LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.
700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D.C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329
www.hpm.com

Food and Drug Administration Reauthorization Act of 2017

September 7, 2017

TABLE OF CONTENTS

EXECUTIVE SUMMARY 5

I. PRESCRIPTION DRUG USER FEE AMENDMENTS OF 2017 5

A. Significant Changes to PDUFA 6

B. FDA's PDUFA VI Performance Goals 7

II. MEDICAL DEVICE USER FEE AMENDMENTS OF 2017 17

A. Significant Changes to MDUFA 18

B. FDA's MDUFA IV Performance Goals 21

III. GENERIC DRUG USER FEE AMENDMENTS OF 2017 23

A. Significant Changes to GDUFA 23

B. FDA's GDUFA II Performance Goals 25

IV. BIOSIMILAR USER FEE ACT OF 2017 27

A. Significant Changes to BsUFA 27

B. FDA's BsUFA Performance Goals 28

V. PEDIATRIC DRUGS AND DEVICES 30

A. Best Pharmaceuticals for Children 30

B. Pediatric Devices 31

C. Early Meeting on Pediatric Study Plan 31

D. Development of Drugs and Biological Products for Pediatric Cancers 32

E. Additional Provisions on Development of Drugs and Biological Products for Pediatric Use 33

VI. REAUTHORIZATIONS AND IMPROVEMENTS RELATED TO DRUGS 34

A. Reauthorization of Provision Relating to Exclusivity of Certain Drugs Containing Single Enantiomers 34

B. Reauthorization of the Critical Path Public-Private Partnerships 34

C. Reauthorization of Orphan Grants Program 35

D. Protecting and Strengthening the Drug Supply Chain 35

E. Patient Experience Data 35

F. Communication Plans 35

G. Orphan Drugs 35

H. Pediatric Information Added to Labeling 36

I. Sense of Congress on Lowering the Cost of Prescription Drugs 37

J. Expanded Access 37

K. Tropical Disease Product Application 38

VII. MEDICAL DEVICE INSPECTION AND REGULATORY IMPROVEMENTS 38

A. Risk-based Inspections for Devices 38

B. Improvements to Inspections Process for Device Establishments 38

C. Certificates to Foreign Governments for Devices 39

D. Facilitating International Harmonization 40

E. Fostering Innovation in Medical Imaging 40

F. Risk-based Classification of Accessories 41

G. Device Pilot Projects 43

H. Regulation of Over-the-Counter Hearing Aids 43

I. Report on Servicing of Devices 43

VIII. IMPROVING GENERIC DRUG ACCESS 44

A. Priority Review of Generic Drugs 44

B. Enhancing Regulatory Transparency to Enhance Generic Competition 44

C. Competitive Generic Therapies & Incentivizing Competitive Generic Drug Development 45

D. Accurate Information About Drugs with Limited Competition 46

E. Suitability Petitions 46

F. Inspections 47

G. Reporting on Pending Generic Drug Applications and Priority Review Applications & GAO Study of Issues Regarding First Cycle Approvals of Generic Medicines 47

IX. OTHER PROVISIONS 47

A. Technical Corrections 47

B. Annual Report on Inspections 48

C. Streamlining and Improving Consistency in Performance Reporting 49

D. Analysis of Use of Funds 49

E. Facilities Management 49

EXECUTIVE SUMMARY

On August 18, 2017, President Trump signed into law the Food and Drug Administration Reauthorization Act ("FDARA"), Pub. L. No. 115-52, ___ Stat. ___ (2017), which primarily amends both the Federal Food, Drug, and Cosmetic Act ("FDC Act") and Public Health Service Act ("PHS Act").[1] In addition to reauthorizing and amending several drug and medical device provisions that were scheduled to sunset, FDARA also makes several changes to the law concerning medical device manufacturer inspections, and addresses access to generic drugs. The law significantly changes the FDC Act and the PHS Act in several respects that will have considerable short- and long-term effects on the regulated industry and the Food and Drug Administration ("FDA").

FDARA includes nine titles, the first five of which concern drug and medical device user fee and pediatric-related programs. Title VI includes a potpourri of changes to the law styled as improvements related to drugs. Title VII makes significant changes to the law to enhance FDA's medical device inspection process. Title VIII is intended to improve generic drug access and creates a new 180-day exclusivity incentive to encourage the development of so-called "competitive generic therapies." Finally, Title IX makes technical and miscellaneous changes to the law.

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

I. PRESCRIPTION DRUG USER FEE AMENDMENTS OF 2017

FDARA reauthorizes the Prescription Drug User Fee Act ("PDUFA") through Fiscal Year ("FY") 2022. PDUFA was first enacted in 1992 to generate revenue from user fees paid by drug and biologic manufacturers in exchange for FDA's agreement to expedite the review process (known as "Performance Goals") for sponsors submitting certain New Drug Applications ("NDAs") and Biologics License Applications ("BLAs"). PDUFA has been reauthorized every five years since 1992, with the current iteration being the sixth PDUFA ("PDUFA VI").

[1] A copy of FDARA (H.R. 2430) is available at https://www.congress.gov/115/bills/hr2430/BILLS-115hr2430enr.pdf. A House Report on H.R. 2430, H.R. Rep. No. 115-201 (2017), is available at https://www.congress.gov/115/crpt/hrpt201/CRPT-115hrpt201.pdf.

A. Significant Changes to PDUFA

The current overall PDUFA use fee structure and the fee setting process were established in 1992 with the enactment of PDUFA I. Since PDUFA I, there have been three types of user fees: (1) an application fee due upon the submission of original NDAs, BLAs, and certain supplements; (2) an annual fee for each prescription drug establishment identified in an NDA or BLA that manufactures the prescription drug product or biological product; and (3) an annual fee applicable to each product covered by an approved NDA or BLA.

PDUFA VI significantly alters the user fee program structure and related mechanisms. These changes are intended to enhance administrative efficiency, to achieve increased predictability and stability of fee amounts and revenues, and to improve FDA's ability to engage in long-term financial planning.

Under PDUFA VI, two fee types will be in effect beginning in FY 2018: (1) an application fee (either a full fee or one-half of a full fee depending on whether or not the original NDA or BLA contains "clinical data"); and (2) an annual prescription drug program fee. Both the application fee for certain supplements and the annual establishment fee under previous law have been eliminated. Other than eliminating the supplement application fee, the statutory provisions governing assessment of the application fee remain the same as under PDUFA V.

The new annual prescription drug program fee is largely a retooled version of the product fee under previous PDUFA iterations. The fee, which must be paid by the NDA or BLA holder by the later of the first business day on or after October 1st of each fiscal year or the first business day after the enactment of an appropriations act concerning the collection and obligation of user fees, is assessed with respect to each "prescription drug product" identified in an NDA or BLA. A "prescription drug product" is described as a drug with a specific strength or potency in final dosage form subject to an approved NDA or BLA, that is dispensed only with a prescription, and that is listed in FDA's Orange Book (not including drug products in the discontinued section of the Orange Book) for an NDA. See FDC Act § 735(3) (21 U.S.C. § 379g(3)). This provision does not apply to multi-source drugs, i.e., drugs subject to generic competition, or to the generic competitors themselves. Certain orphan drugs are also exempt. Importantly, no more than five prescription drug program fees can be assessed with respect to any single NDA or BLA. Thus, if there are seven strengths approved under a single NDA, FDA will assess only five prescription drug program fees for that NDA.

Under PDUFA V, the three fee types (i.e., application, establishment, and product fees) generated a total revenue amount set by the statute that was adjusted annually. Of the total revenue amount determined for a fiscal year, one-third was derived from each of the three fee types. Under PDUFA VI, FDA and industry agreed to shift a greater proportion of the target revenue allocation to more predictable fee-paying types. For FY 2018, the annual base revenue amount is $878,590,000 and is adjusted annually for FYs 2019-2022. Of the total revenue amount determined for a fiscal year, 20 percent is derived from application fees, and 80 percent is derived from annual prescription drug program fees.

B. FDA's PDUFA VI Performance Goals

FDA's PDUFA VI Performance Goals Letter,[2] summarized below, covers a wide range of drug development-related activities, including commitments to ensure the effectiveness of the human drug review program for various types of applications.

Review Performance Goals for Drug Marketing Applications. The Goals Letter set the current review performance goals for various types of drug marketing applications as follows:

Table 1: Original and Resubmitted Applications and Supplements

Submission Cohort	Standard	Priority
NME NDAs and Original BLAs	90% in 10 months of the 60 day filing date	90% in 6 months of the 60 day filing date
Non NME NDAs	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmissions	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmissions	90% in 6 months of the receipt date	90% in 6 months of the receipt date
Original Efficacy Supplements	90% in 10 months of the receipt date	90% in 6 months of the receipt date
Class 1 Resubmitted Efficacy Supplements	90% in 2 months of the receipt date	90% in 2 months of the receipt date
Class 2 Resubmitted Efficacy Supplements	90% in 6 months of the receipt date	90% in 6 months of the receipt date

[2] The PDUFA VI Performance Goals are available at https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf.

Table 2: Manufacturing Supplements

	Prior Approval	All Other
Manufacturing Supplements	90% in 4 months of the receipt date	90% in 6 months of the receipt date

The NME NDA and Original BLA "Program." To promote transparency and communication between the FDA review team and the applicant, FDA reauthorized "the Program" for review of all New Molecular Entity New Drug Applications (NME NDAs) and original BLAs, including applications that are resubmitted following a Refuse-to-File decision, received from October 1, 2017, through September 30, 2022 (i.e., FYs 2018-2022).

The Program is intended to "promote the efficiency and effectiveness of the first cycle review process and minimize the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics." PDUFA VI Performance Goals at 7.

The Program outlines a standard approach for review of NME NDAs and original BLAs, but allows for the FDA review team and the applicant to discuss and reach a mutual agreement on the timing and nature of interactions between the applicant and FDA through what is known as a "Formal Communication Plan." Id. The Formal Communication Plan will specify any elements of the Program that FDA and the sponsor agree are unnecessary. Id.

If an application reviewed in the Program is for a product that the FDA review team identifies as meeting an important public health need, and the review team determines that a first-cycle approval is likely for the application, the team intends to make "every effort to conduct an expedited review and act early on the application." Id. at 7-8.

The parameters of the Program include, among other things, a pre-submission meeting that is "strongly encouraged," a mid-cycle communication "to provide the applicant with an update on the status of the review of their application," and a late-cycle meeting at which the FDA review team, appropriate team leaders and supervisors, and the applicant will discuss the status of the review of the application. Id. at 8-12.

The goal for inspection times was reauthorized (6 months of original receipt for priority applications and within 10 months of the date of original receipt for standard applications), as was a quality system approach that implements a tracking system to

document review team performance of key milestones for each of the applications reviewed under the Program.

At the pre-submission meeting, "FDA and the applicant will agree on the content of a complete application for the proposed indication(s)," including "preliminary discussions on the need for REMS or other risk management actions." Id. at 8. In addition, "FDA and the applicant may also reach agreement on submission of a limited number of application components not later than 30 calendar days after the submission of the original application," such as the submission of updated stability data. Id. at 8-9.

The description of the Program cautions that "[i]f the applicant does not have a pre-NDA/BLA meeting with FDA, and no agreement exists between FDA and the applicant on the contents of a complete application or delayed submission of certain components of the application, the applicant's submission is expected to be complete at the time of original submission." Id. at 9.

As part of the Program, priority and standard NME NDAs and original BLAs will be subject to different review goals as compared to other applications. FDA will review and act on 90 percent of standard NME NDA and original BLA submissions within 10 months of the 60-day ***filing*** date, and 90 percent of priority NME NDA and original BLA submissions within 6 months of the 60-day ***filing*** date. Use of the filing date instead of the submission date essentially means that the reviews are slated to take place within 12 months (standard review) and 8 months (priority review) from application submission.

