

**Testimony of Cartier Esham, Ph.D., Chief Scientific Officer  
Biotechnology Innovation Organization**

**House Energy and Commerce Committee Hearing:  
*FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics***

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Chairman Pallone, Ranking Member McMorris Rodgers, Chairwoman Eshoo, and Chairman Guthrie, on behalf of BIO we appreciate the opportunity to speak with you today about the seventh reauthorization of the Prescription Drug User Fee Act (PDUFA VII). At the outset of the negotiation process there was strong alignment about which topics needed to be addressed in the PDUFA VII Commitment letter and the discussions during the process benefitted from learnings we were gathering during the COVID-19 pandemic. BIO strongly urges timely reauthorization of PDUFA VII and BsUFA III to ensure the FDA is best able to continue to meet its mission to protect and promote public health. I am Dr. Cartier Esham, Chief Scientific Officer at BIO. BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organization across United States in more than 30 other nations. While our membership includes most of the large, international biopharmaceutical companies, most of our members are small biotechnology companies working on cutting-edge biomedical innovations. These companies are pre-revenue and take enormous risks every day to develop the next generation of biomedical breakthroughs for the millions of patients suffering from diseases for which there are no effective cures or treatments today. BIO is proud of their innovative spirit and dedication to improving the lives of patients and their families.

The Prescription Drug User Fee Act (PDUFA) was created by Congress in 1992 and authorizes FDA to collect fees from companies that produce certain human drug and biological products. PDUFA is reauthorized by Congress every 5 years and serves to provide the FDA with resources through fees paid by biopharmaceutical companies that are additional to those provided by Congress through appropriations. Congressional support and the PDUFA program together have made FDA the strongest and most advanced regulatory agency in the world. Since initial enactment of PDUFA, user fees have played an important role in ensuring effective and efficient processes are aligned with the continual advancement of scientific and medical innovation. The result is more innovative treatments and therapies are first approved in the United States providing our citizens with faster access to innovative medicines than anywhere

else in the world. Additionally, the PDUFA program serves to ensure the FDA has the resources, capabilities, and processes in place to chart a well-understood pathway from discovery to availability of cutting-edge medicines. This is important not only to regulators, patients, and the biopharmaceutical industry, but also to the entrepreneurial community that contributes significant investments in high-risk early-stage innovative medicines. Today, it can take anywhere from 10 to 15 years at an average cost approximately a \$1 billion or more to advance a drug or biological product from a good idea to an approved product that benefits patients.<sup>1,2</sup> A well-run and understood pathway to approval is critical to maintaining U.S. leadership in investment, development, and availability of next-generation medicines.

### **Overall Goals for PDUFA VII**

Each user fee Commitment Letter has continued to build upon the efforts of previous agreements. The enacted PDUFAs have collectively worked to ensure effective and timely reviews, improve safety management, enable the Agency to keep pace with medical and scientific advancements, and allow for earlier issue identification and resolution where possible. Fundamentally, PDUFA VII is designed to build upon existing processes to strengthen review fundamentals, enhance accountability and transparency, ensure stable growth of the program, and initiate or advance critical medical and scientific advancements. The following testimony will describe the content and benefit of critical provisions addressing each of the following seven primary themes included in the PDUFA VII Commitment Letter:

- Strengthen scientific dialogue and advance innovation
- Support the next wave of advanced biological therapeutics
- Enhance patient-centric drug development, review and protections
- Modernize regulatory evidence generation and drug development tools
- Enhance innovation in manufacturing and product quality reviews
- Advance digital technologies and information technology (IT) infrastructure

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<sup>1</sup> Olivier J. Wouters, PhD; Martin McKee, MD, DSc; Jeroen Luyten, PhD. Estimated Research and Development Investment Needed to Bring a New Medicine to Market JAMA. 2020, 323(9).

<sup>2</sup> Joseph A. DiMasi; Henry G. Grabowski; Ronald W. Hansen. Innovation in the pharmaceutical industry: New estimates of R&D costs. 2016. Journal of Health Economics. 2016, Vol. 47.

