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Senate Health, Education, Labor & Pensions Committee Hearing:

FDA User Fee Agreements: Advancing Medical Product Regulation and Innovation for the Benefit of Patients

April 5th, 2022

Introduction

Good morning, Chairwoman Murray, Ranking Member Burr, and Members of the Committee. My name is Cartier Esham, and I am the Chief Scientific Officer at the Biotechnology Innovation Organization, or BIO. BIO appreciates the opportunity to speak with you today about key priorities we believe will improve regulatory oversight and transparency, as well as enable biopharmaceutical companies to modernize the clinical development paradigm to one that is more patient-centric, efficient, and inclusive. Congress has built a strong foundation over many years that has served to expedite patients' access to safe and effective therapies, and helped innovators develop next-generation medicines that have improved the lives of patients and their families. We look forward to working with this Committee to continue to building on these efforts and urge that the Committee proceed with the timely reauthorization of the Prescription Drug User Fee Act and Biosimilar User Fee Act to ensure FDA can continue to meet its mission to protect and promote public health.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and more than 30 other nations. While our membership includes most of the large, international biopharmaceutical companies, the majority 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.

Since the initial enactment of the Prescription Drug User Fee Act (PDUFA) in 1992, user fees have played a key role in ensuring that effective and efficient regulatory processes keep pace with the continual advancement of scientific and medical innovation. As a result, more innovative treatments and therapies are first approved in the United States, providing our citizens with faster access to innovative medicines. Additionally, the PDUFA program ensures that FDA has the resources, capabilities, and processes in place to establish a clear and direct pathway from initial scientific discovery to widespread availability of cutting-edge medicines. This benefits not only regulators, patients, and the biopharmaceutical industry, but also the entrepreneurial community that makes significant investments in high-risk, early-stage, innovative medicine development. Today, it can take anywhere from 10 to 15 years at an average cost of approximately $1 billion or more to advance a single drug or biological product from a promising idea to an approved product that benefits patients.[1,2] A well-run and comprehensible pathway to approval is critical to maintaining U.S. leadership in investment, development, and availability of next-generation medicines.

The Prescription Drug and Biosimilar User Fee Acts (PDUFA and BsUFA) have collectively worked to ensure effective and timely reviews, improve drug and biologics safety monitoring, enable the Agency to keep pace with medical and scientific advancements, allow for earlier and

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[1] 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).
[2] Joseph A. DiMasi; Henry G. Grabowskibi; Ronald W. Hansen. Innovation in the pharmaceutical industry: New estimates of R&D costs. 2016. Journal of Health Economics. 2016, Vol. 47.

more frequent FDA-sponsor engagement to identify and resolve drug and biologic development challenges, and provide the support necessary to ensure that advanced medicines are available to patients as efficiently and safely as possible. These user fee programs, which are reauthorized by Congress every five years, provide FDA with the authority to collect fees from companies that produce certain human drugs, biologics, medical devices, and generics. These user fees, in addition to the resources provided through direct appropriations from Congress, have ensured that FDA is a global leader in regulatory advancement and oversight. Last year, 76% of novel drugs approved by FDA's Center for Drug Evaluation and Research (CDER) were approved in the U.S. before any other country.[3]

User fee programs are not fee-for-service programs, and fees paid by a company for a medical product application are not tied to the review of that particular application. Instead, these fees support a wide range of regulatory programs and ensure FDA has the resources, capabilities, and processes in place to maintain clear regulatory pathways and keep pace with medical and scientific innovation. The PDUFA and BsUFA agreements currently under consideration continue to advance those goals and activities and include additional commitments that will strengthen review fundamentals, enhance accountability and transparency, ensure stable growth of successful existing regulatory programs, and foster innovative scientific advancements.