First Cycle Review Management. FDA updated its GRMP guidance to include review activities added to the human drug review program since its finalization in 2005, as well as to articulate principles surrounding FDA communication with applicants and internal review timeframes. This was an effort to ensure efficient and effective first cycle reviews. FDA is scheduled to publish a draft guidance by the end of FY 2018 outlining the review process.

Review of Proprietary Names to Reduce Medication Errors. FDA will now set review goals for proprietary names during development (as early as end-of-phase two), and during their review of a marketing application. Id. at 13. For proprietary name review during drug development, FDA has set a goal to review 90 percent of proprietary name submissions filed within 180 days of receipt. Id. For proprietary name review during application review, FDA has set a goal to review 90 percent of NDA/BLA proprietary name submissions filed within 90 days of receipt. Id.

Major Dispute Resolution. Dispute resolution for procedural and scientific matters involving the review of human drug applications and supplements will also be

restructured to include set procedures and performance goals. Id. 13-14. For procedural or scientific matters involving the review of human drug applications and supplements that cannot be resolved at the signatory authority level, FDA has set a goal of providing answers to 90% of appeals within 30 calendar days from the Center's receipt of the appeal. Id.

Clinical Holds. FDA outlined measurable goals and objectives for clinical hold responses. The Center should respond to 90 percent of sponsors' complete responses to a clinical hold within 30 days of the Agency's receipt of the submission. Id. at 15.

Special Protocol Question Assessment and Agreement. FDA set procedures and performance goals for the evaluation of certain protocols and issues to assess design adequacy according to the scientific and regulatory requirements identified by the sponsor. Id. at 15-16. The Goals Letter specifies that the sponsor should submit a limited number of specific questions about the protocol design and regulatory requirements for which the sponsor seeks agreement. Id. at 15. Within 45 days of receipt, FDA will provide a written response to the sponsor that includes an assessment of the protocol and answers to questions posed by the sponsor. Id.

Protocols that qualify for this program include: carcinogenicity protocols, stability protocols, and Phase 3 protocols for clinical trials that will form the basis of an efficacy claim. Id. The Goals Letter states that "[t]he fundamental agreement here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident." Id. at 15-16. FDA has set a goal of completing and returning 90 percent of special protocol assessments to the sponsor within the specified timeframe.

Meeting Management Goals. FDA set procedures and performance goals for meeting management administration (e.g., responding to meeting requests, scheduling meetings, receipt of meeting background packages). FDA will publish draft guidance on formal meetings between FDA and sponsors, further outlining the intended performance goals of meeting management by September 30, 2018. Id. at 20.

Table 3 below indicates the timeframes for FDA's response to a meeting request. FDA plans to respond to meeting requests and provide notification within the response times noted below for 90 percent of each meeting type. Id. at 16-17.

Table 3: Timeframes for FDA's Response to a Meeting Request

Meeting Type	Response Time (Calendar Days)
A	14
B	21
B (EOP)	14
C	21

Table 4 below indicates the timeframes for the scheduled meeting date following receipt of a formal meeting request, or in the case of a written response, the timeframes for the Agency to send the written response. Id. at 17-18. If the requested date for any meeting is greater than the specified timeframe, the meeting date should be within 14 calendar days of the requested date. Id. FDA plans to hold 90 percent of meetings within the timeframe for each meeting type, and to send 90 percent of written responses within the timeframe for each meeting type. Id. at 18.

Table 4: Timeframes for the Scheduled Meeting Date

Meeting Type	Meeting Scheduling or Written Response Time
A	30 calendar days from receipt of meeting request
B	60 calendar days from receipt of meeting request
B (EOP)	70 calendar days from receipt of meeting request
C	75 calendar days from receipt of meeting request

Table 5 below lists the timing of the Agency's receipt of the sponsor background package for each meeting type. Id.

Table 5: Timing of Agency's Receipt of Sponsor Background Package

Meeting Type	Receipt of Background Package
A	At the time of the meeting request
B	30 calendar days before the date of the meeting or expected written response
B (EOP)	50 calendar days before the date of the meeting or expected written response*
C	47 calendar days before the date of the meeting or expected written response*

* If the scheduled date of a Type B (EOP) or C meeting is earlier than the timeframes specified in Table 4, the meeting background package will be due no sooner than six calendar days and seven calendar days following the response time for Type B (EOP) and C meetings specified in Table 3, respectively.

FDA intends to send 90 percent of preliminary responses to the sponsor's questions contained in the background package no later than five calendar days before the meeting date for Type B (EOP) and C meetings. Id. at 19. Not later than three calendar days following the sponsor's receipt of FDA's preliminary responses for a Type B (EOP) or C meeting, the sponsor must notify FDA of whether the meeting is still needed, and if so, the agenda for the meeting. Id.

FDA plans to issue meeting minutes to 90 percent of sponsors within 30 calendar days of the date of the meeting. Id. The Goals Letter states, however, that in order to qualify for these performance goals, the sponsor must submit a written request to the review division which contains: (1) a statement of the purpose of the meeting; (2) a list of specific objectives/outcomes; (3) a proposed agenda; (4) a list of planned external attendees; (5) a list of requested Center attendees; and (6) the date that the meeting background package will be sent to the Center. Id. The Agency must also concur that the meeting will serve a useful purpose. Id. at 19-20.

The Regulatory Science Program. As part of the PDUFA VI Performance Goals, FDA will extend its regulatory science program "[t]o ensure that new and innovative products are developed and available to patients in a timely manner." Id. at 20.

In order to develop better communication between FDA and sponsors during the drug development process, FDA will maintain a dedicated drug development communication and training staff in CDER and CBER. Id. The staff will serve as a "liaison" to facilitate interactions between sponsors and each Center by serving as a point of contact for sponsors who have general questions about drug development or who are having difficulty communicating with the review team for their IND. Id. at 20-21. The communication staff will also provide training to the review organizations on best practices for communication with sponsors. Id. at 21.

In addition to efforts by FDA's dedicated communication staff, FDA will contract with an independent third party to perform an independent assessment of current communication practices. Id. FDA will convene a public workshop by the end of March 2021 to discuss the findings of this independent assessment. Id. The workshop will include feedback from sponsors and FDA review teams. Id. Using the information collected by the third-party review, FDA will update the current guidance on "Best Practices for Communication Between IND Sponsors and FDA During Drug Development" no later than one year following the public workshop. Id.

The success of the Breakthrough Therapy Program will be further prioritized through the dedication of additional resources that will allow FDA to continue to work

closely with sponsors throughout the designation, development, and review process. Id. at 22.

FDA will establish a process for Type C meetings early in development, which must be accompanied by a full briefing document at the time of the meeting request. Id. In doing so, more accurate consultations on the feasibility of a surrogate as a primary endpoint to support accelerated or traditional approval can be provided. Id.

CDER and CBER's Rare Disease Program Staff will be integrated into review teams for rare disease development programs and application review. Id. at 22-23. Their "unique expertise on flexible and feasible approaches to studying and reviewing such drugs" will result in the advancement of the development of drugs for rare diseases. Id. at 23. The Rare Disease Program will also continue to provide training to all CDER and CBER review staff related to the development, review, and approval of drugs for rare diseases. Id. All staff activities must be included in the PDUFA annual performance report. Id.

CBER and CDER will reinforce the development of drug-device and biologic-device combination products through its regulatory authority and breadth. Id. at 22-23. They will develop staff capacity and capability across the medical product centers and the Office of Combination Products, including participation in the core review team. Id. FDA will also streamline the process for combination product review by establishing MAPPs and SOPPs to promote efficient, effective, and consistent combination product development and review. Id. at 23-26.

FDA will contract with an independent third party to assess the current practices for review of combination drugs. Id. at 26. FDA will publish the final report from the assessment on its website no later than the end of FY 2020. Id. By the end of FY 2019, FDA will publish draft guidance or update previously published guidance describing considerations related to drug-device and biologic-device combination products on the following topics: (1) bridging studies and (2) patient-oriented labeling. Id.

The PDUFA VI Performance Goals will also require a stronger use of "real world" data in regulatory decision-making. Id. at 27. By the end of FY 2018, at least one public workshop will be conducted, and by FY 2021, activities in the form of pilot studies and methodology development projects to address outstanding concerns will be initiated and published in a draft guidance. Id.

Regulatory Decision Tools to Support Drug Development and Review. Regulatory decision tools that better aid the drug development process will be augmented to provide a more meaningful patient and caregiver contribution throughout the regulatory

engagement. Id. The staff capacity will be strengthened in order to supplement and utilize patient-focused methods, including Patient-Reported Outcomes ("PROs"). Id. at 28. A series of guidance documents, centered on approaches and methods focused on bridging initial patient-focused drug development meetings with meaningful patient and caregiver input will also be created. Id. at 28-29. FDA will prioritize the patient and caregiver voice by holding public workshops to gather input prior to the issuance of guidances, and will supply a repository of publicly available tools and resources. Id. Existing MAPPs and SOPPs will be revisited to include suggested approaches to incorporating an increased patient focus, and a public workshop exploring practices most able to enhance patient engagement in clinical trials will be held by the end of FY 2019. Id. at 29.

The PDUFA VI Performance Goals will further the Agency's implementation of structured benefit-risk assessment in regulatory decision-making that was previously outlined in PDUFA V. Id. FDA will publish a progress update to the current implementation plan by March 31, 2018. Id. Further, a public meeting regarding the application of the benefit-risk framework throughout the human drug lifecycle will convene by the end of FY 2019. Id. at 29-30. FDA will also enhance benefit-risk assessments by publishing a draft guidance for new drugs and biologics by the end of FY 2020. Id. at 30. FDA will conduct an evaluation of the implementation of the benefit-risk framework beginning in FY 2021, and will revise relevant MAPPs and SOPPs to include new approaches to incorporating the benefit-risk framework into drug review. Id.

FDA plans to advance Model-Informed Drug Development ("MIDD") by facilitating the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical sources. Id. FDA will do this by developing its regulatory science and review expertise in MIDD approaches, convening a series of workshops, starting a pilot program for these approaches starting in FY 2018, publishing a draft guidance by end of FY 2019, and revising relevant MAPPs or SOPPS and/or review templates to incorporate the evaluation of these approaches. Id. at 30-31.

FDA will enhance its capacity to review complex adaptive, Bayesian, and other novel clinical trial designs. Id. at 31. FDA will do this by developing the staff capacity to enable processes to facilitate appropriate use of these types of methods, conducting a pilot program starting in FY 2018, convening a public workshop by end of the second quarter of FY 2018, publishing a draft guidance by end of FY 2018, and developing and revising relevant MAPPs, SOPPs, and/or review templates to incorporate guidelines for evaluating these designs. Id. at 31-33.

FDA will enhance its capacity to support analysis data standards for product development and review by developing staff capacity to review and provide feedback on

the readiness of submitted analysis data sets and programs for review, as well as to assist with FDA development and updating of therapeutic area user guides to support these review activities. Id. at 33. FDA will convene a public workshop by the end of FY 2019 and will collaborate with external stakeholders and participate in public workshops. Id. By the end of FY 2020, FDA will develop/revise relevant MAPPs and SOPPs. Id.

Finally, FDA will enhance the drug development tools qualification pathway for biomarkers by developing staff capacity to enhance biomarker qualification review, piloting processes to engage external experts to support review of submissions, convening a public meeting by the end of FY 2018, publishing draft guidances by the end of FY 2018 and FY 2010, developing and revising relevant MAPPs and SOPPs, listing biomarker qualification submissions that are in the qualification process, publishing review and summary documents for qualified biomarkers, and maintaining traditional channels for engaging FDA outside of the qualification pathway. Id. at 33-34.

