COMMITTEE ON
ENERGY & COMMERCE
CHAIRMAN FRANK PALLONE, JR.

MEMORANDUM

February 1, 2022

To: Subcommittee on Health Members and Staff

Fr: Committee on Energy and Commerce Staff

Re: Hearing on "FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics"

On **Thursday, February 3, 2022, at 10:30 a.m. (EST), in the John D. Dingell Room, 2123 of the Rayburn House Office Building, and via Cisco WebEx online video conferencing**, the Subcommittee on Health will hold a hearing entitled "FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics."

I. BACKGROUND

The Prescription Drug User Fee Act (PDUFA), first passed in 1992 and reauthorized five times since then, authorizes the Food and Drug Administration (FDA) to collect user fees from companies producing certain human drug and biological products. These fees supplement funds appropriated to FDA to ensure New Drug Applications (NDAs) and Biologics License Applications (BLAs) are reviewed in a timely manner. Similarly, the Generic Drug User Fee Amendments (GDUFA) and the Biosimilar User Fee Act (BsUFA) authorize FDA to collect fees to supplement appropriated funds to ensure generic drugs and biosimilar product applications receive timely reviews. The most recent user fee reauthorizations (PDUFA VI, GDUFA II, and BsUFA II) were enacted as part of the FDA Reauthorization Act of 2017, and expire on September 30, 2022. Prior to every user fee reauthorization, FDA and representatives from industry negotiate proposed user fees and performance goals, which may include new initiatives to facilitate drug development, new guidance the agency will provide, modified practices, and other proposals. The final performance goal letters for PDUFA VII, GDUFA III, and BsUFA III, which will cover fiscal years (FY) 2023 through 2027, were transmitted to Congress on January 12, 2022.[1]

[1] U.S. Food and Drug Administration, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027* (Jan. 12, 2022) (www.fda.gov/media/151712/download) (PDUFA VII); U.S. Food and Drug Administration, *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027* (Jan. 12, 2022) (www.fda.gov/media/153631/download) (GDUFA III); U.S. Food and Drug Administration, *Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027* (Jan. 12, 2022) (www.fda.gov/media/152279/download) (BsUFA III).

The performance goal letters contain FDA's commitments on review timelines, hiring estimates, and program enhancements for each review program. Substantial changes to the review programs and new initiatives are described below.

II. PDUFA VII

A. Review Goal Dates

PDUFA VII maintains the current drug review timelines of reviewing 90 percent of applications within 10 months with a 60-day filing date for standard applications, and 90 percent of applications within six months with a 60-day filing date for priority applications.

B. Post-Marketing Requirements Communication and Review

FDA may require sponsors to conduct post-marketing studies or other requirements after a product is approved in certain circumstances, including under the Accelerated Approval pathway, the Animal Rule, and the Pediatric Research Equity Act, and where necessary to assess known, potential, and signals of serious risks related to the use of the drug. These are known as post-marketing requirements (PMRs). Through PDUFA VII, FDA will establish processes by which FDA will communicate details on what PMRs FDA expects will be required earlier than under current practice. The communication from FDA will include the required study's purpose, critical study design elements, including the type of study and population included, timelines for discussions and engagement on the PMR for the remainder of the review cycle, and any specific known, potential, or signals of serious risks. Under these new processes, FDA will communicate details no later than eight weeks prior to the PDUFA action goal date for standard applications, and no later than six weeks prior to the PDUFA action goal date for priority applications.

Additionally, FDA will establish processes under which applicants will request a review of existing PMRs, and request release from such requirements under certain circumstances.

C. Split Real Time Application Review Pilot Program

FDA will also establish the Split Real Time Application Review (STAR) program to speed patient access to novel uses for existing therapies. In some cases, this program may lead to approvals one month earlier than otherwise expected under the PDUFA timelines. Under the STAR program, FDA will begin earlier reviews of applications to indicate that an existing approved drug could be used for certain unmet medical needs, if the following criteria are met: (1) a sponsor has data from an adequate and well-controlled investigation that indicates an existing drug may demonstrate substantial improvement over other available therapies on a clinically relevant endpoint; (2) the drug is intended to treat a serious condition with an unmet medical need; (3) no aspect of the submission is likely to require a longer review time; and (4) there is no chemistry, manufacturing, or control (CMC) information that would require a foreign manufacturing site inspection.