Highlighting a few key topics that are most important to BIO, our member companies, and, most importantly, the patients we serve, we would like to emphasize the importance of promoting effective scientific dialogue between FDA and sponsors of medical product development programs, enabling the utilization of regulatory tools that are more effective and support broader and more meaningful understandings of clinical outcomes for all patients, the incorporation of

[3] https://www.fda.gov/media/155227/download

patient perspectives in clinical trials and post-approval data collection, and the necessity to provide the resources and capacity needed to meet the demands and opportunities of the digital age. The COVID-19 pandemic has shown us that decentralized clinical trials, digital health technology tools, and other innovations utilized during the pandemic have the potential to improve how we develop medicines that meet the needs of patients and greatly reduce the burden on clinical trial participants, especially for those who belong to historically underserved populations and for those who suffer from rare diseases, where clinical trial populations are small and geographically dispersed. We urge an on-time reauthorization of FDA's user fee programs to allow the enactment of the PDUFA VII and BsUFA III Commitment Letters that will continue to advance meaningful integration of the patient voice and experience into drug and biosimilar biological product development and review processes, build upon important lessons learned from the pandemic, and pave a path forward to a clinical development paradigm that is more effective, more informative, and more inclusive.

Overall Goals for PDUFA VII

Each user-fee Commitment Letter has continued to build upon the efforts of previous agreements. The following testimony will describe the content and benefit of critical provisions addressed in seven primary themes included in the PDUVA VII Commitment Letter:

1. Strengthen scientific dialogue and advance innovation
2. Support the next wave of advanced biological therapeutics
3. Enhance patient-centric drug development, review, and protections
4. Modernize regulatory evidence generation and drug development tools
5. Enhance innovation in manufacturing and product quality reviews
6. Advance digital technologies and information technology (IT) infrastructure
7. Enhance FDA hiring, retention, and financial management

Strengthen scientific dialogue and advance innovation

A goal of PDUFA VII most critical to advancing innovation involves enhancing and strengthening scientific dialogue between sponsors of applications and FDA. To that end, FDA, for the first time, will provide consistent timelines for Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) meetings and expand the scope of these meetings to include products regulated by the Center for Drug Evaluation and Research (CDER). INTERACT meetings have been critical for sponsors of innovative biological products who face unique challenges that could otherwise delay entry into clinical development. FDA will also establish a new Type D meeting that enables FDA and sponsors to engage in more rapid and focused conversations about innovative approaches or unique challenges that will allow for earlier resolution of discrete issues. The Commitment Letter also formalizes a process where sponsors can submit clarifying questions to FDA following a meeting to ensure alignment on expectations and requirements. We collectively recognized that establishing and following best practices for productive meetings is a shared responsibility between biopharmaceutical companies and FDA.

There are at least 7,000 known rare diseases collectively impacting over 25 million Americans with new rare diseases identified each year. Because rare diseases have limited or no treatment options and lack well-established regulatory precedents, the development and review of these medicines introduces additional challenges that must be overcome to deliver new therapies to patients who need them. Key among these challenges is reaching agreement with regulators about determining the appropriate efficacy endpoints to support approval of innovative medicines for rare diseases. The current mechanisms for companies with rare disease treatments in their pipeline to collaborate with FDA has not consistently provided avenues for much needed discussions about these unique issues, which can cause delays in the development and availability of medicines to these patients who often lack options. The

Rare Disease Endpoint Advancement (RDEA) pilot program in PDUFA VII will provide avenues for focused engagement opportunities that will serve to advance and share learnings and enable more efficient drug development and review process for all rare disease medicines.

The Commitment Letter will establish a Split Real Time Application Review (STAR) pilot program for certain applications that are intended to treat a serious condition with an unmet need. The pilot builds on the concepts that have proven successful for FDA's Real Time Oncology Review (RTOR) program and expands them to other disease areas to enable more timely reviews and availability of these medicines to vulnerable patient populations. The STAR pilot will improve both the s and industry's workload management by allowing sponsors of applications to submit their applications in two parts rather than one, 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.