- Enhance FDA hiring, retention, and financial management

**Strengthen scientific dialogue and advance innovation**

One of the most important goals of PDUFA VII critical to advancing innovation is to continue to enhance and strengthen scientific dialogue between sponsors of applications and the FDA. To that end, FDA will provide timelines and expand the Initial Targeted Engagement for Regulatory Advice (INTERACT) pre-Investigational New Drug Applications (INDs) meetings to include clinical development programs intended to be reviewed by CDER as well as CBER that have a novel challenges where early engagement with the FDA is critical to avoiding delays in advancing entry into to the clinic. These have been previously limited to products under review by CBER. FDA will also establish a new Type D meeting that enables the FDA and sponsors to engage in focused conversations about innovative approaches or unique challenges that will allow for earlier resolution of issues and understanding of what is required to better ensure stronger applications for review. The Commitment Letter also provides for a process where sponsors can submit clarifying questions to the FDA following a meeting to better ensure aligned understanding of expectations and requirements. We collectively recognized that best practices for productive meetings is a shared responsibility between biopharmaceutical companies and the FDA. PDUFA VII calls for the training of FDA staff and a public workshop to discuss and share best meeting practices that will inform the publication of updated guidance documents describing how to conduct and prepare for meetings that are productive, informative, and serve to efficiently advance clinical development programs and review processes more consistently.

There are at least 7,000 known rare diseases collectively impacting over 25 million Americans and new rare diseases are identified each year. Providing treatments and cures for these patients is complicated by the fact that the development and review of these medicines is often conducted without well-established regulatory precedents because there are limited or no available treatments for these diseases. Clinical trial populations for rare diseases are small and our understanding of the natural history of the disease may be limited which create additional challenges for those developing innovative treatments and cures and for those that are regulating their approvals. Key among these challenges is reaching agreement with regulators about determining the appropriate efficacy endpoints to support approval of innovative medicines for rare diseases. Additionally, the current mechanisms for companies of rare disease drug development programs to collaborate with FDA has not consistently provided

avenues for much needed discussions about these unique issues and can cause delays in advancing the development and availability of medicines to these patients which often have limited or no options. The Rare Disease Endpoint Advancement pilot program in PDUFA VII will provide avenues for focused engagement opportunities for a designated number of eligible applications that have a proposed novel efficacy endpoint. This pilot program also includes commitments such as public workshops and guidance documents that will serve to share learnings and advance more efficient development and review approaches and processes for all rare disease medicines to provide much needed cures or improved quality of life for these patients and their families.

The Commitment Letter will establish a Split Real Time Application Review (STAR) pilot program for certain supplemental New Drug Applications (NDAs) that are intended to treat a serious condition with an unmet need. The pilot is built on the concepts that have proven successful for the Real Time Oncology Review (RTOR) program. The STAR pilot is designed to improve workload management by allowing sponsors of applications to submit their applications in 2 parts allowing for earlier review of key components such as proposed labeling, clinical protocols and topline efficacy and safety results prior to the final application submission. The objective of this pilot is to enable more timely reviews and availability of these medicines similar to the observed RTOT program results. This pilot will also enable the FDA to assess potential benefits or challenges of expanding this program in the future which will be shared via a public workshop that includes an opportunity for feedback prior to the next PDUFA reauthorization.

Biopharmaceutical companies and the FDA recognize the importance of post-marketing requirements (PMRs) to ensure timely availability of information on the safety and efficacy of certain therapies to patients when further post-approval studies are warranted. PDUFA VII aligns processes to ensure necessary discussions are occurring in a manner that allow for more effective assessments of whether a PMR is needed and provide timelines that enable more thoughtful development of PMR studies. PDUFA VII will also establish stronger processes for the continued evaluation of PMRs post-approval to ensure requirements are being met and/or remain scientifically valid.