FDA Drug Safety System. FDA will continue to use user fees to enhance and modernize the U.S. drug safety system. These efforts will include the adoption of new scientific approaches; improving the utility of existing tools for detecting, evaluating, preventing, and mitigating adverse events; standardizing and integrating REMS into the healthcare system; enhancing communication and oversight of pre- and post-market review staff; and improving tracking and oversight of safety issues. Id. at 34.

FDA will use user fees to provide resources to (a) expand the Sentinel System and integrate the system into FDA pharmacovigilance activities and (b) provide timely and effective evaluation and communication of postmarketing safety findings to sponsors. Id. at 34-35.

By the end of FY 2019, FDA will hold a public meeting to discuss current and emerging Sentinel projects and to seek stakeholder feedback regarding gaps in the current system. Id. at 35. By the end of FY 2020, FDA will establish MAPPs and SOPPs to inform sponsors about the planned use of Sentinel to evaluate safety signals. Id. By the end of FY 2020, FDA will facilitate integration of Sentinel into the human drug review program, and will develop a comprehensive training program for review staff. Id. By the end of FY 2022, FDA will analyze and report on the impact of Sentinel. Id. at 36.

By the end of FY 2019, FDA will update MAPPs and SOPPs concerning tracking postmarketing safety signals to include consistent and timely notification to a sponsor (1) when a serious safety signal involving a product is identified and (2) to the extent practicable, not less than 72 hours before public posting of a safety notice. Id. By the end of FY 2022, FDA will conduct an assessment of how its data systems and processes support review, oversight, and communication of postmarketing drug safety issues. Id.

Management of User Fee Resources. FDA plans to modernize its user fee structure to improve the predictability of FDA funding and sponsor invoices, simplify the administration of user fees, and enhance the ability of financial mechanisms to improve management of PDUFA program funding. Id. at 37.

No later than the second quarter of FY 2018, FDA will publish a PDUFA program resource capacity planning and modernized time reporting implementation plan. Id. FDA will also staff a resource capacity planning team to implement and manage a capacity planning system across the PDUFA program. Id. FDA will contract an independent accounting or consulting firm to evaluate options and provide recommendations for a new methodology to assess changes in the resource and capacity needs of the human drug review program. Id.

FDA has committed to assuring financial transparency and efficiency in the way user fees are administered, allocated, and reported. Id. at 37-38. To that end, FDA will contract with an independent third party to evaluate the PDUFA program resource management during FY 2018. Id. at 38. FDA will publish a five-year financial plan not later than the second quarter of FY 2018. FDA will also hold a public meeting no later than the third quarter of each fiscal year starting in FY 2019 to discuss the PDUFA five-year financial plan. Id.

FDA Hiring and Retention of Review Staff. FDA plans to improve hiring and retention of review staff by (a) modernizing the hiring system infrastructure and augmenting system capacity; (b) augmenting hiring staff capacity and capability; (c) establishing a dedicated function to ensure needed scientific staffing for medical product review; (d) setting clear goals for drug review program hiring; and (e) providing comprehensive and continuous assessment of hiring and retention. Id. at 39-41.

Information Technology. FDA plans to improve the predictability and consistency of the electronic submission process and enhance transparency and accountability of FDA IT-related activities. Id. at 42. FDA will improve the electronic submission process by publishing and maintaining up-to-date documentation, publishing targets for Electronic System Gateway (ESG) availability, posting ESG operational status on the FDA website, and publishing submission instructions to use in the event of ESG service disruption. Id.

FDA will provide expert technical support for electronic submission to FDA review staff, including submission navigation and troubleshooting. Id. at 43. FDA also invites industry to provide feedback and/or participate in user acceptance testing before implementing significant changes to the submission processes. Id.

FDA has set several timeline goals for these improvements. Id. By December 31, 2017, FDA will publish target timeframes for the expected submission upload duration(s) and the timeframe between key milestones and notifications. Id. By September 30, 2018, FDA will implement the ability to communicate electronic submission milestone notifications, including final submission upload status, to the sender or designated contact. Id. By December 31, 2017, FDA will implement a process to provide advance notification of systems and process changes. Id.

FDA plans to enhance transparency and accountability of electronic submission and data standards activities by (1) holding quarterly meetings between FDA staff and industry about current challenges and needs; (2) holding annual public meetings to seek stakeholder input about the electronic submission system (starting no later than September 30, 2018); (3) posting, at least annually, metrics of ESG performance (by December 31, 2017); (4) incorporating strategic initiatives in support of PDUFA goals into the FDA IT Strategic Plan; and (5) collaborating with Standards Development Organizations and publishing a data standards action plan and FDA Data Standards Catalog. Id.

FDA Performance Management. FDA will improve performance management by conducting studies to assess the other PDUFA VI performance goals. Id. at 44-45.

Progress Reporting. FDA will include information on the Agency's progress in meeting the PDUFA VI performance goals in the annual PDUFA Performance Report. Id. at 45. FDA will also include information on the Agency's progress in hiring new staff in the annual PDUFA Financial Report. Id.

II. MEDICAL DEVICE USER FEE AMENDMENTS OF 2017

The Medical Device User Fee Amendments of 2017 ("MDUFA IV") supplements FDA's funding of device regulation, with the goal of increasing the speed and efficiency of the Agency's review of new devices, as well as improving the safety and effectiveness of marketed devices. MDUFA was first enacted in 2002, and was reauthorized in 2007 and, most recently, in 2012 for FYs 2013-2017.[3]

[3] Medical Device User Fee and Modernization Act ("MDUFMA"), Pub. L. No. 107-250, 116 Stat.1588 (2002); FDA Amendments Act, Pub. L. No. 110-85, Title II, 121 Stat. 823, 842 (2007) ("MDUFA II"); FDA Safety and Innovation Act ("FDASIA"), Pub. L. No. 112-144, 126 Stat. 993 (2012) ("MDUFA III").

A. Significant Changes to MDUFA

Add User Fees for De Novo Petitions. *De Novo* petitions are the regulatory pathway for the classification of a novel low to moderate risk type of device. Until now, *De Novo* petitions have not been subject to user fees. Beginning in FY 2018, FDA may begin charging a user fee equal to 30% of the PMA user fee for a *De Novo*. See FDC Act § 738(a), as amended by FDARA § 203(a)(2). By way of example, in FY 2018, the PMA user fee will be $294,000, which means that the *De Novo* fee will be at least $88,200. See id. § 738(b), as amended by FDARA § 203(b)(2). With the inflation adjustment permitted by the statute, the *De Novo* fee for FY 2018 will be $93,229. See FDA, Notice, Medical Device User Fee Rates for Fiscal Year 2018, 82 Fed. Reg. 41,029 (Aug. 29, 2017).

The *De Novo* user fee will grow each year (as PMA fees grow), reaching $98,700, before inflation, in FY 2022. See FDC Act § 738(b), as amended by FDARA § 203(b)(2). In FY 2018, the *De Novo* user fee will be more than 20 times the user fee for previously classified Class I and II devices requiring premarket submission. See id. This significant financial burden may slow the rate of new *De Novo* petitions, a pathway that has seen a significant increase in usage since the process was streamlined under FDASIA. *De Novo* petitions will not be accepted for review until the user fee is paid. See id. § 738(f)(1), as amended by FDARA § 203(g). At the same time, there will be somewhat more certainty in the timelines for a *De Novo* review, which may encourage greater use, especially by investment-driven start up device companies.

There are two exceptions to the new *De Novo* user fee. First, *De Novo* petitions for devices intended solely for pediatric use are exempt. See id. § 738(a), as amended by FDARA § 203(a)(2). Second, small businesses submitting a *De Novo* petition may seek a fee waiver equivalent to the waivers for a Premarket Approval Application ("PMA"). See id. § 738(d), as amended by FDARA § 203(d).

Baseline User Fees and Adjustment. FDARA gradually increases baseline Medical Device Fees for FY 2018 – 2022. See id. § 738(b), as amended by FDARA § 203(b)(2). The fee for a PMA in FY 2018 will be $294,000, increasing to $329,000 by FY 2022. See id. The fee for 510(k) applications in FY 2018 will be $4,375, increasing to $4,978 by FY 2022. See id. These increased fees are expected to produce an estimated revenue of $1 billion in industry payments during MDUFA IV.

FDASIA included a provision that allowed FDA to waive medical device fees, or reduce applicable fees, in the interest of public health. The sum of all fee waivers and reduction in any FY was limited to 2 percent of less of the total fee revenue amounts

established under FDASIA. See id. § 738(f). This provision has been removed by FDARA § 203(f).

Reduction in Small Business Fee Waivers for Establishment Registration. Prior to enactment of FDARA, a small business submitting a 510(k) application could see a user fee waiver equal to 50 percent of the 510(k) user fee. See id. § 738(e)(2)(C). Beginning in FY 2018, these same small businesses will only be eligible for a 25 percent reduction in the 510(k) user fee. See id. § 738(e)(2)(C), as amended by FDARA § 203(e).

Conformity Assessment Pilot Program. Voluntary consensus standards are technical standards by various parties including governments and standard setting organizations. These standards can play an important role in establishing the safety and performance criteria for many aspects of medical device design and manufacturing. These standards often support claims of safety and effectiveness in premarket submissions. Applicants currently have the option of including a Declaration of Conformity in their premarket submissions attesting that their devices conform to applicable consensus standards. However, these standards vary widely in terms of technical complexity; which makes it challenging for applicants and FDA reviewers to determine whether standards have been appropriately incorporated in regulatory submissions.

To explore a potential solution to this problem, FDARA enacted the Pilot Accreditation Scheme for Conformity Assessment. See id. § 514, as amended by FDARA § 205. The program aims to enlist accredited laboratories with the expertise to evaluate device submissions according to consensus standards recognized by the Agency. Device manufacturers can have tests conducted at recognized, accredited test labs and submit to FDA a determination from the test laboratory that their device conforms to the standards tested. See id. § 514, as amended by FDARA § 205(d)(1). FDA will rely on the results from the accredited test laboratory for the purpose of premarket review. See id. § 514, as amended by FDARA § 205(d)(1)(B).

On or before September 30, 2018, FDA will hold a public meeting "to discuss and obtain input and recommendations from stakeholders regarding the goals and scope of, and a suitable framework and procedures and requirements for," the program. See id. § 514, as amended by FDARA § 205(d)(3). No later than September 30, 2019, FDA will issue a draft guidance establishing the goals and implementation of the program, and FDA will finalize the draft guidance within the subsequent two years. This program will expire at the end of FY 2022 unless renewed in the next user fee negotiations.

Changes to Devices Eligible for Third-Party Review. Currently, the FDC Act states that third-party review is *not* permitted for Class III devices and Class II devices which:

- Are intended to be permanently implantable or life sustaining or life supporting; or
- Require clinical data.

See id. § 523(a)(3)(A). Class III devices are still ineligible. FDARA also adds to the ineligible list devices submitted through the *De Novo* pathway and devices receiving breakthrough designation. See id. § 523(a)(3), as amended by FDARA § 206(1)(A). All permanently implantable or life sustaining or life supporting devices, including Class II devices of this type, are also ineligible unless FDA determines otherwise. See id.

Class II devices requiring clinical data are no longer ineligible for third-party review. See id. This change could potentially affect future FDA regulatory oversight of laboratory developed tests ("LDTs"). In FDA's attempts to actively regulate LDTs, one logistical roadblock has been resources. FDA simply would not be able to handle the volume of premarket submissions associated with LDTs. FDA could use third-party reviewers to assist with this increased burden; however, most diagnostic test submissions contain clinical data. The section of the FDC Act prohibiting submissions containing clinical data from undergoing third-party review, therefore, prevented the Agency from looking to third-parties for premarket review. With this prohibition now removed from the FDC Act, FDA's position in the LDT debate has improved.

FDA will issue a draft guidance regarding the factors it will use to determine whether a Class I or II device is eligible for third-party review, and the Agency will finalize the guidance within 24 months from issuance of the draft. On the same day the guidance is finalized, FDA will also publish a list of Class I and II devices eligible for third-party review. Until this new list is published, the current list of devices eligible for third-party review is still in effect.