Biopharmaceutical companies and 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 includes commitments to ensure necessary PMRs are identified and communicated earlier in the review process and enable the development and implementation of more thoughtful study designs. This will better ensure that these PMRs are completed on time and avoids delays in confirmatory trials. PDUFA VII will also stablish stronger processes for the continued evaluation of PMRs post-approval to ensure requirements are being met, issues can be resolved, and the studies remain scientifically valid.

Support the next wave of advanced biological therapeutics

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 products under development

compared to only 93 products in 2015, a trend that is expected to continue 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 with 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 CBER's workload caused by increased regulatory submission volume as projected over the next 5 years as well as keep pace with scientific and technological advancements. As part of the commitment, FDA will facilitate a better understanding of patient perspectives on gene therapy products, including cell-mediated gene therapy, and provide greater clarity on expedited pathways for regenerative medicines. FDA will streamline and harmonize processes, procedures, and interactions by enhancing, improving, and issuing guidance describing best practices for communication related to aspects of Cell and Gene Therapy product development, including the use of novel trial designs.

Enhance patient-centric drug development, review, and protections

One of the most important goals of PDUFA VII involves continuing to advance the systematic integration of patient perspective data into drug development 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 themselves evaluated benefits, risks, and needs. PDUFA VI advanced this work by holding a series of public meetings and publishing guidance that provided information about how to determine the most important impacts to patients, how to measure disease impact, and how to incorporate Clinical Outcome Assessments (COAs) into clinical development and review processes.

During PDUFA VII, 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. 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 FDA's 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 product development. FDA will also seek public input on which diseases areas have the greatest need for Standard COA development. Additionally, FDA will work to increase shared understandings about how patient preference studies can inform meaningful benefit-risk assessments in therapeutic areas, which is of very high value to the patient community.

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, 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. The agreement establishes an Advance RWE pilot program that will provide shared learnings with the public and inform the publication of guidance increasing broad knowledge about how and when RWE can be utilized in future applications.

Complex innovative trial designs can be more efficient, improve patient outcomes, and produce high-quality information faster compared to traditional trial designs. PDUFA VII will continue both the Complex Innovative Trial Design and Model-Informed Drug Development (MIDD) pilot programs which enable the utilization of these tools and approaches more broadly. Additionally, the Agreement will enhance the drug development tool (DDT) qualification pathway for biomarkers by retaining and enhancing staff capacity and piloting processes that enhance 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.

To enhance FDA's 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. PDUFA VII will modernize and improve Risk Evaluation and Mitigation Strategies (REMS) approaches and processes through new guidance documents and timelines for feedback to companies on REMS methodologies. Newly allocated resources will expand and optimize FDA's electronic safety database (the Sentinel program) including supporting the integration of Sentinel and BEST (Biologics Effectiveness and Safety) systems, and FDA will advance knowledge about how Sentinel data can be used for regulatory purposes (*e.g.,* PMRs, PMCs and labeling) and how real-world evidence (RWE) may be used for evaluating the effectiveness of medicines. Collectively, these improvements and advancements in FDA's drug safety system will improve patient protections and utilization of this vast data resource to gain deeper insights about the benefits and risks of medicines for all patients.

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 has 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 enable more consistent review of high-quality information requests from sponsors. FDA will also engage a third party to assess, seek public comment, and provide recommendations about how these processes can be optimized to support modernization of CMC-related processes.

To address the outsized hindrance of timely availability of innovative treatments for serious and life-threatening diseases undergoing expedited reviews due to CMC issues, FDA will publish new internal documents to better align CMC communications and processes to meet the desired timelines for approval decisions more consistently. The FDA will also establish a CMC Development and Readiness Pilot (CDRP) in both CDER and CBER to provide additional opportunities for engagement between FDA and sponsors that will help companies meet critical CMC milestones. Learnings from this pilot and an associated public workshop will inform 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 effectively and efficiently manufacture high-quality complex medicines. PDUFA VII will work to identify and remove current barriers to the utilization and adoption of advanced manufacturing technologies. 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. We are pleased that this Committee included a focus on manufacturing in the PREVENT Pandemics Act, and BIO supports the pathways for reviews of technologies established under Sections 506 and 518 of that bill which will enhance these PDUFA goals and facilitate the adoption of advanced manufacturing.