### **Support the next wave of advanced biological therapies**

Advancing the new wave of biological therapies is a top priority for BIO member companies. A 2020 analysis by BIO found that there were 231 gene therapy programs under development

compared to 93 programs in 2015, a trend that is expected to grow in the coming years. To ensure that new and innovative cell and gene therapy products are developed and available to patients in a timely manner, the Commitment Letter will provide FDA the resources and capacity needed to address the growing workload of the Cell and Gene Therapy Program. This will enable FDA to maintain the level of highly-trained and experienced Cell and Gene Therapy staff needed to address the growing number CBER workload projected over the next 5 years, as well as keep pace with scientific and technological advancements.

Specifically, PDUFA VII establishes commitments, engagements and publication of information or guidance to advance shared understandings about the inclusion of patient perspective data in the development of cell and gene therapies, the utilization of novel endpoints and innovative clinical trial designs for small patient populations. CBER will also issue Question and Answer guidance addressing frequently asked questions and commonly faced issues to better inform clinical development programs about the current thinking of FDA. Additionally, CBER will hold public meetings and issue guidance of utilization for capturing post approval safety and efficacy data for cell and gene therapy products and update guidance on expedited pathways for regenerative medicines including information to better align expectations for Chemistry, Manufacturing and Controls (CMC) readiness which has been a barrier to timely access to breakthrough cell and gene therapies. And lastly, PDUFA VII includes commitments by CBER to work with key stakeholders to foster the development and accessibility of non-proprietary knowledge (e.g. standards), manufacturing advancements, and manufacturing components that will serve to better facilitate the development, review, production and availability of these innovative therapies domestically and around the world.

### **Enhance patient-centric drug development, review and protections**

One of the most important goals of PDUFA VII are the commitments to continue to advance the systematic integration of patient perspective data into drug development programs and review processes. This work began in earnest under PDUFA V with the establishment of the Voice of the Patient Program that supported public meetings where patients provided insights about their conditions and how they evaluated benefits, risks and needs. PDUFA VI advanced this work by holding a series of public meetings and the publication of guidance that provided information about how to determine the most important impacts to patients, how measure disease impact and how to incorporate Clinical Outcome Assessments (COAs) into clinical development programs and review processes.

During PDUFA VII, the FDA will continue this critical work by continuing to strengthen capacity and knowledge through the expansion of training opportunities for FDA staff and ability to better engage external methodological experts. The FDA will seek public input on methodologies and approaches for the submission of high-quality patient perspective data designed to inform benefit-risk assessments and inclusion of information in the label. PDUFA VII will provide supplementary support to the FDA to support the continued development of a publicly available virtual catalog of Standard Core Sets of COAs and related endpoints that will help make possible the broader utilization of patient perspective data in clinical development programs. The FDA will also seek public input on which diseases areas have the greatest need for the Standard COA development. Additionally, the FDA will work to increase shared understandings about how patient preference studies can inform meaningful benefit-risk assessments in therapeutic areas.

To enhance the FDA drug safety system, PDUFA VII provides resources and processes that will enable the adoption of new scientific approaches designed to improve the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events. Steps will be taken to modernize and improve Risk Evaluation and Mitigation Strategies (REMS) approaches and processes. Specifically, PDUFA VII will update guidance to better ensure appropriate and sufficient safety evidence are collected and provide information about what type of data are needed to eliminate the need for a REM. Further, goals will be put in place to allow for consistent and timely feedback on submitted REMS methodologies and protocols. Resources will also be provided to continue to expand and optimize the FDA's electronic safety data base (the Sentinel program) including supporting the integration of Sentinel and BEST (Biologics Effectiveness and Safety) systems. Additionally, the FDA will build on current communications and advance knowledge about how Sentinel data can be used for regulatory purposes (e.g. PMRs, PMCs and labeling) and to advance understandings about how real-world evidence (RWE) may be used for evaluating the effectiveness of medicines. Collectively, these improvements and advancements in the FDA the drug safety system will improve patient protections and utilization of this vast data resource to gain deeper and continual understandings about the benefit and risks of medicines.