Transition to Solely Electronic Submission. Currently, Pre-Submissions and premarket submissions are submitted in both hard copy and electronic copy ("eCopy"). On or before October 1, 2019, FDA will issue a draft guidance outlining a program for submission of eCopies only for all Pre-Submissions and premarket submissions. FDA will issue a final guidance within one year of issuing the draft.

B. FDA's MDUFA IV Performance Goals

Under the MDUFA III Performance Goals and Procedures, FDA steadily increased the percentage of medical device submissions that met the review time goals from FYs 2013 to 2017. According to the MDUFA Performance Goals and Procedures for FY 2018-2022 ("MDUFA IV Performance Goals" [4]), FDA will maintain these timeliness standards for PMA and 510(k) submissions. The MDUFA IV Performance Goals now also set goals for Pre-Submissions and *De Novo* petitions.

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

- Within 15 calendar days, communicate with the applicant regarding whether its application has been accepted for filing review. This goal is unchanged from MDUFA III.

- Within 45 days of FDA's receipt of the application, communicate with the applicant regarding the application's filing status, including providing specific reasons for any refusal to file. This goal is unchanged from MDUFA III.

- Within 90 calendar days of the filing date of the application, communicate with the applicant through a "Substantive Interaction"[5] for 95 percent of submissions. This goal is unchanged from MDUFA III's FY 2016 and FY 2017 goal.

- Within 180 "FDA Days,"[6] issue a "MDUFA decision"[7] for submissions that do not require Advisory Committee input for 90 percent of submissions. This goal is unchanged from MDUFA III's FY 2016 and FY 2017 goal.

---

4 The MDUFA IV Performance Goals and Procedures are available at https://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM535548.pdf.

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

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

7 A "MDUFA decision" is a final decision on the application. For original PMAs, these can be decisions that the application is approved, approvable, approvable pending GMP inspection, not approvable, withdrawn, or denied. For 180-day PMA supplements or

- Within 320 FDA Days, issue a MDUFA decision for submissions that require Advisory Committee input for 90 percent of submissions. This goal is unchanged from MDUFA III's FY 2017 goal.

- For PMA submissions that receive a MDUFA decision of approvable, FDA will issue a decision within 60 days of the sponsor's response to the approvable letter, as resources permit, but not to the detriment of meeting the quantitative review timelines and statutory obligations. This is a new goal.

MDUFA IV Performance Goals at 5-6.

With regard to 180-day PMA supplements, FDA's goal is to communicate with applicants through a Substantive Interaction within 90 calendar days of FDA's receipt of the submission for 95 percent of submissions. See id. at 7. This goal is unchanged from MDUFA III's FY 2016 and FY 2017 goal. For 180-day PMA Supplements, FDA will issue a MDUFA decision within 180 FDA Days for 95 percent of submissions. See id. This is a new goal. The prior goal for 180-day Supplements was 95 percent of submissions within 90 days. For real-time PMA supplements, FDA will issue a MDUFA decision within 90 FDA Days for 95 percent of submissions. See id. This goal is unchanged from FYs 2015-2017.

The 510(k) performance goals are unchanged from FY 2017 with FDA's goals being:

- Within 15 calendar days, communicate with the applicant regarding whether the submission has been accepted for review.

- Within 60 calendar days, communicate with the applicant through a Substantive Interaction for 95 percent of submissions.

- Within 90 FDA Days, issue a MDUFA Decision for 95 percent of submissions.

Id. at 8.

---

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

With regard to *De Novo* petitions, FDA will issue a new guidance regarding the process, including a "refuse to accept" checklist. See id. at 7. The performance goals are not particularly stringent, although they increase somewhat each year. FDA must issue a MDUFA decision within 150 FDA Days of receipt of the submission for 50 percent of *De Novo* petitions received in FY 2018, 55 percent in FY 2019, 60 percent in FY 2020, 65 percent in FY 2021, and 70 percent in FY 2022. See id. Just like with PMAs and 510(k)s, if a decision has not been reached within the MDUFA goal, FDA will discuss with the applicant all outstanding issues with the submission preventing FDA from reaching a decision. See id.

Importantly, for PMAs, 510(k)s, and *De Novos*, FDA now aims to include "a statement of the basis for the deficiencies (e.g., a specific reference to applicable section of a rule, final guidance, recognized standard unless the entire or most of document is applicable)." See id. at 5, 7, and 8. If the review Division cannot trace a deficiency in this manner, the reviewer "will cite the specific scientific issue and the information to support its position." See id. Deficiency letters will also now undergo supervisory review prior to issuance to ensure the deficiencies cited are relevant to a classification determination. See id.

With regard to Pre-Submissions, FDA will issue a revised guidance regarding the Pre-Submission program by October 1, 2018 to further clarify the program, including frequently asked questions. See id. at 4. Within 15 calendar days of receipt of a Pre-Submission, FDA will notify the sponsor regarding whether the Pre-Submission has been accepted for review and, if applicable, regarding scheduling of the meeting or teleconference. See id. at 3. FDA will provide written feedback regarding the issues raised in the Pre-Submission meeting request within the 70 calendar days of receipt or 5 calendar days prior to a scheduled meeting, whichever is earlier. See id.

III. GENERIC DRUG USER FEE AMENDMENTS OF 2017

With the success of the initial implementation of the Generic Drug User Fee Amendments of 2012 ("GDUFA I"), FDARA reauthorizes the program with the adoption of the second iteration of the law: GDUFA II. Like the previous version of GDUFA, GDUFA II is intended to supplement congressional funding for FDA review of generic drug applications. GDUFA II establishes faster review of priority submissions, enhances pre-ANDA programs, and modifies the user fee structure.

A. Significant Changes to GDUFA

In order to ensure stability of revenue, GDUFA II markedly changes the structure of the generic drug user fee program by adding a program fee for all approved ANDA

holders. The generic drug user fees collectively are intended to generate $493.6 million in funding for FDA in FY 2018 and adjusted annually thereafter. See FDA, Notice, Generic Drug User Fee Rates for Fiscal Year 2018, 82 Fed. Reg. 41,026 (Aug. 29, 2017).

GDUFA II expands generic user fees to an additional category of fees. While application fees, facility fees, and Drug Master File fees still collectively comprise 65 percent of the generic drug user fee revenue, 35 percent arises from a new "program fee" for ANDA holders. The program fee assesses user fees to ANDA holders based on the number of approved ANDA applications held on the fee due date, October 1 of each fiscal year. A small business program fee is assessed for each entity, including its affiliates, that holds between 1 and 5 ANDAs; an entity that owns between 6 and 19 ANDAs is assessed a medium size operation generic drug applicant program fee; an entity that owns 20 or more ANDAs is assessed a large size operation generic drug applicant program fee. The small business program fee is equal to one-tenth of the large size operation generic drug applicant fee while a medium size is equal to two-fifths of the large size. ANDAs for which a written request for withdrawal of approval has been submitted by April 1 of the previous fiscal year are not included in the total number of approved ANDA applications. FDARA § 303(b)(2)(E)(ii).

Previously, 56 percent of fees were derived from generic drug facilities; GDUFA II drastically reduces this percentage to 20 percent and includes contract manufacturing organization facilities in the facility fee requirement for the first time. Contract manufacturing facilities are assessed one-third the amount of a facility fee for a non-contract manufacturing facilities. Additionally, the fee for a foreign facility is now $15,000 higher than a domestic facility rather than between $15,000 and $30,000 higher. Seven percent of fees, rather than 14 percent, are derived from Active Pharmaceutical Ingredient facilities with the same $15,000 additional fee for foreign facilities rather than domestic. See id. § 303(b)(2)(D).

ANDA application fees now comprise 33 percent of the generic drug user fee revenue rather than 24 percent, but the previous user fees for prior approval supplements ("PASs") have now been removed. See id. § 303(b)(2)(C). This was done because the number of PASs filed is too variable to make reliable revenue predictions. See Testimony of Janet Woodcock before the U.S. House of Rep. Comm. on Energy and Commerce Subcomm. on Health (Mar. 2, 2017). Finally, five percent of revenue, down from six percent, is derived from Type II pharmaceutical ingredient Drug Master Files ("DMF") referenced in a generic drug submission. See FDARA § 303(b)(2)(B).

While FDASIA introduced the requirement that FDA must refund 75 percent of the application fee if the submission is not received by FDA within the meaning of the FDC Act § 505(j)(5)(A) for reasons other than failure to pay user fees, GDUFA II

authorizes such a refund for ANDAs withdrawn prior to being received. See FDARA § 303(a)(4)(D). Additionally, FDA must refund 100 percent of the application fee if the Agency initially receives the ANDA under section 505(j)(5)(A) and subsequently determines that an exclusivity period precluded receipt of the application. See id.

Penalties for failure to pay user fees remain the same, and GDUFA II introduces additional consequences for failure to pay the generic drug program fee. See id. § 303(f)(3). These consequences include the addition of the entity to the publicly available arrears list and the refusal to receive any ANDA from such entity. See id. In addition, all drugs marketed pursuant to an ***approved*** ANDA held by the entity or its affiliate will be deemed misbranded. See id.

Finally, GDUFA II introduces a requirement that each entity that owns an ANDA or its designated affiliate must submit to FDA a list of all approved ANDAs owned by the entity and any approved ANDAs owned by any affiliates. See id. § 303(i).

B. FDA's GDUFA II Performance Goals[8]

In GDUFA II, all ANDAs and ANDA amendments would fall within a single, consolidated review goals scheme; however, GDUFA II categorizes ANDAs and their amendments as either "standard" or "priority." Under GDUFA II, FDA has committed to review and act on 90 percent of standard original ANDAs within 10 months of the date of ANDA submission and to review 90 percent of priority original ANDAs within 8 months of submission if the applicant submitted a complete, accurate, and unchanged Pre-Submission Facility Correspondence 2 months prior to ANDA submission.

With respect to ANDA amendments, GDUFA II commits FDA to reviewing and acting on 90 percent of standard major ANDA amendments within 8 months of amendment submission if preapproval inspection is not required and within 10 months if preapproval inspection is required. For priority major ANDA amendment submissions, FDA committed to reviewing and acting on 90 percent of priority major amendments within 6 months when no preapproval inspection is required and 8 months when it is required; however, if the priority applicant requiring preapproval inspection does not submit a complete and accurate Pre-Submission Facility Correspondence 2 months prior to amendment submission, FDA has 10 months to review and act on 90 percent of these amendments. FDA will review and act on 90 percent of standard and priority minor ANDA amendments within 3 months of the date of submission.

---

[8] The GDUFA II Performance Goals are available at https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf.

Even though application fees are no longer required for PASs, FDA commits to review goals for both standard and priority PASs. Ninety percent of standard PASs will be reviewed and acted on within 6 months of submission if preapproval inspection is not required and within 10 months if preapproval inspection is required. Priority PASs are reviewed within four months of submission if preapproval inspection is not required. If it is required, FDA will review and act on 90 percent of PASs within 8 months if the applicant submits a Pre-Submission Facility Correspondence 2 months prior to the date of PAS submission; otherwise, FDA will review and act on a priority PAS within 10 months. These same goals apply to major amendments to PASs while minor amendments have a goal of three months from the date of amendment submission.

FDA also commits to other reviews under GDUFA. For example, FDA will complete initial completeness assessment review for 90 percent of Type II API DMFs within 60 days of the later of the submission date or fee payment date. And FDA will review and respond to 90 percent of standard controlled correspondences within 60 days of submission and 90 percent of complex controlled correspondences within 120 days of submission.