If determined eligible, applicants will be able to submit their efficacy application in two parts. The first part will include most of the required components of an efficacy supplement to

an NDA or BLA, but will not be required to include final clinical study reports for the required investigations and clinical technical document summaries. Instead, it will include a document with topline results from required investigations. FDA will begin review of Part 1 of the application upon receipt. Then, two to three months later, the applicant will submit the second part of the application, which will include the full clinical study reports intended to support the proposed indication and required clinical technical document summaries. The application is completed upon receipt of Part 2 and the PDUFA timeline begins. Because FDA will begin review of the application earlier in the process, the agency will aim to take action at least one month earlier than the applicable PDUFA goal date, of six or ten months.

D. New Meeting Types

The performance goals letter sets out two new meeting types that can take place between sponsors and FDA. First, requests for new "Type D" meetings (which are added to existing Type A, B, B (EOP), and C meetings) can be submitted when a sponsor has no more than two focused topics it would like to discuss with the agency, such as a follow-up question that raises a new issue after a formal meeting (i.e. more than just a clarifying question), or a general question about an innovative development approach that does not require extensive, detailed advice.

Additionally, Initial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meetings are intended to address novel questions and unique early development challenges prior to filing an application for an investigational new drug (IND). For example, a sponsor may request an INTERACT meeting even before a pre-IND meeting to ask a novel question about toxicity studies necessary to get an IND, or the development of innovative devices with a drug or biologic.

E. Rare Disease Endpoint Advancement (RDEA) Pilot Program

Because drug development for rare diseases regularly faces challenges related to a lack of regulatory precedent, small trial populations, and a limited understanding of disease natural history, it can be difficult for developers to determine which endpoints will show an investigative drug's efficacy in treating rare diseases.[2] To allow for repeated, intensive interactions between rare disease drug sponsors and the agency, FDA will establish a pilot program. This program will offer additional engagement opportunities to facilitate the development of new endpoints that could better measure efficacy in fighting rare diseases, with a focus on addressing challenges of trial designs using small populations. Beginning in the fourth quarter of FY 2023, FDA will accept up to one proposal to join this program. It will then be expanded to up to one proposal per quarter, or up to three proposals per year, in FY 2024 through 2027. Additionally, FDA will conduct up to three public workshops to discuss topics relevant to developing endpoints for rare diseases.

[2] U.S. Food and Drug Administration, *From our Perspective: Encouraging Drug Development for Rare Diseases* (www.fda.gov/drugs/news-events-human-drugs/our-perspective-encouraging-drug-development-rare-diseases) (Feb. 29, 2016).

F. Combination Product Development

FDA has proposed a number of activities to advance development of drug-device and biologic-device combination products, including new guidance to help determine when and for what combination products a human factor validation study must be included with an application after a sponsor conducts an analysis of whether risk mitigation strategies are needed. Human factor validation studies are used to examine, eliminate, and mitigate use-related hazards, such as challenges with administering a product that may be inhaled or injected. In addition, FDA will implement new procedures for answering specific questions about how such studies should be designed.

G. Advancing Real-World Evidence for Use in Regulatory Decision Making

Real-world evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from an analysis of real-world data, such as electronic health records and product and disease registries.[3] FDA has proposed the creation of a new Advancing RWE Program under which the agency will identify approaches for generating RWE that can be used for effectiveness labeling or to meet post-approval study requirements, develop processes to promote consistent decision-making and shared learning across the agency, and promote awareness on how RWE can support regulatory decisions by FDA. Under this pilot, FDA will solicit applications asking sponsors to describe the regulatory questions they plan to address with RWE, the proposed RWE study design, and the potential real-world data sources they may use to support their design. FDA will select one or two applicants in the first two years of the program, and one to four applicants in the latter three years of the program. FDA will meet with the selected applicants up to four times to address those issues, and will convene a public workshop or meeting no later than December 31, 2025, with a focus on how to generate RWE that could meet regulatory requirements for effectiveness labeling or meeting post-approval study requirements. FDA will then use the pilot program to update existing RWE-related guidance or generate new draft guidance.