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 FDA to increase its capacity and ability to meet the demands and opportunities of the data and digital age. Increasing utilization of cloud technologies is necessary for FDA to meet the growing needs, demands, and advantages of modern-day development and review of innovative medicines. Today's medical product applications have large and/or complex data sets that require high-quality repository and analytical capabilities. PDUFA VII activities and resources, collectively, will enable FDA to make the necessary changes to meet these needs. These advancements will serve to improve the quality of applications submitted to FDA and improve our ability to better understand the benefits and risks of medicines to all patients before and after they are approved.

First, FDA will continue to meaningfully advance its Data and Technology Modernization Strategy to improve both FDA's enterprise needs and to advance key PDUFA objectives such

as completing transition to a cloud-based system. 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, FDA will launch a series of demonstration projects in collaboration with external partners to improve the core capabilities necessary for reviewing data captured via digital technology tools. We expect continued growth in the utilization of 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. 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.

Enhance FDA hiring, retention, and financial management

PDUFA VII continues to build upon the resource management and fiscal accountability provisions included in PDUFA 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 FDA can 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 FDA to attract and retain leading medical and scientific professionals. Specifically, PDUFA VII provides 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 FDA will also share its plans to address issues raised.

BSUFA III 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 and meeting best practices, modernizing IT capabilities, advancing 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 key beneficial provisions included in the BsUFA III Commitment Letter most important to our member companies and the patients we serve.

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, FDA will now provide a new meeting structure that enables FDA and sponsors of applications to engage in focused conversations on a narrow set of issues. BsUFA III also reforms the biosimilar initial advisory (BIA) [4] advisory meeting process 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.

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. 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 continue to support more efficient and better understood processes for the approval of interchangeable biosimilars. FDA will hold a scientific workshop to discuss shared learnings and remaining challenges to the development of interchangeable biosimilars that will

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[4] 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.

help 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, FDA will publish a strategy document describing the specific actions FDA will implement to facilitate development of interchangeable biosimilars.

To advance regulatory science in this field, 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, FDA will publish guidance that will serve to improve communication of important biosimilar labeling information to patients and their caregivers and better facilitate resolution of manufacturing issues. Specifically, 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.

Priorities for Advancing Medical Product Regulation and Innovation for the Benefit of Patients

BIO strongly supports the objectives and activities outlined in the PDUFA VII and BsUFA III commitment letters. These commitments, in addition to other key pieces of legislation and initiatives from Congress and the pharmaceutical industry, will facilitate innovation that benefits all patients served by our member companies. The testimony below outlines additional priorities that we believe will support this objective.

Building a New Clinical Development Paradigm: More Inclusive, More Patient Centric and More Informative About Clinical Outcomes for All Patients

BIO is committed to enhancing clinical trial diversity, and we included this commitment as part of our BIOEquality Agenda launched in 2020. The COVID-19 pandemic highlighted the urgent need to remove barriers and advance solutions that enable clinical trials to be more representative of the patients being treated. Scientific advancements are providing opportunities to establish clinical development and post-approval data collection approaches that can improve our understanding of clinical outcomes for all patients. The PDUFA VII Commitment letter will provide resources, capacity, and the development of guidance that will significantly advance regulatory certainty and promote the acceptance of real-world data/evidence (RWD/RWE) and digital health tools (DHTs) like remote monitoring devices, cell phones, and smart watches that are essential in more broadly enabling the utilization of decentralized or non-traditional clinical trial locations.

