GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS

Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115

Majority (202) 225-2927
Minority (202) 225-3641

MEMORANDUM

March 20, 2017

To: Subcommittee on Health Democratic Members and Staff

Fr: Committee on Energy and Commerce Democratic Staff

Re: Hearing on "Examining FDA's Prescription Drug User Fee Program"

On **Wednesday, March 22nd, at 10:15 a.m., in room 2322 of the Rayburn House Office Building**, the subcommittee will hold a hearing on the reauthorization of the Prescription Drug User Fee Act.

I. BACKGROUND

Passed into law in 1992, the Prescription Drug User Fee Act (PDUFA) authorizes the U.S. Food and Drug Administration (FDA) to collect fees from companies producing certain human drug and biological products. Commonly referred to as "user fees", these collected fees supplement appropriated funds to ensure the timely review of new drug applications (NDAs) and biologic license applications (BLAs). PDUFA must be reauthorized every five years. Most recently, PDUFA V was authorized in 2012. PDUFA VI must be authorized by September 30, 2017.

II. PDUFA VI

PDUFA VI will contain several modifications which have been previously deliberated and agreed upon by both FDA and industry. Of note, PDUFA VI 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. Major changes are detailed below.

A. Changes in Fee Structure

The current fee structure is made up of three components – application fees, establishment fees, and product fees. These fees are aggregated and used to cover the costs associated with activities involved in reviewing human drug applications. In 2017, FDA is estimated to collect $866 million in PDUFA user fees.[1] Several changes in fee structure have been proposed under PDUFA VI to reduce administrative inefficiency and increase predictability of annual PDUFA funding levels:

- Product fees, known as PDUFA program fees, will replace the combined fees from product fees and establishment fees. Supplement fees will be eliminated.
- The fee setting methodology will be modified to create an annual base revenue amount.
- New methodology will be implemented to adjust fees based on application workload.
- The 5th-year offset and final year adjustment provisions will be replaced with an annual "operating reserve adjustment" to maintain appropriate operating reserves on a year-to-year basis.

It is estimated that FDA will collect an average of approximately $1 billion per year under the new fee structure negotiated in PDUFA VI.

B. Inclusion of Patient Perspective Information in Regulatory Decision-Making

Under PDUFA V and Patient Focused Drug Development Initiative, FDA committed to holding up to 20 public meetings focused on different disease areas to discuss how to systematically gather and utilize patients' perspectives on their medical conditions and treatments. PDUFA VI builds off these efforts by investing further resources and staff capacity into patient-focused drug development with dedicated experts incorporated into the review divisions to work with patients, advocates, and stakeholders. FDA will also develop a series of guidances regarding approaches to collecting meaningful patient and caregiver input for use in regulatory decision-making and labeling. The agency will also host a public workshop on enhancing patient engagement in clinical trials.

C. Benefit-Risk Assessment

FDA uses a benefit-risk assessment framework to evaluate the safety of developing drugs. During PDUFA V FDA committed to several goals to enhance this framework, and PDUFA VI builds on that progress.

PDUFA VI includes several commitments to help sponsors and the public better understand FDA's approach to benefit-risk assessment. By March 31, 2018, FDA will publish an update to the benefit-risk assessment implementation plan. By end of FY2019, FDA will hold at least one public meeting to gather stakeholder input on the benefit-risk framework. By the end of FY2020, FDA will publish draft guidance on benefit-risk assessments for new drugs and biologics. Included in the draft guidance will be FDA's decision-making context and framework, with case studies to be used as examples of applying the benefit-risk framework through the

[1] Department of Health and Human Services, *HHS FY 2017 Budget in Brief – FDA* (https://www.hhs.gov/about/budget/fy2017/budget-in-brief/fda/index.html#fn3).

human drug lifecycle. Guidance will also be issued on the appropriate interactions between a sponsor and FDA during drug development, as well as on the appropriate approaches to communicate the outcomes of FDA benefit-risk assessments to the public. Note that FDA will update relevant Standard Operating Policy and Procedure (SOPPs) and Manual of Policies & Procedures (MAPPs) as needed for implementation. In FY2021, FDA will conduct an evaluation of the implementation of the benefit-risk framework. The evaluation will assess how reviewers apply the framework, and will identify best practices. The results of a similar framework evaluation conducted during PDUFA V will serve as the baseline for PDUFA VI.