H. Patient-Focused Drug Development

Patient-focused drug development (PFDD) is used to help incorporate patients' experiences, perspectives, needs, and priorities in drug development and evaluation.[4] In PDUFA VII, FDA has proposed to strengthen staff capacity and engage external experts to support the review of patient experience data. FDA has also proposed to issue a Request for Information (RFI) to seek public input on methodological issues associated with PFDD, including how the data should be submitted and evaluated in the context of benefit-risk assessment and product labeling. FDA will hold at least two public workshops on the issue, and no later than September

[3] U.S. Food and Drug Administration, *Real World Evidence* (www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence) (accessed Jan. 28, 2022).

[4] U.S. Food and Drug Administration, *CDER Patient-Focused Drug Development* (www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development) (accessed Jan. 28. 2022).

30, 2026, will publish draft guidance on the use and submission of patient preference information to support regulatory decision making.

I. Sentinel Maintenance and Improvement

FDA will use user fee funds to maintain the Sentinel Initiative, which analyzes health care data to monitor safety of regulated products on the market. FDA will also enhance Sentinel to address questions of product safety and advance the understanding of how RWE can be used to study effectiveness. Specifically, within these efforts, FDA will develop a consistent approach for PMRs and commitments related to studying outcomes of pregnancies in women exposed to drugs and biologics.

J. Enhanced Communication, Quality Reviews, and Manufacturing

To facilitate an efficient application review, including to ensure that a particular drug is being manufactured when FDA conducts an inspection related to that drug, FDA has committed to communicate its intent to conduct an inspection at least 60 days before doing so on pre-approval inspections. FDA still maintains an ability to conduct inspections at other times as warranted.

Additionally, FDA will conduct a public workshop on innovative manufacturing technologies for drugs and biologics, including barriers to their adoption. The workshop will address, among other things, regulatory strategies for the adoption of advanced manufacturing technologies.

K. Center for Biologics Evaluation and Research (CBER) Capacity Enhancements

User fee funds will support substantial staff increases at CBER to enhance the development, review, and approval of cell and gene therapy products. CBER intends to undertake activities related to PFDD on gene therapy products, novel trial designs for small patient populations for these products, and expedited programs for the development of regenerative medicine therapies.

L. Allergenic Extract Products

Since it was first enacted, PDUFA has excluded allergenic extract products, which are used for the diagnosis and treatment of allergies, from being subject to user fees and performance goals. PDFUA VII incorporates allergenic extract products into the user fee program. As such, all allergenic extract product applications submitted after October 1, 2022, will be subject to the user fees and goals in PDUFA VII.

M. Staff Hiring

FDA will hire a total of 210 full time equivalent (FTE) positions in FY 2023, 79 FTE in FY 2024, 44 FTE in FY 2025, 15 FTE in FY 2026, and four FTE in FY 2027 for the human drug review program.

III. GDUFA III

A. Review Goal Dates

GDUFA III generally maintains the goal dates established under GDUFA II. FDA will act on most original generic drug applications (called abbreviated new drug applications, or ANDAs) within 10 months of when they are submitted, and will act on most priority ANDAs within eight months of when they are submitted. However, under GDUFA III, if a sponsor tells FDA that the manufacturing site is not ready for inspection when submitting the application, the goal date will be extended to 15 months. If, within 15 months of submitting the application, the site becomes ready, sponsors can move that date up by amending their application. If no notice is given that the site is ready for inspection within 30 days of the goal date, FDA will extend the goal date by an additional 15 months (i.e., FDA will not have to act until 30 months after the sponsor initially applied).