BIO stands ready to work with Congress, the Administration, and stakeholders to create a more expansive, inclusive, and sustainable clinical development ecosystem. We need to modernize the regulatory system to accept innovative tools and approaches that enable increased

participation in clinical trials from underrepresented communities and the ability to collect data that improve our understanding of clinical outcomes for all patients. In addition to important legislation addressing these issues that will be discussed today, BIO has provided this Committee with legislative proposals we believe are essential to removing barriers and establishing a regulatory framework that is more inclusive and representative of the patients we serve.

The lack of reliable data sources capturing U.S. demographics is a challenge that must be resolved. Incomplete or outright missing demographic data for many disease areas leads to poorly or inaccurately informed enrollment targets and action plans during drug development. While FDA regulations require sponsors to present a summary of safety and effectiveness data by demographic subgroups within their trials, it is difficult to compare this data to epidemiological data to understand whether enrollment targets are representative of the disease population. Sponsors also lack certainty regarding innovative clinical trial designs that could improve trial diversity. Traditional clinical trial designs are typically geographically centralized around academic medical centers and associated with significant burden for patients, such as multiple mandatory visits to the clinic. This creates significant challenges when recruiting individuals who are geographically dispersed, unable to travel, or unable to take leave from work. By contrast, modern trial designs that embrace innovative tools and methods, like digital health technologies, decentralized clinical trials, and RWD/RWE, have demonstrated success in facilitating trials and driving diverse enrollment throughout the COVID-19 pandemic[5], but companies currently lack a regulatory framework to fully leverage such techniques and tools.

We need to re-examine and update approaches to and criteria for the establishment of inclusion and exclusion criteria and advance approaches to data collection for approved medicines that

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[5] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789002

enhance our understanding of benefits and risks for all patients and enable that information to be more transparent and available to patients and their care givers. Our proposal requires public meetings with comment periods and the publication of guidance on each of these topics that together will work to remove present-day barriers and establish a regulatory framework that promotes inclusive and representative clinical development and review processes.

To help build a more expansive, inclusive, and sustainable clinical trial network infrastructure, BIO also recommends that HHS conducts a series of public roundtable discussions that converge stakeholders from FDA, NIH, CDC, community organizations, industry, and clinical research organizations (CROs) to discuss, develop, and implement recommendations that will serve to create a more expansive and inclusive clinical development infrastructure. Roundtable discussion topics could include establishing a publicly available database of well-indexed active clinical trialists, establishing clinical trialist training programs and mentoring networks for investigators/trialists serving underrepresented communities, and establishing a publicly available database of community engagement organizations supported by NIH. HHS should also establish new or leverage existing programs for a federally funded clinical trial investigator fellowship pilot program for women, members of the LGBTQIA+ community, and racial and ethnic minorities to help increase participation of underrepresented populations in clinical trials.

To promote diversity and inclusion for workforce development in the STEM community, BIO also recommends requirements for FDA and NIH to improve transparency around hiring, retention, and promotion practices within their organizational leadership and scientific workforces. Requirements should outline clear objectives for staff and leadership diversification and include a regular reporting cadence to Congress on metrics related to progress on these objectives. Such provisions would work synergistically with human resources (HR) authorities established by the 21st Century Cures Act of 2016 that enable FDA to build and maintain a talented workforce that keeps pace with rapid scientific and technical advancements in the

biopharmaceutical industry. These HR authorities grant FDA increased flexibility to streamline the hiring process for recruits with specific scientific, technical, and professional occupations. They also established a new pay authority enabling FDA to compete with the private sector and academia when recruiting and retaining highly qualified candidates for these key positions. Together, these activities would strengthen the federal public health workforce in terms of talent, expertise, and diversity.

We acknowledge that removing regulatory barriers and enhancing and developing data sources and infrastructure will not address all existing barriers to inclusive clinical trial participation, including language and health literacy disparities and historical mistrust of certain clinical research tactics and ethics. We have established a website, The Power of Participation (www.ctpop.org), for patients, designed to help assess and locate clinical trial opportunities and identify patient and community organizations they may find helpful. We remain committed to working with stakeholders across the public health spectrum to provide meaningful educational materials for all patients.