D. Biomarker Qualification Program

The Biomarker Qualification Program (BQP) engages with external stakeholders to develop biomarkers that aid in the drug development process. According to FDA, a biomarker is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions". Some examples include body temperature, blood pressure, and cholesterol values. Through BQP, sponsors may request regulatory qualification of a biomarker for a particular context of use in drug development.

As part of PDUFA VI, FDA will enhance the biomarker qualification review by increasing base capacity and piloting procedures to include external experts in the review process. By the end of FY2018, FDA will hold a public meeting to discuss a taxonomy for biomarkers used in drug development and a framework to support biomarkers under the taxonomy. The framework will include scientific criteria to determine acceptance of a biomarker qualification submission and essential elements of a formal biomarker qualification plan. FDA will also publish draft guidance on the proposed taxonomy. By the end of FY2020 FDA will publish draft guidance on evidentiary standards for biomarker qualification, supplemented with more focused guidance on specific biomarker uses and contexts.

FDA will publicly list in-process biomarker qualification submissions, to be updated quarterly. Following qualification of a biomarker FDA will also post reviews and summary documents that outline the qualification program and data supporting a qualification decision.

E. Inclusion of Real-World Evidence in Regulatory Decision-Making

Real-world evidence (RWE), while lacking a formal definition, consists of the data or information gathered outside of randomized, controlled clinical trials. This could include EHRs, claims data, disease registries, or data from personal devices or health applications. While FDA is considering the possibilities of using RWE, there are challenges to incorporating this type of information into the approval process. Questions regarding how data is generated and appropriately applied must be investigated before incorporation of RWE.

To address these challenges and questions, FDA has established several deadlines. By the end of FY2018, FDA will hold at least one public workshop with key stakeholders to obtain input on RWE in regulatory decision-making. The workshop(s) will include discussions on the benefits of incorporating RWE, accessibility of RWE, and appropriate contexts for use of RWE.

By the end of FY2019 FDA will initiate appropriate activities, such as pilot studies or methodology development projects, which aim to address the key concerns about RWE. By the end of FY2021 FDA will use the results from aforementioned activities to publish draft guidance on how RWE can contribute to regulatory decision-making. A revised draft or final guidance will arrive within 18 months after the close of the public comment period.

F. Combination Product Review

According to FDA, combination products are "therapeutic and diagnostic products that combine drugs, devices, and/or biological products." Combination products, by nature, involve many components that must be reviewed by CBER, CDER, and the Center for Devices and Radiological Health (CDRH). Each component of the combination product must be reviewed through the appropriate channels, and this can impact the regulatory process. FDA has made several commitments regarding combination product review for PDUFA VI:

- Staff capacity will be developed across each Center and the Office of Combination Products (OCP) to address combination product reviews in an expeditious manner. Staff will be responsible for providing expertise and promoting best practices throughout the review process. The addition of staff will focus on review of Current Good Manufacturing Practice (cGMP), engineering aspects, human factors, bridging study protocols and study reports, and labeling. Staff training will begin by December 31, 2018.
- By December 31, 2017, FDA will complete a lean process mapping for combination product review to improve workflow and communication among Centers. FDA will also begin tracking workload and timelines for cross-center consultations to properly allocate resources.
- By September 30, 2018, FDA will outline the Agency's process for internally resolving any scientific or regulatory issues that arise during review.
    - FDA will establish MAPPs and SOPPs as necessary for combination product development and review. Documents topic areas include Human Factor Assessments, quality assessment, and patient-oriented labeling and will be completed throughout 2019.
- By September 30, 2018, FDA will establish submission procedures for Human Factors protocols. In FY2019, FDA will establish timelines to review and provide comment on the protocols for Human Factors studies.
- FDA will contract with an independent third party to assess current practices for combination drug product review. The assessment will identify best practices and areas for improvement by FDA review staff and sponsors. A final report of the assessment will be published online by the end of FY 2020.
- By the end of FY 2019, FDA will update or publish draft guidance on bridging studies and patient-oriented labeling. Guidelines will be finalized by end of FY2022.

