency reforms, including provisions aimed at improving various FDA regulatory processes and priorities, ensuring drug supply chain safety, and preventing drug shortages. The Act 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 *Alert* provides an overview of the statute's drug and biologic provisions and their impact on the pharmaceutical and biotechnology industries.

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Prescription Drug User Fees

The Prescription Drug User Fee Act (PDUFA) was enacted by Congress in 1992 to enable user fee payments by the drug industry to supplement congressional appropriations to FDA in return for Agency commitments to outlined performance goals. PDUFA includes three types of fees — **application fees**, **establishment fees**, and **product fees** — which have resulted in reduced review times for new drug applications (NDAs) and biologics license application (BLAs) over the past 20 years. PDUFA has also generated other regulatory improvements, including increased FDA communication 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 over $700 million in fiscal year 2013 and higher amounts in the remaining four years as adjusted for inflation and workload. The fees continue to be divided equally into thirds to account for the three types of fees.

The new fee amount represents an increase from PDUFA IV in exchange for FDA's commitment to attaining newly outlined performance goals. FDA lobbied for the fee increase in order to better address the challenges posed by added drug safety regulatory commitments and the growth of overseas drug manufacturing.[2] In particular, FDA has agreed to work toward ensuring the timely review of NDAs and BLAs, enhancing regulatory science to expedite drug development, modernizing the drug safety system and the process of pharmacovigilance, and improving the efficiency of NDA and BLA reviews through electronic submissions and standardized electronic application data. The Agency has also agreed to an independent third-party assessment of FDA's performance in its NDA and BLA reviews, among other reporting and assessment commitments.[3]

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), which established the generic drug approval pathway. FDA received almost 1,000 ANDAs in the past year alone, but generic drug sponsors never paid the user fees that their brand-name drug counterparts have 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.[4]

The Generic Drug User Fee Act (GDUFA) enacted in FDASIA is intended to address these key issues. Like PDUFA, GDUFA was negotiated between FDA, the generic drug industry and other public stakeholders. Under this 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 drug facilities, and other FDA efficiency commitments. The legislation includes two types of fees — **application fees** and **facility fees** — set out in the following fee provisions totaling $299 million annually, to be adjusted for inflation and workload in fiscal years 2014–2017:

- $50 million of the 2013 fees will be generated from a **one-time ANDA backlog fee**, under which anyone with an ANDA pending as of October 1, 2012 without tentative approval from FDA will be subject to a fee for each application.
- 6 percent of each year's fees will be generated from **drug master file (DMF) fees**, under which anyone with a Type II active pharmaceutical ingredient (API) DMF will be subject to a one-time fee the first time the DMF is referenced in a generic drug submission by an initial letter of authorization.[5]
- 24 percent of each year's fees will be generated from **ANDA and prior approval supplement filing fees**, with the fee for a prior approval supplement amounting to half of the ANDA fee.[6] Applicants will be required to submit additional fees if their submissions contain information regarding API manufacturing that does not reference a Type II API DMF and a DMF fee has not previously been paid with respect to the information.
- The remaining 70 percent of each year's fees will be generated from **facility fees**, with 56 percent coming from **finished generic drug product manufacturing facilities** and 14 percent coming from **API manufacturing facilities**. 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 US facilities. Facilities producing both finished generic drugs and APIs will be required to pay both types of fees.

Under GDUFA, generic companies will face significant penalties for failure to pay the new user fees. For example, failure to pay the one-time ANDA backlog fee will result in an applicant's placement on an arrears list, such that no new ANDA or supplement submitted by the applicant or any of its affiliates will be "received" for purposes of section 505(j)(5)(A) of the FDCA until the fee is paid. Section 505(j)(5)(A) states that FDA must approve (or decline to approve) an ANDA within 180 days *of its receipt*; thus, failing to pay the fee can prevent or significantly postpone later generic approvals. In addition, failure to pay an ANDA filing fee will render the application 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 marketing exclusivity period to "first applicants" who file s*ubstantially complete* ANDAs with paragraph IV patent certifications; thus, failing to pay this fee could result in loss of the exclusivity period if another ANDA filer attains "first applicant" status in the interim. As the most severe punishment, failure to pay a facility fee can result in all drugs or APIs manufactured in the facility misbranded under the FDCA.

As with PDUFA, GDUFA requires FDA to report to Congress on its performance goals. FDA's outlined GDUFA performance goals include a commitment to completing most ANDA reviews in 10 months, where the current time for approval is around 31 months (including FDA question and applicant response times), and conducting risk-based biennial facility inspections with the goal of achieving parity of inspection frequency between foreign and domestic firms by 2017.[7] FDA has also committed to implementing many efficiency enhancements and regulatory science initiatives, including a stated plan to strive to review all "first applicant" ANDAs within 30 months of submission to avoid 180-day exclusivity forfeiture under the FDCA.[8]

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.[9] Although biosimilars are intended to be for biologics what generics drugs are for brand-name drugs, the molecular complexity of biologics poses many new challenges for both FDA and the burgeoning biosimilars industry.[10]

The new Biosimilars User Fee Act (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. Under BSUFA, the biosimilars industry will pay four types of fees — **product development fees**, **application fees**, **establishment fees**, and **product fees** — set out in the following fee provisions:

- An **initial product development fee** of 10 percent of the PDUFA application fee rate will be 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 percent of the PDUFA application fee rate will be 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, but the sponsor will be required to pay a **reactivation fee** of 20 percent of the PDUFA application fee rate if it subsequently requests a new meeting or submits an IND for the product.