Accelerated Approval Brings Life Changing Treatments to Patients who Urgently Need Them

BIO continues to strongly support the Accelerated Approval Pathway (AAP) for reviewing safe and effective therapies that address critical unmet patient needs in serious and life-threatening disease states. This pathway has proven to be very effective in addressing some of the most pressing public health needs and has been foundational to extending and saving countless lives since its enactment. As of June 2021, 269 new drugs or biologics to treat serious or life-threatening diseases or conditions with high unmet medical needs have been approved through this pathway, extending, and in certain cases, saving patients' lives by providing novel therapies

earlier than would have been possible using the traditional pathway[6]. Medicines approved through this pathway meet FDA's well-established approval standard of safety and effectiveness. The AAP is essential to providing timely access to treatments where there is an unmet need and for patients who lack therapeutic options.

Since the AAP was established in 1992[7], the pathway has led to the approval of treatments that have significantly improved the care of patients suffering from many different diseases, including rare cancers, Human Immunodeficiency Virus (HIV), bacterial infections, multiple sclerosis, sickle cell disease, and other serious and life-threatening conditions. The AAP encourages scientific and medical advancement by allowing the use of surrogate or intermediate clinical endpoints that are reasonably likely to predict clinical benefit to support approval. Prior to the establishment of the AAP, patients with HIV recognized the need for a new pathway as the development of treatments using traditional endpoints of disease progression and death were prohibitory to providing access to much needed treatments for patients suffering from this deadly disease. The AAP enabled the approval of the first HIV/AIDS treatment based on the use of surrogate endpoints (viral load and CDR count) which served to prolong and save the lives of millions of patients. The PDUFA VII agreement includes commitments that will strengthen the AAP, such as advancing surrogate endpoint development through the RDEA Pilot Program and providing avenues for earlier and more timely discussions on the design of post-market requirements to avoid delays in confirmatory trials. (PMRs), which are critical to confirming the clinical benefits of products receiving accelerated approval[8]. The Commitment Letter will also serve to advance regulatory understandings about when and how RWE may be

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[6] https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals

[7] In 1992, and partially codified in 1997, FDA instituted the Accelerated Approval regulations (21 CFR 314 Subpart H and 601 Subpart E) to formalize the process for approving drugs to treat serious conditions that filled an unmet medical need based on a study of surrogate endpoints.

[8] Sponsors planning to use surrogate endpoints as primary efficacy endpoints also gained an opportunity to consult with FDA earlier in the drug development process through Type C Surrogate Endpoint meetings established during PDUFA VI.

used to support PMRs that may significantly improve the ability to complete PMRs in a more effective and efficient manner, modernizing the conduct of confirmatory trials required by the AAP.

Patients have consistently voiced their support for the use of AAP over the last 30 years. We have all seen how this pathway has led to more timely access to treatments that improve, extend, and save lives and has been foundational to continued advancements in the treatment of serious and life-threatening diseases. BIO looks forward to working with the Committee to ensure that the Accelerated Approval Pathway is working efficiently, effectively, and as intended.

Closing Comments

BIO member companies are committed to advancing innovation on behalf of all patients, especially in areas of unmet medical need. Our members constantly adapt to keep pace with technological and scientific advancements that create opportunities to develop new therapies for patients without any other options. The regulatory framework established and refined over multiple reauthorization cycles by Congress, including members of this Committee, enables our member companies to collaborate with the academic, advocacy, and patient communities to develop innovative solutions to health challenges that have historically left patients with little to no hope.