Further, FDA agrees to additional program and review enhancements. GDUFA II establishes a pre-ANDA program to clarify regulatory expectations for prospective applicants early in product development and promote more efficient review. For a complex product, FDA will establish product development meetings to provide advice on ANDA development programs; pre-submission meetings to discuss the content and format of an ANDA; and mid-review cycle meetings to discuss deficiencies, concerns, and next steps. For non-complex products, FDA agrees to establish metric goals for the issuance of product-specific guidance to assist in generating evidence needed to support generic approval.

GDUFA II also provides an enhanced ANDA review program. The program is intended to expand the frequency and scope of communication between sponsors and reviewers and allow opportunities to correct deficiencies during the review cycle. Deficiencies are to be communicated starting at mid-point of review and continue on a rolling basis rather than in the Complete Response Letter to give applicants the opportunity to correct deficiencies during the review cycle. The Regulatory Product Manager will also communicate in advance about any major deficiencies or delays.

FDA also commits to several DMF review program enhancements. These include the communication of DMF review comments issued in parallel to the issuance of review comments relating to the DMF for the ANDA, as well as teleconferences to clarify deficiencies. Upon full scientific review, FDA will issue a “First Adequate Letter,” and

upon complete review and approval of the ANDA referencing the DMF, FDA will issue a "No Further Comment" letter. Finally, FDA commits to issuing a guidance regarding post-approval changes to Type II API DMF and for ANDA applicants who reference such DMFs.

GDUFA II requires FDA to issue guidance and conduct outreach to foreign regulators with respect to facility assessments. FDA will enhance the speed and transparency of communications concerning facility assessment and update its existing, publicly available facility compliance status database. GDUFA II also enhances accountability and reporting of progress towards GDUFA II goals and user fee resources evaluated by an independent third party.

FDA's GDUFA II commitments and enhancements are designed to increase the odds of first cycle approval, reduce the number of cycles to approval, and expand consumer access to quality, less expensive generic medicines.

IV. BIOSIMILAR USER FEE ACT OF 2017

FDARA also implements the first reauthorization of the Biosimilar User Fee Amendments ("BsUFA II") adopted in FDASIA in 2012 ("BsUFA I") and attempts to "overcome some of the unexpected challenges encountered with BsUFA I." Testimony of Janet Woodcock before the U.S. House of Rep. Comm. on Energy and Commerce Subcomm. on Health (Mar. 2, 2017). In particular, FDA struggled to meet its performance goals in BsUFA I; BsUFA II is therefore intended to improve predictability of funding levels and management of resources to permit more meetings and quicker advice. See id.

A. Significant Changes to BsUFA

BsUFA II makes relatively modest structural changes to BsUFA I. Like GDUFA, Congress removed the supplement fee in an effort to enhance predictability and removed the establishment fee for manufacturers. Congress adopted an additional annual biosimilar biological product fee called the "program fee." FDARA § 403(a)(13). The program fee is an annual fee and requires each entity named as the applicant in a biosimilar biological product application ("aBLA") to pay an annual fee for each biosimilar biological product identified in an approved aBLA as of October 1 of the fiscal year that does not appear on FDA's list of discontinued products. Id. This fee is due on October 1 of each fiscal year. Id. The fee is limited to once for each product for each fiscal year, but entities will not be assessed more than five biosimilar biological program fees in a fiscal year. Id.

In total, FDA intends to generate $45 million in total revenue from biosimilar user fees for FY 2018, to be adjusted in subsequent years. Id. § 403(b). All adjustments are to be published in the Federal Register and include a discussion of the methodologies used to determine such adjustments. FDARA § 403(c). However, the statute limits the annual adjustments to an increase of no more than $9 million per year and fee revenues may not be increased by more than 25 percent per year. Id. Additionally, fees assessed for a fiscal year may not exceed the total costs of the process for the review of biosimilar biological product applications. Id. The allocation structure of the revenue collected from biosimilar user fees is left to the discretion of FDA. Id. § 403(b).

B. FDA's BsUFA Performance Goals

In the BsUFA II Commitment Letter,[9] FDA agrees to an application review model similar to that of PDUFA VI for NME NDAs and original BLAs. It is intended to promote efficiency and effectiveness of first cycle review to support quicker application approvals. Under BsUFA II, FDA commits to reviewing and acting on 90 percent of original aBLAs within 10 months of the 30 day filing date and 90 percent of resubmitted original aBLAs within 6 months of receipt. Ninety percent of supplements with clinical data are to be reviewed within 10 months while 90 percent of resubmitted supplements with clinical data will be reviewed within 6 months. FDA commits to a gradual increase in the percentage of manufacturing supplements requiring approval that it will review within 4 months of receipt, starting at 70 percent in FY 2018 and rising to 90 percent by FY 2022. FDA will review and act on 90 percent of all other manufacturing supplements within 6 months of receipt.

Major amendments to any aBLA, supplement with clinical data, or resubmission may extend the BsUFA goal date by three months. This includes major new clinical study reports, re-analysis of previously submitted data, and Risk Evaluation and Mitigation Strategies. A major amendment to a manufacturing supplement may extend the goal date by two months. The addition of a manufacturing facility to an application may also extend the goal date by three months. However, only one extension may be given in any review cycle.

Adopting the PDUFA VI model, BsUFA II's goals also apply a "Program" to the review of all aBLAs to promote the efficiency and effectiveness of the first review cycle. The Program involves:

- a pre-submission meeting;
- the original application submission;

[9] The BsUFA II Performance Goals letter is available at https://www.fda.gov/downloads/forindustry/userfees/biosimilaruserfeeactbsufa/ucm521121.pdf.

- a Day 74 Letter, which communicates substantive review issues identified during initial filing review;

- review performance goals;

- mid-cycle communication, which provides a status report on the review of the application, including any significant issues and major concerns identified by the review team;

- late-cycle and Advisory Committee meetings;

- inspections to be completed within 10 months of original receipt of the application to allow 2 months to address deficiencies; and

- an assessment of the Program conducted by an independent contractor.

BsUFA II also establishes meeting management goals. Formal BsUFA meetings between sponsors and FDA consist of a Biosimilar Initial Advisory meeting to discuss a development program and BPD Type 1-4 meetings. Rather than the 90 days in BsUFA I, BsUFA II commits FDA to hold Biosimilar Initial Advisory meetings within 75 calendar days from receipt of the meeting request. BPD Type 2 meetings will occur within 90 calendar days, instead of 75 days as in BsUFA I, from receipt of the meeting request and meeting package. These goals will also be phased in from 80 percent in FY 2018 to 90 percent in FY 2022.

The BsUFA Commitment Letter also requires FDA to publish a revised draft guidance on Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants no later than September 30, 2018 and update the draft guidance on Best Practices for Communication Between IND Sponsors and FDA During Drug Development by December 31, 2018. FDA commits to publishing draft or final guidance describing the following:

- Considerations in Demonstrating Interchangeability with a Reference Product (draft on or before Dec. 31, 2017);

- Statistical Considerations for the Analysis of Analytic Similarity Data Intended to Support Demonstration of "Highly Similar" for Biosimilar Products (draft on or before Dec. 31, 2107);

- Processes and Further Considerations Related to Post-Approval Manufacturing Changes for Biosimilar Biological Products (draft on or before March 31, 2019);

- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (revised or final guidance on or before May 31, 2019);

- Nonproprietary Naming of Biological Products (revised or final guidance on or before May 31, 2019); and

- Labeling for Biosimilar Biological Products (revised or final guidance on or before May 31, 2019).

- Considerations in Demonstrating Interchangeability with a Reference Product, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, and Nonproprietary Naming of Biological Products have all been published or finalized.

Finally, FDA commits to improving the administration of the BsUFA program. Specifically, FDA intends to strengthen the staff capacity to develop, clarify, and communicate policy and information to the public, including maintaining the Purple Book. FDA will improve hiring, retention, and training of review staff. Additionally, FDA will work to simplify the administration of user fees and improve management of the program funding. Finally, FDA will conduct activities to enhance transparency of the BsUFA program's resources and enhance efficiency in the user fee program.

V. PEDIATRIC DRUGS AND DEVICES

A. Best Pharmaceuticals for Children

Originally enacted as part of FDAMA in 1997, the Best Pharmaceuticals for Children Act ("BPCA") provided a number of incentives for research and development of treatments for pediatric diseases, including six months marketing exclusivity for conducting certain pediatric-specific clinical studies. Congress reauthorized the BPCA in 2002, Pub. L. No. 107-109, 115 Stat. 1408 (2002), and made BPCA permanent as part of the 2012 FDA Safety and Innovation Act ("FDASIA"), Pub. L. 112-144, 126 Stat. 993 (2012). In addition to the pediatric marketing exclusivity incentive, the BPCA directs the National Institutes of Health ("NIH") to facilitate, fund, and prioritize clinical research into potential treatments for pediatric diseases. Funding for NIH grants is again reauthorized in FDARA § 501, providing an additional $25 million in NIH awards each year for an additional five years, through FY 2022.

Of interest, NIH funding for research into treatments of pediatric diseases is broadened to specifically include "identification of biomarkers for such diseases, disorders, or conditions." Additionally, FDARA § 501(2) requires NIH to make all reports of studies funded by the BPCA available on NIH's website and via an FDA public docket, where the public can submit comments on the research and reported results.

B. Pediatric Devices

Within one year after the enactment of FDARA, the Department of Health and Human Services ("HHS") will hold a public meeting regarding "the development, approval or clearance, and labeling of pediatric medical devices." See FDC Act § 515A(a)(3), as amended by FDARA § 502(d)(1). In its annual report regarding pediatric use of devices, FDA will also be required to include additional new information regarding pediatric devices, including devices used off-label for pediatric use which FDA determines could benefit pediatric patients, and the number of pediatric devices that receive a humanitarian device exemption (HDE) each year. See id. § 515A(a)(3), as amended by FDARA § 502(a)(2).

The Pediatric Medical Device Safety and Improvement Act of 2007 ("PMDSIA") provides for grants to nonprofit organizations to promote pediatric device development. See PMDSIA § 305. FDARA amends PMDSIA by requiring recipients of such grants to, among other things, provide "regulatory consultation to device sponsors in support of the submission of an application for a pediatric device, where appropriate." See id., as amended by FDARA § 502(c)(1)(C).

C. Early Meeting on Pediatric Study Plan

The Pediatric Research Equity Act ("PREA"), Pub. L. No. 108-155, 117 Stat. 1936 (2003), requires most drug and biological product sponsors to conduct pediatric studies unless the applicant has obtained a waiver or deferral. PREA was reauthorized as part of the FDA Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) ("FDAAA"), and made permanent as part of the 2012 FDASIA.

Under PREA, for new drugs and biologics, FDA has historically encouraged sponsors to meet with FDA as early as possible to discuss the initial pediatric study plan, but the FDC Act has only required that such a plan be submitted to FDA no later than 60 days after the end-of-phase 2 meeting and that FDA hold a meeting with the sponsor to discuss the plan within 90 days of its submission. See FDC Act § 505B(e)(2). FDARA § 503, however, expressly codifies FDA's policy for earlier meetings reflected in draft guidance since 2005. That guidance (still in draft form and yet to be finalized), states

that "[f]or products for life-threatening diseases, the review division will provide its best judgment at the end-of-phase 1 meetings on whether pediatric studies will be required under PREA and, if so, whether the submission will be deferred until after approval." FDA, Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act, 6 (Sept. 2005). This position was reiterated in 2016 in a draft guidance regarding pediatric study plans. FDA, Draft Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans, 3 (Mar. 2016). FDARA § 503 amends FDC Act § 505B(e)(2)(C) to require FDA to meet with sponsors of drugs or biological products intended to treat serious or life-threatening diseases within 30 days of a sponsor's request to have such a meeting or during the end-of-phase 1 meeting.