- **Application fees** will be equal to the PDUFA application fee rate reduced by the cumulative amount paid by the sponsor in product development fees for the product. The fees for applications and supplements for which clinical safety or effectiveness data are not required will be half the amount of the PDUFA application fee rate with the same cumulative development fee reduction.
- **Establishment fees** and **product fees** will be equal to the PDUFA rate for each type of fee.

FDA has stated that the novel product development fees are intended to enable FDA to meet with biosimilar sponsors and facilitate development of this new type of product in order to bring the first biosimilars to market.[11] Unlike other user fees, biosimilar product development fees cannot be waived, reduced or refunded. BSUFA imposes several penalties for failure to pay the user fees, including refusal of biosimilar product development meetings, refusal of receipt of INDs, financial holds prohibiting continuation of biosimilar clinical investigations, and refusal to accept biosimilar product applications or supplements.

As with other user fee programs, FDA must report to Congress on its BSUFA performance goals. Similar to the PDUFA performance goals, FDA's goals for biosimilars include review timeline goals for biosimilar product application submissions and other efficiency and consistency goals.[12] FDA has stated that it will use the fees to develop the scientific, regulatory, and policy infrastructure necessary for FDA to review biosimilar submissions going forward.[13]

Pediatric Drugs

The Best Pharmaceuticals for Children Act (BPCA) was enacted in 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. The Pediatric Research Equity Act (PREA) was enacted in 2003 to provide FDA with authority to require pediatric studies when a sponsor submits an application for an approved drug seeking a new indication, active ingredient, dosage form, dosing regimen or route of administration. The BCPA and PREA work together to spur more pediatric drug studies to provide accurate labeling for pediatric treatments where little information existed before. Until now, both laws had to be reauthorized every five years, akin to the user fee programs.

FDASIA permanently reauthorizes the BPCA and the PREA and enacts several provisions intended to enhance the development of pediatric data. For example, the legislation includes new provisions on pediatric study plans, including requirements for sponsors to submit their study plans to FDA and meet with FDA before submitting pediatric assessments. The Act also encourages more studies in neonates and rare pediatric diseases, and imposes new FDA reporting requirements every five years to evaluate the effectiveness of the pediatric research programs. However, FDASIA also includes provisions that ease the BCPA and PREA requirements for sponsors, including new FDA authority to extend pediatric study deferrals, and a new requirement that FDA must issue a noncompliance letter to a sponsor before it considers a product misbranded for the sponsor's failure to submit required pediatric assessments.

Drug Supply Chain

FDASIA includes several changes to Agency authorities, policies, and procedures in order to enhance the FDA safety network for an ever-growing and increasingly globalized drug supply chain. One major reform is the Act's requirement for FDA

to implement a new risk-based schedule for drug facility inspections. To do so, FDA is required to implement a new facility identifier system into its establishment registration structure for both domestic and foreign establishments engaged in the manufacture, preparation, propagation, compounding or processing of drugs. The Agency must then link the unique facility identifier system with other relevant databases and use the information to identify and inform its risk-based inspections.

Other major changes are focused on import safety and counterfeit drugs. The legislation gives FDA explicit extraterritorial jurisdiction over any violation of the FDCA relating to any article intended for import into the United States. It also increases the penalties for intentionally adulterating a drug and intentionally selling or dispensing counterfeit drugs, and establishes criminal penalties for counterfeit drug trafficking.

Generating Antibiotic Incentives

Legislators have, as of late, strongly expressed the need for new strategies to combat the rise of antibiotic resistance. FDASIA takes aim at this 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 aureaus (MRSA) pathogen. Applications for such "qualified infectious disease products" are eligible to receive priority review and fast-track status, in addition to five extra 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.

Drug Approval and Patient Access

One of the major 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 enhance and clarify FDA's current fast-track and accelerated approval programs, and 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. The legislation states that these provisions may result in fewer, smaller and shorter clinical trials, with the goal of expediting patient access to these drugs without compromising the Agency's high standards for drug approval. In addition, the law requires FDA to consult with external experts on rare diseases in developing regulatory policy, and creates a demonstration project that provides transferable priority review vouchers to companies that develop drugs for pediatric rare diseases.

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.[14] FDA in turn promulgated an interim final rule regarding advanced anticipated drug shortage reporting,[15] 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.[16]

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 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. The legislation also requires FDA to coordinate with the Attorney General to address shortages of controlled substances, and provides for expedited inspections of drug facilities and expedited reviews of drug applications if such actions could help mitigate or prevent drug shortages. The law gives FDA authority to apply these provisions to biologics by regulation if it finds such inclusion would benefit the public health.