In 2021 alone, FDA approved 60 new therapeutic products between CDER and CBER, including treatments to prevent and mitigate the impact of COVID-19. 27 of these new drugs were first-in-class, up from 21 first-in-class approvals in the previous year. There were 26

approvals for rare disease treatments that received orphan drug designations.[9,10] FDA staff adapted to unforeseen challenges to fulfill their mission to protect and promote public health, and industry continues to adapt as well. In addition to efforts from regulators, these life-changing and life-saving approvals would not have been possible without unwavering commitment by our member companies to create innovative treatments and ensure that they reach the patients who urgently need them. The biopharmaceutical industry supports and shares FDA's mission to protect and promote public health by ensuring access to safe and effective drugs and biological products for patients, and this shared commitment enabled continued progress towards this mission despite unprecedented obstacles posed by the pandemic. This reauthorization is an opportunity to build on lessons learned from responding to the COVID-19 public health emergency and incorporate these innovations into the regulatory paradigm.

Companies continue to invest in and develop advanced manufacturing technologies that offer the promise of increased capacity and efficiency to help expedite production, enhance product quality, and address shortages of essential medications. Innovation in new drug and biologic development has been robustly incentivized by the modern drug/biologic regulatory framework at FDA, and BIO continues to work with members of Congress to tackle unprecedented technical and regulatory challenges like those associated with investment in advanced manufacturing technologies and tools to modernize medical product development and distribution.

Drug development for patient populations with unique needs, such as the pediatric community, remains a priority for BIO and our members, and we celebrate the many successes that benefit

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[9] https://www.fda.gov/media/155227/download
[10] https://www.raps.org/news-and-articles/news-articles/2022/1/fda-approved-more-first-in-class-drugs-more-with-a#:~:text=Other%20drugs%20approved%20by%20CDER,treatment%20options%20for%20rare%20diseases.

our youngest patients stemming from these efforts. Today, we have numerous therapies with pediatric indications, including for neonates, that are making a measurable difference for these patients and their families. We have seen advancements across a range of conditions, including recent drug approvals in sickle cell, cystic fibrosis, pediatric rheumatologic conditions, and even Ebola, and we are optimistic about the breakthroughs to come. BIO is committed to building on this progress by delivering more innovative medicines to pediatric patients.

PDUFA VII and BsUFA III include provisions to enhance drug development with the goal of advancing novel therapies for patients, including in disease areas with an unmet medical need and which have proven to be more challenging areas for developing therapies, like rare diseases and pediatrics. Leveraging advances in science, enhancing the application of drug development tools, and modernizing clinical trials are critical to continuing to improve the drug development paradigm and regulatory processes for these medicines so we can better serve these patients and their families.

These commitments will build on the numerous provisions Congress has enacted over the years to help foster the development of promising therapies for children, including the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). The most recent PDUFA reauthorization bill (The FDA Reauthorization Act of 2017) included new requirements for pediatric studies of certain cancer drugs that FDA is in the process of implementing. The initial impact of that legislation is beginning to work through the development cycle and BIO and its member companies will continue to work with FDA to ensure effective implementation of these programs.

The Orphan Drug Act (ODA) is a critical tool used to incentivize the expensive and heavily uncertain investment necessary to bring therapeutics for rare and orphan diseases to market. It is difficult to identify a more successful and consequential regulatory incentive than the ODA. Before it passed, there were merely a handful of treatments for rare disease patients. Today,

we have hundreds of life changing treatments for these patients with countless more in the pipeline. We celebrate scientific progress that has led to innovative medical product development alongside patients, parents, and caregivers who have new treatment options, and sometimes even cures, that were previously unthinkable. While there is now immense hope for even the rarest diseases, many more are still waiting. There are thousands of identified rare diseases afflicting patients across the globe, many of which still have no alternative or meaningful treatments on the market. Given the tremendous risk, capital, and time it takes to discover and develop such medicines, the rare disease development paradigm should be handled with the utmost care and with significant consideration for potentiality of unintended consequences.

BIO strongly supports timely enactment of 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. We look forward to working with Congress to advance proposals that support a new clinical development paradigm that is more expansive, inclusive, and patient-centric and continues to incentivize the development and timely delivery of next-generation medicines that save and improve the lives of patients and their families.