D. Development of Drugs and Biological Products for Pediatric Cancers

As mentioned above, PREA requires pediatric assessments for most new drug and biological products. One notable exception has been for orphan products. FDC Act § 505B(k) states that, unless otherwise required by regulation, PREA "does not apply to any drug for an indication for which orphan designation has been granted." To date, FDA has not promulgated any regulation that would require compliance with PREA for any orphan product. On the contrary, FDA has specifically reiterated the PREA exemption via regulation; 21 C.F.R. § 314.55(d) unconditionally exempts all orphan-designated products from PREA requirements.

FDARA § 504 amends the PREA provisions in the FDC Act to require pediatric assessments for certain drugs and biological products intended to treat adult and pediatric cancers, even if such products are designated as orphan products. As amended, FDC Act § 505B(a)(1)(B) specifies molecularly targeted cancer products as those drug or biological products that are (1) "intended for the treatment of an adult cancer" and (2) "directed at a molecular target the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer." FDARA § 504(a). The orphan product exemption is amended by FDARA § 504(b) to expressly state that products that meet the new FDC Act § 505B(a)(1)(B) criteria are not exempt from PREA even if they are designated as orphan products.

Congress directs FDA, in consultation with the National Cancer Institute, to hold a public meeting within one year of enactment during which FDA will solicit input regarding: what molecular targets are "substantially relevant" to pediatric cancers; what data should be required to satisfy the PREA requirements (i.e., what pediatric studies should be required); the process for updating the list of molecular targets subject to PREA requirements; barriers to conducting clinical trials in pediatric cancer populations;

how FDA can encourage research in pediatric cancer; how FDA can facilitate collaboration among pediatric cancer networks and sponsors of same-in-class products; and how to avoid discouraging research and development of orphan products intended to treat such cancers. Within two years of enactment, FDA is directed to issue guidance regarding implementation of FDARA § 504. Five years after enactment, GAO is directed to conduct a study regarding implementation of FDARA § 504 and submit its report to FDA, the House Energy and Commerce Committee, and the Senate Health, Education, Labor, and Pensions ("HELP") Committee.

E. Additional Provisions on Development of Drugs and Biological Products for Pediatric Use

In 2007, FDAAA established the Pediatric Review Committee ("PeRC"), which is an internal committee charged with reviewing Written Requests under the BPCA and deferral and waiver requests under PREA. The PeRC will now also be provided with copies of any responses that FDA gives to sponsors regarding proposed pediatric studies as well as copies of any letters issued under FDC Act § 505B(d)(1) to sponsors who fail to submit required PREA pediatric assessments. FDARA § 505(a) and (e). The PeRC is also directed to include expertise in pediatric rare diseases as part of its core capabilities. FDARA § 505(f).

With respect to sponsor submissions regarding pediatric studies, FDA is directed to respond to such submissions within 120 days (FDA had no statutory timeline for its reviews previously). Id. § 505(b).

FDARA further directs FDA "to develop and implement a plan to achieve, when appropriate, earlier submission of pediatric studies." Id. § 505(c). The plan is constructed to include earlier discussions with sponsors regarding pediatric study plans as well as earlier issuance of requests for pediatric studies. See id.

The Office of Pediatric Therapeutics, which was established as part of the BPCA 2002 reauthorization, had been temporarily required to include staff with experience in neonatology. That temporary requirement was extended in 2012 with FDASIA. FDARA § 505(d) makes the requirement for neonatology experience permanent and directs FDA to issue guidance regarding clinical pharmacology studies in neonates.

Finally, FDA is directed to issue a report to the Secretary, the House Energy and Commerce Committee and the Senate HELP Committee within two years regarding labeling of approved products with orphan designated indications. Specifically, FDA is to report on the use of orphan products in pediatric patients and the adequacy of the labeling of those products for pediatric populations. When combined with the GAO

reports regarding mandatory pediatric studies for certain pediatric cancers, discussed above in section V.D, it will be interesting to see whether Congress later seeks to remove the orphan product PREA exemption in its entirety or to continue a piece-meal roll-back of that exemption.

VI. REAUTHORIZATIONS AND IMPROVEMENTS RELATED TO DRUGS

A. Reauthorization of Provision Relating to Exclusivity of Certain Drugs Containing Single Enantiomers

FDAAA § 1113 amended the FDC Act to permit the applicant of a 505(b)(1) NDA for an enantiomer (that is contained in an approved racemic mixture) containing full reports of clinical investigations conducted or sponsored by the applicant (and that does not rely on information in another NDA), among other things, to "elect to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug" so as to qualify for a period of five-year New Chemical Entity ("NCE") exclusivity. FDC Act § 505(u)(1). Thus far, FDA has awarded a single period of NCE exclusivity based on the election provided for under FDC Act § 505(u). FDC Act § 505(u) was scheduled to sunset on September 30, 2012. See id. § 505(u)(4).

FDASIA § 1107 reauthorized FDC Act § 505(u) for an additional five years, such that the provision was scheduled to sunset on September 30, 2017. FDARA § 601 reauthorizes FDC Act § 505(u) for an additional five years, such that the provision is now scheduled to sunset on September 30, 2022.

B. Reauthorization of the Critical Path Public-Private Partnerships

FDASIA § 1102 amended FDC Act § 566 to authorize $6 million in appropriations for each of FYs 2013 through 2017. See FDC Act § 566(f), as amended by FDASIA § 1102. FDC Act § 566 was added to the law by FDAAA § 603, and provides for the establishment of certain partnerships between FDA and eligible non-profit and higher education institutions to advance FDA's Critical Path Initiative. The Critical Path Initiative is FDA's effort to modernize the scientific process through which a potential drug, biologic, or medical device is transformed from discovery into a medical product. FDARA § 602 reauthorizes the Critical Path Public-Private Partnerships through FY 2022.

C. Reauthorization of Orphan Grants Program

FDARA § 603 reauthorizes the Orphan Grants Program to defray the costs of developing drugs, devices, and medical food for rare conditions through FY 2022.

D. Protecting and Strengthening the Drug Supply Chain

FDARA § 604 amends FDC Act § 801(d) to restrict the import of prescription drugs into the United States for commercial use if such a drug is manufactured outside the United States unless authorized by the manufacturer and the manufacturer has labeled the drug to be marketed in the United States. Exceptions include drugs on FDA's drug shortage list, and drugs imported by a pharmacist or wholesaler from Canada pursuant to HHS/FDA regulations. This section also creates imprisonment and fine penalties that can be leveraged against persons who knowingly make, dispense, or hold for sale/dispense a counterfeit drug.

E. Patient Experience Data

FDARA § 605 amends FDC Act § 569C, which was amended in the 21st Century Cures Act enacted in December 2016 to require a statement of patient experience data submitted and reviewed at the time of approval of new drugs and biologics, by revising the definition of patient experience data to specifically include physical and psychosocial impacts of a condition, or related therapy or clinical investigation.

F. Communication Plans

FDARA § 606 amends the FDC Act § 505-1(e)(3) to allow the communication plan for a Risk Evaluation and Mitigation Strategy ("REMS") to include information to health care providers about the limitations or patient care implications of drug formulations or properties and how those formulations or properties may be related to serious adverse drug events.

G. Orphan Drugs

FDARA § 607 amends FDC Act § 527 to effectively codify FDA's orphan drug regulations, see 21 C.F.R. § 316.3(b)(3), to require that the sponsor of a designated drug or biological product that is the same as an approved product for the same rare disease or condition demonstrate that its product is "clinically superior" to the previously approved product (i.e., that the subsequent product is demonstrated to have greater efficacy, greater safety, or provides a major contribution to patient care) in order to obtain a period of 7-year orphan drug exclusivity.

This change in the law, which, according to a "rule of construction," does not "affect any determination under [FDC Act §§ 526 and 527] made prior to the date of enactment of [FDARA]," FDARA § 607(b), is a response to a 2014 court ruling that "the plain language of the Orphan Drug Act requires the FDA to recognize exclusivity" if a company obtains approval of a drug designated as an orphan drug, and that FDA's regulatory requirement that a demonstration of clinical superiority is needed to obtain orphan drug exclusivity is not supported by the statute. Depomed, Inc. v. U.S. HHS, 66 F. Supp. 3d 217 (D.D.C. 2014).

FDARA § 607 also requires FDA to "publish a summary of the clinical superiority findings" after the Agency grants orphan drug exclusivity on the basis of a demonstration of clinical superiority. FDC Act § 527(e), as amended by FDARA § 607(a).

H. Pediatric Information Added to Labeling

FDARA § 608 amends FDC Act § 505A(o), which is part of the Best Pharmaceuticals for Children Act ("BPCA"), to extend the provision to 505(b)(2) NDAs and to clarify the types of exclusivity covered.

By way of background, FDC Act § 505A(o), previously titled "Prompt approval of drugs under section 505(j) when pediatric information is added to labeling," allowed only an ANDA applicant to omit from its labeling certain patent- and/or exclusivity-protected information concerning the pediatric use of a drug, and to include a disclaimer with respect to the omitted information. The BPCA neither addressed the omission or retention of protected pediatric information from 505(b)(2) NDA product labeling, nor did the BPCA address the use of disclaimers for protected pediatric use information that is omitted from 505(b)(2) NDA product labeling.

Previously, if FDA determined that protected pediatric information is important safety information and must be retained in 505(b)(2) NDA product labeling for reasons of safe use, then FDA would not approve an affected 505(b)(2) NDA until the expiration of exclusivity. FDA could, however, approve an ANDA for a similar product because of FDC Act § 505A(o). Thus, the statute created an inequity among ANDA and 505(b)(2) NDA applicants. FDARA § 608 remedies this inequity to make FDC Act § 505A(o) equally applicable to ANDA and 505(b)(2) NDA applicants.[10]

[10] FDARA § 608 was proposed, and ultimately enacted, as a result of an FDA Law Blog post that first raised the issue. See Kurt R. Karst, FDA Law Blog, "Should the Best Pharmaceuticals for Children Act be Amended to Accommodate 505(b)(2) NDA Labeling Carve-outs?" (Mar. 6, 2017).

I. Sense of Congress on Lowering the Cost of Prescription Drugs

FDARA § 609 implores HHS to commit to engagement with Congress to take administrative actions and enact legislation that will lower the cost of prescription drugs for consumers and reduce the burden of such cost on taxpayers, while balancing the need to encourage innovation, as well as striving to increase competition and prevent anticompetitive behavior related to the timely availability of generic drugs and biosimilars.

J. Expanded Access

FDARA § 610 requires FDA, in coordination with NIH, to convene a meeting (within 270 days after the date of enactment of FDARA) to discuss clinical trial inclusion and exclusion criteria to inform a report on the meeting and the issuance of guidance (within one year of the report) regarding eligibility criteria for clinical trials.

The meeting must include a discussion of the rationale for, and potential barriers for patients created by, inclusion and exclusion criteria. It must also discuss how appropriate patient populations can benefit from the results of trials that employ alternative designs. The meeting will cover barriers to participation in clinical trials, including (1) information regarding potential risks and benefits of participation; (2) regulatory, geographical, and socioeconomic barriers; and (3) the impact of exclusion criteria on enrollment of particular populations, including infants and children, pregnant and lactating women, seniors, individuals with advanced disease, and individuals with co-morbid conditions.

The meeting will also include discussion of trial designs and methods, including expanded access protocols that increase enrollment in more diverse patient populations, when appropriate, while facilitating collection to establish safety and effectiveness. Finally, the meeting will discuss how changes in inclusion and exclusion criteria may impact the complexity and length of clinical trials, the data needed to establish safety and effectiveness, and potential approaches to mitigating those impacts.

The draft guidance must address methodological approaches that sponsors may take to broaden eligibility criteria, develop eligibility criteria so they more accurately reflect the patients most likely to receive the drug, and use these criteria in the context of rare disease drug development.