The remaining drug shortage provisions focus on developing the information necessary to implement a better drug shortage prevention framework going forward. Among other things, they require FDA to maintain an up-to-date drug shortage list and establish a task force to enhance the Agency's drug shortage response strategies, and they require actions from the Drug Enforcement Administration (DEA) with regard to shortages of controlled substances. The law also permits hospitals within the same health system to repackage drugs into smaller units to alleviate drug shortages.

Additional Amendments and Provisions Pertinent to the Pharmaceutical and Biotechnology Industry

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

- FDA must issue guidance on its policy regarding Internet and social media promotion of regulated medical products.
- FDA must work with other regulatory authorities and international organizations to foster uniform global clinical trial standards, facilitate the use of foreign data in FDA regulatory submissions and minimize the need for sponsors to conduct duplicative studies.
- Drug sponsors will be permitted to submit modifications to an approved risk evaluation and mitigation strategy (REMS) outside of a full REMS reassessment, and FDA must review minor REMS modifications within 60 days of receipt.
- FDA must issue guidance clarifying that all drug, generic drug, biologic and biosimilar applications must be submitted electronically.
- FDA must solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions.
- FDA will have greater flexibility under its conflict of interest rules, allowing it to fill advisory committee vacancies with experts who have a financial interest that could be affected by the advice given to FDA with respect to the matter before the advisory committee, provided FDA adequately discloses the nature of such interest.

Several provisions are aimed at moving generic drugs to the market more quickly, and they will result in significant new considerations and consequences for generics

and innovators alike. These provisions include the following:

- The period within which a "first applicant" must obtain tentative approval of its ANDA in order to avoid forfeiting its 180-day marketing exclusivity will be extended from 30 months to 40 months initially, then 36 months starting October 1, 2015.
- A 270-day deadline will be established for FDA to respond to petitions requesting a determination on whether a reference listed drug (RLD) was withdrawn from the market for reasons of safety or effectiveness, which determines whether a sponsor can reference the RLD in its ANDA.
- The timeframe for FDA to respond to petitions requesting a stay of action on an ANDA due to scientific or medical questions with the application will be shortened from 180 days to 150 days.[17]

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.

Conclusion

Though 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.

Endnotes

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

[2] *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 Congr. (2012) (statement of Janet Woodcock, M.D., Director, FDA Center for Drug Evaluation and Research) [hereinafter *FDA User Fees 2012*].

[3] *See* FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf.

[4] *See FDA User Fees 2012, supra* note 2.

[5] FDASIA defines "Type II active pharmaceutical ingredient drug master file" as a submission of information to FDA by a person that intends to authorize the Agency to reference the information to support approval of a generic drug submission without the submitter having to disclose the information to the generic applicant.

[6] The Act defines "prior approval supplement" as a request for FDA approval of a change in the drug substance, drug product, production process, quality controls, equipment, or facilities covered by an approved ANDA when that change has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

[7] *See* FDA, Generic Drug User Fee Act Program Performance Goals and Procedures (Draft), http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

[8] Under section 505(j)(5)(D) of the FDCA, an otherwise eligible "first applicant" forfeits its 180-day exclusivity marketing period if any of the enumerated forfeiture events occur, one of which is failure to obtain tentative approval of the application within 30 months of filing. Note, however, that another provision of FDASIA extends this 30-month timeframe to 40 months initially, and 36 months starting in 2015.

[9] The Patient Protection and Affordable Care Act was recently upheld by the US 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 path for the new user fee program.

[10] 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* John Manthei & Carolyne Hathaway, *Opening the Door for Generic Biologics: FDA Releases the First Guidance Documents Implementing the Biosimilar Approval Pathway*, Bloomberg BNA Pharmaceutical Law & Industry Report (Mar. 3, 2012).

[11] *See FDA User Fees 2012*, *supra* note 2.

[12] *See* FDA, Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf.

[13] *See FDA User Fees 2012*, *supra* note 2.

[14] Exec. Order No. 13588, 76 Fed. Reg. 68,295 (Nov. 3, 2011).

[15] Applications for Food and Drug Administration Approval to Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance, 76 Fed. Reg. 78,530 (proposed Dec. 19, 2011) (to be codified at 21 C.F.R. pt. 314).

[16] *See FDA User Fees 2012*, *supra* note 2.

[17] This provision is aimed at accelerating the timeline for generic and biosimilar approvals, assumingly based on the evaluation that most petitions for a stay of action will be denied by the Agency. The Congressional Budget Office estimated that this provision, as compared to others, would have the most significant effect on market entry by lower-priced generic drugs, and in turn result in greater savings to the healthcare system. *See* Congressional Budget Office Cost Estimate: H.R. 5651: Food and Drug Administration Reform Act of 2012 (May 24, 2012), *available at* http://www.cbo.gov/sites/default/files/cbofiles/attachments/hr5651.pdf.

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