**Modernize regulatory evidence generation and drug development tools**

Advancing innovative, patient centric drug development tools, and modernizing the regulatory evidence generation paradigm is a top priority for BIO member companies. Advancements in science and technology offer real opportunities to reduce patient burden, improve ability to recruit and conduct effective clinical trials and provide more informative analyses of benefit and risk pre and post approval. PDUFA VII will continue to build on several key initiatives that were launched under PDUFA VI. Under this Commitment Letter the FDA will advance the use of real-world evidence (RWE) to support approval of labeling claims, approval of new indications and to satisfy post approval study requirements. There will be an Advance RWE pilot program established that provides increased interactions for a select number of applications that collectively will provide shared learnings with the public and inform the publication of guidance increasing broad knowledge about how and when RWE can be utilized. PDUFA VII will also continue both the Complex Innovative Trial Design and Model-Informed Drug Development (MIDD) pilot programs which similarly provide increased engagement and publication of learnings to enable the utilization of these tools and approaches more broadly. Complex innovative trials such as adaptive and Bayesian approaches can be more efficient, improve patient outcomes and produce high-quality information faster. Additionally, the Agreement will work to enhance the drug development tools qualification pathway for biomarkers by retaining and enhancing staff capacity and piloting of processes to engage external experts to support the review of biomarker qualification submissions. High quality biomarkers can accelerate and enable drug development in areas of unmet need, improve clinical trial feasibility and efficiency thus continued improvement of the qualification pathway is beneficial to regulators, the research and development community, and patient communities.

#### **Enhance innovation in manufacturing and product quality reviews**

One of the critical needs for PDUFA VII was to advance innovation in manufacturing and inspection review processes and improve the ability to get medicines to patients in a timely manner. A rate-limiting step for the past several years have been discussions and resolution of chemical manufacturing and control (CMC) issues, especially for innovative biologic therapies and treatments. FDA will improve the timeliness and effectiveness of CMC communications through training and updating CDER and CBER guidance designed to better enable more consistent review of high-quality information requests from sponsors. The FDA will also engage a third party to assess, seek public comment and provide recommendations about how these processes can be optimized.

To address the outsized hindrance of timely availability of innovative treatments for serious and life-threatening diseases undergoing expedited reviews due to CMC issues, the FDA will publish new internal documents to better align CMC communications and processes to better meet the desired timelines for approval decisions. The FDA will also establish a CMC Development and Readiness Pilot (CDRP) at both CDER and CBER. The CDRP pilot is designed to improve CMC readiness for IND applications through increased engagements to improve alignment on what is needed and when to meet critical CMC milestones. Learnings from this pilot will be made available to the public via a public workshop and the publication of a strategy document describing the Agency's plans to revise processes and information about submission strategies to accelerate CMC development.

Over the past several years there have been significant scientific advancements about how to manufacture high-quality complex medicines effectively and efficiently. PDUFA VII will work to identify and remove current barriers to their utilization and adoption. The FDA will conduct a workshop where best practices, case studies and regulatory strategies will be shared and discussed, including how to assess innovative technologies across platform products and sites. These discussions will inform the publication of a draft strategy document about the facilitation of the utilization of innovative manufacturing technologies and inform the publication of guidance, internal process documents and other recommended actions.

During the COVID-19 pandemic, regulators, biopharmaceutical companies and other key stakeholders from around the world held discussions about how best to ensure the continued availability of medicines and meet the needs of providing COVID vaccines and treatments to all in need. Among the results of those discussions were the increased utilization, when appropriate, of alternative tools such as use of information shared by trusted foreign regulatory partners and record requests for assessing manufacturing facilities. PDUFA VII will continue the advancement of those lessons learned by issuing draft guidance about when and how these types of alternative approaches may be utilized beyond the pandemic.

### **Advance digital technologies and information technology (IT) infrastructure**

It is of vital importance that support be provided to the FDA to increase its capacity and ability to meet the demands of the data and digital age. Increasing utilization of cloud technologies is necessary for the FDA to meet the growing needs, demands and advantages of modern-day



development and review of innovative medicines. The clinical development programs and applications of today have large and/or complex data sets that require high-quality repository and analytical capabilities. PDUFA VII activities and resources, collectively, will serve to enable the FDA to make the necessary changes to meet these needs. These advancements will serve to improve the quality of applications submitted to the FDA and improve our ability to better understand the benefits and risks of medicines to all patients before and after they are approved.