G. Innovative Clinical Trials

Innovation in clinical development (referring to the use of complex adaptive, Bayesian, and other novel clinical trial designs) is important to the drug development process and can help to speed the process of bringing clinically effective products to market. However, in developing

innovative clinical trials, uncertainties in the process must be reduced to ensure patient safety. FDA has established several activities in PDUFA VI that will allow for the advancement of innovation in clinical development:

- Staff capacity will be developed to facilitate appropriate use of complex adaptive, Bayesian, and other novel clinical trial designs. This staff will support work of reviewing the evaluation of these designs.
- Starting in FY 2018, FDA will conduct a pilot program for specific innovative trial designs for which computer simulations are necessary to determine trial operating characteristics.
- By end of 2nd Quarter FY2018, FDA will hold a public workshop for the discussion of innovative clinical trial designs, focusing on designs for which computer simulations are necessary to evaluate operating characteristics.
- By end of FY 2018, FDA will publish draft guidance on complex adaptive (including Bayesian adaptive) trial designs.
- By end of FY 2020, FDA will develop or revise relevant MAPPs, SOPPs, review templates and training to incorporate guidelines on evaluating complex clinical trial designs that rely on computer simulations.

Sponsors who do not participate in the pilot program may continue interaction through traditional channels, which will not be affected by the pilot program.

H. Additional Resources for Breakthrough Therapies

The Breakthrough Therapy Designation was established through the Food and Drug Administration Safety and Innovation Act (FDASIA). A breakthrough therapy drug is one that is intended alone or in combination with other drugs to treat a serious or life threatening disease or condition and has preliminary clinical evidence to suggest it would demonstrate substantial improvement over existing therapies on clinically significant endpoints. Breakthrough therapy drugs undergo expedited development and review by FDA and includes the features of the fast track program, intensive FDA guidance on drug development, and organizational commitment from FDA senior managers.

PDUFA VI provides for additional resources to the breakthrough therapy drug program. These resources will allow FDA to continue to work with sponsors throughout the designation, development and review process. It should be noted these additional resources are additive and account for the breakthrough therapy workload.

I. Expansion of The Sentinel System

Launched in 2008, the FDA Sentinel Initiative represents an effort to monitor the safety of regulated products. Sentinel is a national electronic system which allows researchers to monitor the safety of FDA-regulated products including drugs, vaccines, biologics, and medical devices. Adverse events may be reported through Sentinel, and through Sentinel FDA is able to access large amounts of electronic healthcare data from multiple data partners.

PDUFA VI proposes to expand the Sentinel System and further integrate it into FDA drug safety activities. First, user fees would be used to fund enhancement of core capabilities and expanding sources of data. Second, FDA will engage sponsors and the public to discuss the usage of Sentinel data, possible facilitation of data distribution, and general feedback on Sentinel projects and the Sentinel System.

There are several agency goals for the Sentinel Initiative by the end of FY2020. FDA will establish policies and procedures to inform sponsors about the planned use of Sentinel to evaluate safety signals in their respective products. FDA will also facilitate integration of Sentinel into the human drug review program and develop a comprehensive training program for Sentinel review staff. By the end of FY2022, FDA will report on the impact of Sentinel expansion and integration.

III. WITNESSES

Panel I:

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Panel II:

Anne Pritchett
Vice President, Policy and Research
PhRMA

Kay Holcombe
Senior Vice President of Science Policy
Biotechnology Industry Organization

Jeff Allen
President & CEO
Friends of Cancer Research