B. Complex Generic Products

FDA will issue new product-specific guidance to help spur development of more complex generic products, which include generic drugs that have complex ingredients, formulations, routes of delivery (e.g., locally acting products delivered on the skin or eye), or dosage forms (e.g., extended release injectable products), and complex drug-device combination products (e.g., auto-injectors). This product-specific guidance will help generic manufacturers understand how FDA will evaluate generic applications for these drugs. FDA will issue new product-specific guidance on 50 percent of complex new drug products within two years after they are approved, and 75 percent of complex new drug products within three years of approval.

C. Suitability Petitions

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), generic drug applicants may submit an application for a generic drug product that differs from a listed drug in its route of administration, dosage form, and strength, or where an active ingredient is substituted for one of the active ingredients in an approved combination drug, by submitting a "suitability petition."[5] A suitability petition generally shows that the proposed generic drug will be a substitute for the listed drug, despite these differences. More specifically, the petition needs to show that the generic drug is of the same class as the listed drug and is expected to have the same therapeutic effect as the listed drug.[6] In instances where the generic drug includes a difference in its active ingredient, the petition must show that the active ingredient has been previously approved and the generic drug does not meet the definition of a new drug.[7] If FDA grants the petition, the applicant may submit the ANDA without additional safety or effectiveness studies. Under the statute, FDA must approve or disapprove petitions within 90 days; however, some industry

[5] 21 U.S.C. § 355(c)(2).

[6] 21 CFR § 314.93 (2016).

[7] *Id.*

estimates have suggested that petitions could take years to get an answer from FDA, and a backlog has built up.[8]

Under GDUFA III, FDA will phase in assigned goal dates for responding to suitability petitions beginning in FY 2024, with a goal of responding to suitability petitions six months after completing a completeness assessment, up to a maximum of 50 petitions completed for the year. FDA will respond to an increasing number of suitability petitions each year through FY 2027. Those suitability petitions filed prior to FY 2024 will not receive a goal date unless the petitioner withdraws the petition and resubmits. FDA also will begin prioritizing some suitability petitions if they are for a drug product that (1) could mitigate or resolve a drug shortage or prevent future shortages; (2) address a public health emergency; (3) is for a new strength of non-oral drugs that could eliminate waste or mitigate the number of vials needed per dose; or (4) is subject to special review under the President's Emergency Plan for AIDS Relief (PEPFAR).

D. New Meetings in Review Cycle

GDUFA III contains several new opportunities for sponsors to meet with FDA to address deficiencies noted by the agency.

Under GDUFA III, certain sponsors of complex generic drug applications may receive a mid-cycle review meeting in which the applicants can ask for the rationale of any deficiencies noted by FDA in a discipline review letter during the review of the application. Some may also qualify for an enhanced mid-cycle review meeting in which the applicant can ask about pathways to addressing such deficiencies.

In the event that FDA issues a warning letter based on a deficiency in a facility, that facility may request a post-warning letter meeting to get preliminary feedback from FDA on the facility's plans to remediate the deficiencies noted in the warning letter.

Additionally, if a sponsor receives a complete response letter (CRL), indicating FDA will not approve the application, the applicant may request a post-CRL teleconference with FDA to clarify deficiencies identified in the letter.

E. Staff Hiring

FDA will hire 128 staff for the generic drug review program in FY 2023.

[8] FDA Law Blog, *ANDA Suitability Petitions: The Way Back to Normalcy (and Some Sanity)* (Mar. 26, 2019) (www.thefdalawblog.com/2019/03/anda-suitability-petitions-the-way-back-to-normalcy-and-some-sanity/).

IV. BsUFA III

A. Review Goal Dates

Under BsUFA III, FDA will maintain the same goal dates for application submissions and resubmissions as under BsUFA II; the agency will review and act on 90 percent of original biosimilar application submissions within 10 months of the 60-day filing date, and will review and act on 90 percent of resubmitted original biosimilar applications within six months of receipt. However, FDA has introduced a number of new, shorter review periods for certain supplements to applications, based on the type of supplement. For example, if a reference listed product updates its safety information labeling, and a biosimilar then updates its labeling to match, FDA will review and act on this application supplement to reflect this change within three months. The full list of categories of supplements and their timelines are included in the performance goals letter, and FDA will release a guidance or a manual of policies and procedures to help in classifying the different supplements to a licensed biosimilar application within those categories.