First, the FDA will continue to meaningfully advance their Data and Technology Modernization Strategy. This Commitment includes timelines for articulation and communication of goals and communication about how these strategies are developed and implemented and serve to improve both FDA enterprise needs and to advance key PDUFA objectives. Specific needs such as improving the ability to electronically submit applications via increasing band-width of the electronic gateway systems (EGS) and completing transition to a cloud-based system are expected to be completed. The FDA also committed to regular engagement with the biopharmaceutical industry to provide progress updates, share learnings, and discuss challenges in meeting PDUFA VII goals and advancing objectives outlined in the Data and Technology Modernization Strategy.

Second, the FDA will launch a series of demonstration projects to improve the ability to review data captured via digital technology tools. We have seen and expect to see continued growth in the utilization digital technologies as they offer the ability to reduce burdens on patients in clinical trials, better assess clinical outcomes for all patients, and more efficiently collect high-quality data and evidence to support approvals and inform life-cycle management of medicines. Under PDUFA VII, the FDA will engage with external partners to develop core capabilities to ensure high-quality data collection, sharing and review of data, including the adoption of cloud-based technologies, to enable productive regulatory-applicant interactions. The FDA will also launch a series of demonstration projects focused on: enhancing capabilities to effectively receive and review digital health technology derived data; demonstrate utilization of cloud-based technologies to support application-regulator interactions and needs; and, develop technical capabilities needed to enable utilization and review of applications with data collected via digital technology tools. Findings and planned next steps from these demonstration projects will be shared with biopharmaceutical companies and made available to the public on FDA's website.

Third, critical IT modernization and capacity needs for the review of Biologic License Agreements will be provided to CBER to meet the demands of current and future applications that are projected to increase significantly over the next five years. In coordination with the Data Technology Modernization Strategy described above, CBER will develop a specific multi-year modernization roadmap to chart specific steps necessary for CBER to meet current and projected needs necessary to continue to successfully carryout its mission. Specially the roadmap is charged with designing a plan that will enable more efficient and effective exchange of information, data analyses, dissemination of safety information and support consistent review processes. Like the Data Technology Modernization Strategy commitments, communications, progress and next steps will be shared with the biopharmaceutical industry and the public. And lastly, resources will be provided to improve the FDA's bioinformatics capabilities (e.g. Next Generation Sequencing). The use of bioinformatics is expected to grow and provides tremendous insights about the quality, safety, and efficacy of biologics. These additional resources will enable the FDA to conduct in-depth independent analysis of submitted data BLAs and support the publication of guidance documents to ensure up-to-date review criteria and processes for next-generation biologic treatments and therapies.

**Enhance FDA hiring, retention, and financial management**

PDUFA VII continues to build upon the resource management and fiscal accountability provisions included in PDUVA VI. For example, the time reporting system initiated under the previous Agreement will be optimized to allow for time and associated costs to be reported and examined on a more continual basis. Additionally, to strengthen fiscal and staff resource management, accountability, and transparency, PDUFA VII will continue to mature the resource capacity planning system that includes a publication of an updated implementation plan describing how resource capacity planning and time reporting will be improved and implemented over the coming 5-year PDUFA cycle. A third-party assessment of the capacity planning system will be conducted and inform the 5-year fiscal planning activities. Recommendations and findings of this assessment will be included in the annual financial reports. Additionally, FDA will maintain a stronger operating reserve to ensure they are better able to mitigate against disruptions to funding resources and continue to carry out mission critical activities.

Ensuring the FDA is able to recruit and retain world-class personnel is the bedrock for maintaining U.S. regulatory leadership around the world. PDUFA VII continues to provide

resources and tools to better enable the FDA to attract and retain leading medical and scientific professionals. Specifically, PDUFA VII provides the FDA with resources to conduct a third-party assessment of hiring and retention to identify challenges and provide recommendations for the Agency. These recommendations will be made available to the public where the FDA will also share its plans to address issues raised.