This section also includes a number of provisions intended to facilitate Expanded Access. GAO must issue a report (within one year of the report on inclusion/exclusion

criteria) on individual access to investigational drugs through the Expanded Access program. Furthermore, FDA must issue and revise guidance or regulations to streamline the institutional review board of individual patient expanded access protocols. FDC Act § 561A(f) is also amended to require the sponsor of an investigational drug for a serious condition to publish an Expanded Access Policy within 15 days of the drug receiving designation as breakthrough therapy, fast track, or regenerative medicine advanced therapy.

K. Tropical Disease Product Application

FDARA § 611 amends FDC Act § 524(a)(4) to revise the Tropical Disease Priority Review Voucher program to limit eligibility to applications that include one or more new clinical investigations (other than bioavailability studies) that are essential to the approval of the application and were conducted/sponsored by the sponsor of the application and that were not submitted as part of an application in India, Brazil, Thailand, or any country that is a member of the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Cooperative Scheme prior to September 27, 2007. This provision only applies to applications submitted after September 30, 2017.

VII. MEDICAL DEVICE INSPECTION AND REGULATORY IMPROVEMENTS

A. Risk-based Inspections for Devices

FDARA § 701 amends FDC Act § 510(h) to require FDA to switch from biennial inspections to a risk-based schedule for inspecting manufacturers of Class II and Class III devices. The risk-based schedule was already a mandate for inspections of drug manufacturers under section 510(h). In addition to the four risk factors already set forth in section 510(h) (e.g., compliance history), the new provision adds a fifth risk factor just for devices – whether a manufacturer participates in international device audit programs that the Untied States participates in or recognizes. This dovetails nicely with FDA's long-standing effort toward global harmonization of device regulation.

B. Improvements to Inspections Process for Device Establishments

FDARA § 702 amends FDC Act § 704. It requires FDA to update its processes and standards for routine inspections (not those conducted "for cause") to achieve uniformity (with appropriate exceptions), provide advance notice of inspection, provide the establishment with a reasonable estimate of the timeframe (and an opportunity for advance communications), and regulation communications during the inspection regarding its status, "which may be recorded by either party with advance notice and

mutual consent." It will be interesting to see whether FDA consents to such recordings. As to the other ideas, FDA has adopted many of them administratively, although they have not been uniformly implemented in a transparent way. This provision may bring greater certainty that these practices are important routine requirements the Agency must follow (with appropriately defined exceptions) and not mere administratively granted privileges.

Another amendment is to require FDA to provide "nonbinding feedback" within 45 days of a timely request for feedback on the manufacturers proposed action in response to 483 observations "that involve a public health priority, that implicate systemic or major actions, or relate to emerging safety issues (as determined by [FDA])." This provision seems addressed to the difficulty manufacturers sometimes have when proposing major corrective actions in response to a Form 483 of getting FDA to provide views on whether or not such actions are likely to be considered sufficient.

FDA is directed to prepare a draft guidance on its implementation of this provision within 18 months, and to finalize the guidance based upon notice and comment within 12 months after issuing the draft.

Under section 501(j), a drug is adulterated if the manufacturer refuses entry or inspection. That provision is now made applicable to devices. This change raises the stakes when a device manufacturer seeks to limit the bounds of the inspection to what it believes section 704 permits and the investigator disagrees and threatens to find a "refusal."

C. Certificates to Foreign Governments for Devices

One of the most painful consequences of a bad inspection at a U.S. facility has been FDA's refusal to issue Certificates to Foreign Governments ("CFG") until the issues are resolved. CFGs are quite often a requirement to renew licenses and permits to sell in various foreign markets. Although typically linked to a Warning Letter, sometimes a Form 483 can trigger this refusal. Sometimes it can take many months, or more than a year, for FDA to begin issuing CFGs again. During that time period, a manufacturer may find itself unable to renew marketing permits in foreign markets.

As a general matter, FDA's theory has been that a CFG requires a statement that the facility is in substantial compliance with the Quality System Regulation ("QSR") and it should not be issued when there is an outstanding Form 483 or Warning Letter finding that the facility is not in such compliance. There has been very little transparency, however, as to when FDA will refuse CFGs and what it takes to resolve the situation.

FDARA § 704 amends the FDC act § 801 to provide that FDA must provide a written statement of the basis for denying a request for a CFG "and [must] specifically identify the finding upon which such denial is based." If the denial is based on a routine inspectional finding that a facility is out of compliance with the QSR, FDA must "provide a substantive summary of the specific grounds for noncompliance identified by the [inspector]." Furthermore, a CFG may not be denied based upon a Form 483 if the manufacturer "has agreed to a plan of correction in response to such report."

FDA is directed to set up a process that appears to be essentially equivalent to supervisory appeals of significant decisions. In addition, a manufacturer denied a CFG may at any time "request a review in order to present new information" relating to corrective actions.

FDA is directed to issue draft guidance on these new processes within 12 months, followed by a final guidance within another 12 months. This provision is a welcome development that should make FDA's denials of CFGs more transparent, more directly linked to unresolved QSR violations, and easier to lift if appropriate corrective actions are put in place.

D. Facilitating International Harmonization

FDARA § 705 authorizes FDA to recognize auditing organizations that are recognized in foreign countries in order to facilitate international harmonization of device inspections.

E. Fostering Innovation in Medical Imaging

A perennial issue is how FDA can permit innovation in medical imaging devices that outruns the labeling of contrast agents used with these devices. (The contrast agents are regulated as drugs.) For example, a contrast agent might have approved labeling for imaging the liver, but not the lung. If a medical imaging device can safely and effectively use the same contrast agent to image the lung, under current law, FDA cannot clear or approve the device for this use, because doing so would contradict the drug labeling.

FDARA § 706 modifies the FDC Act to address this problem. It would allow FDA to clear or approve a medical imaging device, even when it finds that a new use of a contrast agent departs from the approved drug labeling, if it also finds that the new use does not adversely affect safety or effectiveness. The new use may involve a difference in concentration, rate of administration, route of administration, region, organ or system

of the body, and/or patient population. CDRH is designated to have primary jurisdiction to conduct this review, in consultation with CDER and/or CBER, as necessary.

If the new use is cleared or approved for the medical imaging device, the contrast agent manufacturer is authorized to submit a supplement to CDER and bring the new use into the drug labeling. If the device manufacturer provides a right of reference, the contrast agent manufacturer can refer to the data provided to CDRH to obtain clearance or approval of the new use.

F. Risk-based Classification of Accessories

FDA has historically classified accessories in one of two ways: (1) according to the parent device's classification (either by express inclusion in the classification regulation or by clearance or approval of an accessory under the parent device's classification regulation); or (2) by establishment of a separate classification regulation specific to the accessory type. This classification scheme led to a number of issues. For example, accessories classified according to the parent device's classification were, in at least some instances, being over-regulated.

With regard to accessories that were separately classified, these accessories were presumably classified based on the risk that they present, separately from the parent device. These classification regulations typically classified the accessory as lower risk than the device. For example, Endosseous dental implant accessories are Class I devices whereas Endosseous dental implants are Class II devices. 21 C.F.R. §§ 872.3980 and 872.3640. In practice, however, FDA has not always utilized the appropriate accessory classification regulation, even when it existed, leading to some accessories being classified under the higher, parent device classification regulation.

In short, FDA's scheme for classifying accessories led to some accessories being over-regulated because they are not as risky as the parent device (but they were classified according to the parent device), or a somewhat confusing scheme of certain accessories having their own classification but a subset of those accessories being classified under the parent device classification.

FDA sought to resolve this issue for new types of accessories (i.e., accessories not previously classified according to one of the methods described above) in January 2015 when it released the draft guidance "Medical Device Accessories – Defining Accessories and Classification Pathway for New Accessory Types." The draft guidance acknowledged that some accessories present less risk than the parent device with which they are used and should not, accordingly, be automatically placed in the same class as the parent device. The draft guidance proposed that sponsors should utilize the *de*

novo process for new types of accessories (i.e., not yet classified) for which the risk is less than the parent device. The *de novo* process would allow for the risk-based classification of the new accessory type on its own.

Almost two years after FDA's release of the draft guidance, Congress, apparently agreeing with FDA's proposal, passed the 21st Century Cures Act ("Cures") amending FDC Act § 513(b). The new provision directs the Agency to "classify an accessory . . . based on the risks of the accessory when used as intended . . . notwithstanding the classification of any other device with which such accessory is intended to be used." FDA finalized the draft guidance document with virtually no changes after Congress's change to the law.

Congress's directive in Cures was new – classify devices based on their risk independent of the parent device. FDA's draft and final guidances also only addressed new types of accessories. Thus, neither Congress nor FDA addressed the large body of accessories classified prior to passage of Cures. The only option for reclassification of these accessories would be to submit a petition for reclassification under 21 C.F.R. § 860.123. Petitions for reclassification are seldom used and the Agency is typically slow to respond.

FDARA seeks to solve this problem in section 707 by establishing a streamlined method for classifying and re-classifying accessories based on their risk, separate from the parent device with which they are used. See FDC Act § 513, as amended by FDARA § 707. For accessories not previously classified, when a sponsor submits a 510(k) or PMA for a parent device with an accessory, the sponsor may include a request for classification of the accessory based on its risk. See id. § 513, as amended by FDARA § 707(a). FDA's clearance or approval letter shall include a granting or denial for the sponsor's request. See id.

In addition, for accessories previously classified according to the parent device with which they are used, within one year of the enactment of FDARA and at least once every five years thereafter, FDA will publish a list of accessories that it determines are suitable for classification into Class I. See id. FDA shall consider recommendations from device sponsors. See id.

Alternatively, manufacturers and importers of devices may submit a written request to the Agency for reclassification of an accessory. See id. FDA shall respond to such a request within 85 calendar days of receipt by issuing a written order classifying the accessory or denying the request. See id. If the request is denied, FDA shall provide a detailed description and justification for such determination. Within 30 days of granting a request, FDA shall publish a notice of the reclassification in the Federal

Register. See id. FDA shall also provide the requestor with an opportunity to meet with appropriate Agency personnel prior to submitting such a request. See id.

G. Device Pilot Projects

FDARA § 708 authorizes new pilot projects (and continuance of existing projects) designed to test whether and how FDA can use postmarket data and real world data to improve how it regulates devices. An evaluation report by an independent third party must be provided to Congress by January 31, 2021.

H. Regulation of Over-the-Counter Hearing Aids

The basic federal and state approach to hearing aid regulation has changed little since the 1970s. Yet, the technology has evolved dramatically. One of the emerging new capabilities of the technology is to enable consumers to program the hearing aids to their satisfaction without the intervention of an audiologist. In most states, however, an audiologist by law must dispense hearing aids.

This section directs FDA within three years to promulgate proposed regulations establishing requirements for defining a category of hearing aids that can be safely and effectively sold OTC to individuals with mild to moderate hearing loss. The regulations must be finalized within six months of the close of the public comment period. The category must exclude personal sound amplification products ("PSAPs") that are sometimes sold OTC as hearing aids, but which amplify all sounds and do not permit customization based upon frequencies.

The new regulations will preempt state law that prevents the marketing, sale, and distribution of OTC hearing aids. The preemption does not affect private lawsuits under state law based upon product liability, tort, warranty, contract, or consumer protection law.

FDA must report to Congress on adverse events involving OTC hearing aids within two years after the final regulations are issued.

I. Report on Servicing of Devices

Within 270 days of FDARA's enactment, FDA shall post on its website a report on the "continued quality, safety, and effectiveness of devices . . . with respect to servicing." It appears that Congress wants to understand how FDA regulates servicing now, and whether such regulation can be improved.

VIII. IMPROVING GENERIC DRUG ACCESS

Title VIII of FDARA includes several provisions intended to speed, promote, and enhance generic drug competition.