B. Changes to Meetings in Review Cycle

FDA and industry have agreed to changes in review cycle meetings in BsUFA III. To better manage Biosimilar Initial Advisory (BIA) meetings, where FDA and applicants discuss whether a biosimilar license is feasible for a particular product, FDA has clarified what information should be provided to the agency with the meeting request so the meeting can be productive and FDA can provide meaningful advice.

Additionally, BsUFA III creates a new Type 2a meeting, which is focused on a narrow set of issues requiring input from no more than three disciplines or review divisions at FDA, such as a follow up meeting to ask for feedback on a revised study design, when revisions have been made based on prior FDA feedback. In order to request a Type 2a meeting, sponsors first need to have a BIA or Biological Product Development (BPD) meeting. FDA's goal will be to schedule Type 2a meetings within 60 days of receipt of the meeting request and background package. The Type 2a meeting will differ from a Type 2b meeting, which is intended to discuss a specific issue, such as a proposed study design or endpoints, where FDA may include a substantive review of summary data. FDA will have a goal date of responding to Type 2b meetings within 90 days of receipt of the meeting request and background package.

FDA will also update existing guidance with information about these meetings. In addition, sponsors will have the opportunity to submit clarifying questions to FDA as follow-up to these meetings.

C. Alternative Tools for Inspections

During the coronavirus disease of 2019 (COVID-19) pandemic, FDA has used alternate tools, including the ability to remotely request records for inspection. FDA will issue draft guidance on the continued use of these tools beyond the pandemic, incorporating best practices from the use of those tools no later than September 30, 2023.

D. Interchangeable Biosimilar Development

Interchangeable biosimilar products are those which have been shown to have no clinically meaningful difference from a reference biological product.[9] For patients, the advantage of interchangeable biosimilars is that they generally can be substituted for at the pharmacy counter or provided interchangeably in the hospital settings when reference biologic is prescribed. FDA has licensed only two interchangeable biosimilars, both in the last year.[10] To advance interchangeable biosimilar development, FDA will publish a series of guidance documents, including guidance on developing presentations, container closure systems, and device constituent parts for interchangeable products; labeling and advertising interchangeable products; and post-approval manufacturing changes to approved biosimilar and interchangeable products. FDA will also hold a public workshop to help identify future needs in the interchangeable biosimilar space. Additionally, FDA will launch pilot projects to enhance regulatory science around the data needed to support an interchangeable application and improve efficiency in biosimilar product development.

E. Staff Hiring

FDA will hire 13 staff in FY 2023 and one staff member in FY 2024 for the biosimilar product review program.

V. WITNESSES

Panel I:

Patrizia Cavazzoni, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Peter Marks, M.D., Ph.D.
Director, Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

[9] U.S. Food and Drug Administration, *Biosimilar and Interchangeable Products* (www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products) (accessed Jan. 28, 2022).

[10] U.S. Food and Drug Administration, *FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes* (July 28, 2021) (www.fda.gov/news-events/press-announcements/fda-approves-first-interchangeable-biosimilar-insulin-product-treatment-diabetes) (press release); U.S. Food and Drug Administration, *FDA Approves Cyltezo, the First Interchangeable Biosimilar to Humira* (Oct. 18, 2021) (www.fda.gov/news-events/press-announcements/fda-approves-cyltezo-first-interchangeable-biosimilar-humira) (press release).

Panel II:

Cartier Esham, Ph.D.
Chief Scientific Officer
Executive Vice President, Emerging Companies
Biotechnology Innovation Organization

David Gaugh
Senior Vice President, Sciences and Regulatory Affairs
Association for Accessible Medicines

Reshma Ramachandran, M.D.
Physician-Fellow, Yale National Clinician Scholars Program
Chair, Doctors for America FDA Task Force

Juliana M. Reed
Executive Director
Biosimilars Forum

Lucy Vereshchagina, Ph.D.
Vice President, Science and Regulatory Advocacy
Pharmaceutical Research and Manufacturers of America