### **BsUFA Highlights**

The Biosimilar User Fee Agreement (BsUFA) contains several commitments that have the same goals and objectives as those included in PDUFA VII including, maintaining and improving performance goals for the effective and timely review of biosimilars, improving scientific dialogue, best meeting practices, modernizing IT capabilities, advance utilization of RWE to assess safety and support regulatory decision making, and strengthening the ability to recruit and retain world-class personnel. Below I will highlight a few of the key beneficial provisions included in the BsUFA III Commitment Letter.

### **Improving Scientific Dialogue**

Ensuring timely scientific dialogue throughout the review process is a top priority for BIO member companies. BsUFA will improve the ability to engage in timely and focused discussions through the creation of new and improved meeting opportunities. Specifically, the FDA will now provide a new meeting structure that enables the FDA and sponsors of applications to engage in focused conversations on a narrow set of issues. Under the new structure a sponsor can request a dedicated meeting to discuss feedback on things like revised study designs or discuss CMC post-approval commitment. They can also request a dedicated meeting to discuss specific issues such proposed study designs or review of summary data.

BsUFA III also reforms the biosimilar initial advisory (BIA)<sup>3</sup> advisory meeting process designed to better manage FDA workload and ensure productive discussions about whether licensure of a biosimilar is feasible, and, if so, plans and expectations for the development of that biosimilar.

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<sup>3</sup> A BIA meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the PHS Act may be feasible for a particular product, and if so, general advice on the expected content of the development program.

### **Improving Review Processes of Biosimilar Supplemental Applications**

The BsUFA III agreement will bring more predictability and efficiency to the review of supplements. Specifically, there will be timelines and goals established for 6 different types of supplement categories (updating of label with new safety information (3 mos.), additional indications where new data is not required (4 mos.); removal of an approved indication (4 mos.) additional indications where new data is required (6 mos); additional indications that includes efficacy data (6 mos. for resubmission, 10 mos. for original application); and, applications seeking an initial determination of interchangeability (6 mos. for resubmission, 10 mos. for original application). These commitments will increase efficiency, consistency, and predictability of biosimilar supplemental applications and provide patients with timelier access to these medicines.

### **Advancing the Development and Review of Interchangeable Biosimilars**

BsUFA III will work to continue support more efficient and understood processes for the approval of interchangeable biosimilars. The FDA will hold a scientific workshop to discuss and shared learnings and remaining challenges to the development of interchangeable biosimilars that will serve to help the FDA determine what additional steps need be taken to support the development and availability of these medicines (e.g. additional guidance or research). Following the workshop, the FDA will publish a strategy document describing the specific actions the FDA will implement to facilitate development of interchangeable biosimilars.

To advance regulatory science in this field, the FDA will pilot a regulatory science program that is designed to advance the development of interchangeable products and improve the efficiency of their development. Specifically, this pilot program will work to improve knowledge about how data (including RWE) can be utilized to meet safety standards for determining interchangeability and what methodologies can be utilized to assess the potential impact of differences between proposed interchangeable biosimilars and their reference products. The findings and shared learnings from this pilot program will greatly advance the development, review and availability of interchangeable biosimilar medicines.

### **Interchangeable Biosimilar Labeling and Manufacturing Guidance**

Under BsUFA III the FDA will publish guidance to that will serve to improve communication of important biosimilar labeling information to patients and their caregivers and better facilitate resolution of manufacturing issues. Specifically, the FDA will publish a guidance on labeling for

interchangeable biosimilars, a guidance on promotional labeling and advertising considerations for interchangeable biosimilar products, and a guidance on what information is needed to support post-approval manufacturing changes to approved biosimilar and interchangeable biosimilar products. Collectively, these will serve to provide a greater understanding of what is required for efficient review and approval of changes to labels and manufacturing processes.

**Closing Comments**

BIO strongly supports the PDUFA VII and BsUFA III Commitment Letters. The resources provided will serve to maintain FDA's global leadership and enable the Agency to keep pace with the medical and scientific advances of today and tomorrow. BIO urges Congress to act swiftly and support timely enactment of these vital critical reauthorizations so that the FDA is able efficiently and effectively protect the public and provide timely access to medicines to medicines that improve the lives of patients and their families.