A. Priority Review of Generic Drugs

FDARA § 801 amends FDC Act § 505(j) to create new 8-month priority review pathway for both ANDAs for which the brand-name reference product has less than three approved generics (and for which there are no blocking patents and exclusivities), and ANDAs for products included on FDA's drug shortage list pursuant to FDC Act § 506E. To qualify for priority review, an ANDA applicant must provide FDA with "complete, accurate information regarding facilities involved in manufacturing processes and testing of the drug that is the subject of the application, including facilities in corresponding Type II active pharmaceutical ingredients drug master files referenced in an application and sites or organizations involved in bioequivalence and clinical studies used to support the application" not later than 60 days prior to ANDA submission. FDC Act § 505(j)(11)(B), as amended by FDARA § 801. In anticipation of the enactment of FDARA, FDA issued a guidance document in June 2017, titled "ANDAs: Pre-Submission Facility Correspondence Associated with Priority Submissions," that further discusses the pre-submission facility correspondence process and procedures.

FDARA § 801 also requires FDA to publish an updated list of all drugs for which all patents and periods of exclusivity have expired, and for which FDA has not approved an ANDA referencing the product. Prior to enactment of FDARA, FDA published the first version of this list in June 2017.[11]

B. Enhancing Regulatory Transparency to Enhance Generic Competition

FDARA § 802 is intended to improve communication between FDA and ANDA sponsors about the status of their applications. Specifically, FDARA amends FDC Act § 505(j) to provide that "[u]pon the request of an applicant regarding one or more specified pending applications under this subsection, [FDA] shall, as appropriate, provide

[11] See FDA, List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic, available at https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM564441.pdf.

review status updates indicating the categorical status of the applications by each relevant review discipline." FDC Act § 505(j)(13), as amended by FDARA § 802.

C. Competitive Generic Therapies & Incentivizing Competitive Generic Drug Development

FDARA § 803 amends the FDC Act to add Section 506H, titled "Competitive Generic Therapies," and authorizes FDA to designate a drug as a "competitive generic therapy" upon request by the applicant when there is "inadequate generic competition;" that is, when there is no more than one approved ANDA for its corresponding reference product listed in the Orange Book (not including discontinued products). FDC Act § 506H(b)(3), as amended by FDARA § 803(a). A request for designation of a drug as a "competitive generic therapy" must be made to FDA prior to or concurrent with ANDA submission, see id. § 506H(b)(2), as amended by FDARA § 803(a), and FDA may act on the request within 60 days after receiving the request, see id. § 506H(b)(4), as amended by FDARA § 803(a). FDA is required to issue guidance on the new designation process within 18 months of FDARA's enactment. See FDARA § 803(b).

A generic drug manufacturer who obtains designation of a drug as a "competitive generic therapy" is eligible for certain benefits, including enhanced communications with FDA officials and advice from the Agency. See FDC Act § 506H(c), as amended by FDARA § 803(a).

FDARA § 808 institutes a new 180-day exclusivity period available only to the "first approved applicant" of an ANDA for a "competitive generic therapy." A "competitive generic therapy" is defined as both a drug designated as a "competitive generic therapy" pursuant to FDC Act § 506H, and as a drug for which there are no unexpired patents or exclusivities listed in the Orange Book at the time of ANDA submission. FDC Act § 505(j)(5)(B)(v)(III)(aa), as amended by FDARA § 808. Competitive generic therapy 180-day exclusivity operates in a manner similar to "traditional" 180-day exclusivity in that it prevents FDA from approving another ANDA for the same product until the date that is 180 days after first commercial marketing of the competitive generic therapy. See id. § 505(j)(5)(B)(v)(I), as amended by FDARA § 808. In addition, eligibility for competitive generic therapy 180-day exclusivity may be forfeited if the ANDA applicant "fails to market the competitive generic therapy within 75 days after the date on which the approval of the first approved applicant's application for the competitive generic therapy is made effective." FDC Act § 505(j)(5)(D)(iv), as amended by FDARA § 808.

D. Accurate Information About Drugs with Limited Competition

In an effort to ensure complete and accurate information on approved drug products listed in the Orange Book, FDARA § 804 amends the FDC Act to add Section 506I, titled "Prompt Reports of Marketing Status," and requires NDA and ANDA holders to report certain information to FDA. First, application sponsors must notify FDA in writing "180 days prior to withdrawing [an] approved drug from sale, or if 180 days is not practicable as soon as practicable but not later than the date of withdrawal." FDC Act § 506I(a), as amended by FDARA § 804. Second, application sponsors must notify FDA in writing "within 180 calendar days of the date of approval of the drug if the drug will not be available for sale within 180 calendar days of such date of approval." Id. § 506I(b), as amended by FDARA § 804. Third, within 180-days of FDARA's enactment, NDA and ANDA holders must notify FDA in writing which of their drugs listed in the active section of the Orange Book are available for sale and which drugs ar not marketed or have never been available for sale. See id. § 506I(c), as amended by FDARA § 804. A sponsor's failure to meet any of the reporting requirements above allows FDA to move such sponsor's drugs from the active to the inactive section of the Orange Book. See id. § 506I(d), as amended by FDARA § 804.

E. Suitability Petitions

The FDC Act requires FDA to "approve or disapprove a [suitability] petition . . . within ***ninety days*** of the date the petition is submitted." FDC Act § 505(j)(2)(C) (emphasis added). FDA rarely meets this statutory deadline. Instead, ANDA suitability petitions languish at FDA, sometimes for years, without a decision. See Kurt R. Karst, Letting the Devil Ride: Thirty Years of ANDA Suitability Petitions Under the Hatch-Waxman Act, 40 Wm. Mitchell L. Rev. 1260 (2014).

FDARA § 805 includes a "sense of Congress" provision stating that FDA "shall meet the requirement under [FDC Act § 505(j)(2)(C)] and [21 C.F.R. § 314.93(e)] of responding to suitability petitions within 90 days of submission." FDARA § 805(a). In addition, the GDUFA II Performance Goals Letter states that "FDA aspires to respond to Suitability Petitions in a more timely and predictable manner," and requires FDA to report on the "[n]umber of suitability petitions pending a substantive response for more than 270 days from the date of receipt." GDUFA II Performance Goals Letter at 23. FDARA § 805 also requires FDA to report annually on the number of pending suitability petitions, including the number of petitions pending a substantive response for more than 180 days from Agency receipt. See FDARA § 805(b).

F. Inspections

FDARA § 806 requires FDA to develop and implement within six months of FDARA's enactment "a protocol for expediting review of timely responses to reports of observations from an inspection under [FDC Act § 704]." FDARA § 806. The FDA protocol will apply to inspection report responses pertaining to NDAs and ANDAs "for which the approval is dependent upon remediation of conditions identified in the report," "for which concerns related to observations from an inspection . . . are the only barrier to approval," and "where the drug that is the subject of the application is a drug (i) for which there are not more than 3 other approved [ANDAs] that reference the same listed drug and for which there are less than 6 [ANDAs] tentatively approved; or (ii) that is included on [FDA's drug shortage list]." FDARA § 806. In addition, FDA's protocol will address expedited facility re-inspection and will establish a 6-month timeline for completion of review of inspection report responses. See id.

G. Reporting on Pending Generic Drug Applications and Priority Review Applications & GAO Study of Issues Regarding First Cycle Approvals of Generic Medicines

FDARA § 807 requires FDA to report quarterly on the number of pending and approved ANDAs subject to priority review under new FDC Act § 505(j)(11) and expedited review under new FDC Act § 506H.

FDARA § 809 directs the GAO to study and to issue a report on the rate of ANDAs that are approved on the first review cycle and related issues.

IX. OTHER PROVISIONS

A. Technical Corrections

As its title states, FDARA § 901 largely deals with fixing typographical and other scrivener errors contained in the 21st Century Cures Act ("Cures"). For example, FDARA § 901(b) changes the word "identity" to "identify" in a provision that now correctly requires FDA to "identify opportunities to help advance the development of regenerative medicine therapies and regenerative advanced therapies."

Some of the so-called technical corrections, however, make substantive changes. FDARA § 901(d) extends the timeline FDA is given to implement the program to utilize "real world evidence" by an additional year. Now FDA has until December 13, 2019 to implement this program. FDARA § 901(c) changes the definition of "real world evidence" from data "derived from sources other than randomized clinical trials" to data

"derived from sources other than traditional clinical trials." While this change appears a non-controversial acknowledgement that FDA has permitted studies of non-randomized trials to serve as substantial evidence of effectiveness, the change in the definition's language will limit what data constitutes "real world evidence" and it introduces ambiguity to the definition to the extent that it is not immediately self-evident what types of studies are "traditional clinical trials."

Lastly, FDARA § 901(h) changes the potential for medical device sponsors to provide recommendations for medical device classification panel members. Under the 21st Century Cures Act, "sponsors of medical device submissions" were given the opportunity to provide panel member recommendations to FDA. Now, FDC Act § 513(b)(5)(D), as amended by FDARA § 901(h), permits only "sponsors of medical devices that may be specifically the subject of a review by a classification panel" to make panel recommendations.

B. Annual Report on Inspections

FDARA § 902 requires FDA to post on its website, by March 1st of each year, a detailed report regarding the previous calendar year's inspection activities. Specifically, the report will include:

- The median time from when review staff request an inspection until the start of the inspection;
- The median length of time of inspections, measured from issuance of the Form FDA 482 to the Form FDA 483;
- The median length of time from issuance of a Form 483 to each of sending a Warning Letter, issuance of an import alert, and holding of a regulatory meeting regarding the inspection during which it is concluded that regulatory or enforcement action was indicated;
- The median length of time from each of sending a Warning Letter, issuance of an import alert, and holding of a regulatory meeting regarding the inspection during which it is concluded that regulatory or enforcement action was indicated to resolution of those issues; and
- The number of times a Form FDA 483 was issued that resulted in delay of approval of an application.

C. Streamlining and Improving Consistency in Performance Reporting

FDARA § 903 makes several changes to each of the PDUFA, MDUFA, GDUFA, and BsUFA reporting requirements detailed in Titles I through IV. Specifically, FDARA § 903 requires each user fee program to include quarterly "real time" reports and attempts to harmonize those reports to the extent possible given the differences among the various products governed by the four user fee programs. The goal is to elicit from FDA more consistently reported data and information regarding FDA's progress to reaching goals outlined in each user fee program's goals letter.

D. Analysis of Use of Funds

Similar to FDARA § 903, FDARA § 904 deals with changes to FDA's reporting requirements under each of the four human medical product user fee programs. For each program, FDA is required to issue annual reports to Congress regarding performance goals met and missed, including justifications for missed goals, and is required to meet with members of Congress when requested and to participate in Congressional hearings when requested.

E. Facilities Management

Under FDARA § 905, the Comptroller General of the United States is required to conduct a detailed assessment of FDA's expenses related to maintenance and renovation of facilities during the seven years starting with FDASIA's reauthorization, specifically FYs 2012-2019. Beyond a simple accounting of FDA's facility-related finances, the Comptroller General is asked to assess whether FDA's facilities are managed such that FDA demonstrates it has the "ability to further its public health mission." See FDARA § 905(a)(1)(B). Expressing its current skepticism with FDA's management of its facilities, Congress included provisions in FDARA § 905(b) that strip FDA at the start of FY 2023 (i.e., October 1, 2022) of the ability to allocate user fees for "leasing, maintenance, renovation, and repair of facilities and acquisition, maintenance, and repair of fixtures, furniture, scientific equipment, and other necessary materials and supplies." Rather, FDA is permitted to only use such fees for expenditures for "leasing and necessary scientific equipment." We presume that the Comptroller General's report will be front and center in time for the next round of negotiations in 2022 and that FDA will be very interested in restoring funding for facility, fixture, and furniture acquisition, maintenance, renovation, and repairs.

###

The information in this memorandum is not intended as legal advice. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein. For more information about this memorandum or about FDARA, please contact Kurt R. Karst (kkarst@hpm.com) for issues concerning drug or biological products, or Jeffrey K. Shapiro (jshapiro@hpm.com) for issues concerning medical devices.