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House Energy and Commerce Committee Hearing:
The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight

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Introduction

Good morning, Chairwoman Eshoo, Ranking Member Guthrie, Chairman Pallone, Ranking Member McMorris Rodgers, 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, and to develop next generation medicines that will improve the lives of patients and their families. Congress has built a strong foundation over many years that has served to expedite patients' access to safe and effective therapies. We look forward to working with this Committee to build on these efforts as we discuss proposed legislation under consideration. We also urge that the Committee proceed with the timely reauthorization of the Prescription Drug User Fee Act and Biosimilar User Fee Act to ensure the FDA is able to continue to meet its mission to protect and promote the public health.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations 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.

Key legislation and regulatory programs like the enacted Prescription Drug and Biosimilar User Fee Acts (PDUFA and BsUFA) and 21st Century Cures Act 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 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 provided to patients as quickly and safely as possible. The PDUFA and

BsUFA agreements 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 next-generation 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 the FDA and sponsors of clinical 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 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 timely enactment of the PDUFA VII Commitment Letter that will continue to advance meaningful integration of the patient voice and experience into drug development and review processes, builds upon important lessons learned from the pandemic, and paves a path forward to building a clinical development paradigm that is more effective, more informative, and more inclusive. We stand ready to work with Congress on legislation that advances these priorities.

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

BIO and its members outlined our commitment to enhancing clinical trial diversity 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 a clinical development and post-approval data collection approach that will 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 must advance regulatory alignment on the acceptance of 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[1], but companies currently lack a regulatory framework to leverage such techniques and tools fully.

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

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 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.

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

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[2]. Medicines approved under this pathway must still 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 do not have any available treatments.

Since the AAP was established in 1992[3], 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 on 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.

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

[3] 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.

The PDUFA VII agreement includes commitments to further enable early engagement on what criteria are needed to support utilization of a surrogate endpoint. The Commitment Letter also includes support for the development and implementation of a Rare Disease Endpoint Advancement (RDEA) Pilot Program, which will facilitate collaboration and agreement between sponsors and FDA on appropriate efficacy endpoints that assess outcomes in these particularly vulnerable patient populations. The RDEA Pilot Program will prioritize endpoints with potential applicability to multiple diseases to maximize impact for patients. FDA will also develop their staff capacity to support the complex and intensive review work necessary to evaluate novel endpoints with a focus on the challenges of trials in small populations. These commitments will help ensure scientific rigor and advance regulatory understanding about what is necessary to support the utilization of a surrogate endpoint as a basis for approval.

The AAP also requires that sponsors conduct studies to confirm a continued demonstration of benefit and evaluation of risk. The FDA has the authority to withdraw a treatment from the market if it determines that the benefit has not been confirmed or it is determined that the risk outweighs the benefit. To ensure that the design and implementation of confirmatory trials are more effective, the PDUFA VII Commitment Letter provides avenues for earlier and timely discussions on the design of post-market requirements (PMRs), which are critical to confirming the clinical benefits of products receiving accelerated approval[4]. Both biopharmaceutical companies and FDA recognize the importance of post-marketing requirements 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 early engagement and discussions are occurring in a manner that allow for more effective assessments of PMR needs and enable more thoughtful PMR study designs. PDUFA VII will also establish improved processes for the continued evaluation of PMRs post-approval to ensure requirements are being met and/or remain scientifically valid. The Commitment Letter will also serve to advance regulatory understandings about when and how RWE may be used to support PMRs that may significantly improve the ability to complete PMRs in a more effective and efficient manner.

Patients have consistently voiced their support of 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

[4] 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.

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.

Continuing Momentum with Pediatric Drug Development

BIO member companies are committed to advancing innovations on behalf of all patients, especially in areas of unmet medical need, which includes our commitment to pediatric patients. Drug development is a challenging endeavor for many reasons, including scientific and technical limitations. The research and development of vaccines and therapeutics for children represent some of the most challenging and important areas of drug development.

The challenges innovators face in studying and bringing forward promising medical products for children reflects the unique considerations in developing medical products for this population, which can range from neonates to adolescents and young adults. These considerations include the inherent physiological differences between adults and children, the dynamic that some diseases are different in adults and children, and challenges in designing and carrying out pediatric clinical trials. In some circumstances, a product may first be approved for an adult population, helping to advance the study and development of a product for use in children. However, bringing forward pediatric products often requires a case-by-case, not a "one-size-fits-all," approach.

PDUFA VII includes 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 pediatrics. Leveraging advances in science, enhancing the application of drug development tools, and modernizing clinical trials are all important elements of continuing to strengthen and enhance the drug development paradigm to better serve patients, including in areas with unmet pediatric needs. PDUFA VII 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).

More recently, the last 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.

Pediatric drug development remains a priority for BIO and our members, and we celebrate the many successes that benefit our youngest patients stemming from their 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 looks forward to building on this progress, and we appreciate the opportunity to engage and collaborate with Congress and FDA on these important issues on behalf of the pediatric patients we serve.

Advanced Manufacturing

Advanced manufacturing technologies offer the promise of increased capacity and efficiency that can help sponsors expedite production, enhance product quality, and address shortages of medications essential to public health. As more products rely on platform technologies and more gene therapies are commercialized, our domestic manufacturing capacity and technology must keep pace with product innovation.

While innovation in new drug and biologic development has been robustly incentivized by the modern drug/biologic regulatory framework at FDA, the use of innovative manufacturing technologies and techniques has not had similar support. Many companies, especially smaller ones, often decide that making in-house investments in manufacturing, or taking a risk on a new manufacturing technology offered by a contract manufacturer, is not feasible. Once a product is approved, manufacturing processes used during the initial application become the standard for the product, because any changes require additional supplemental applications, regulatory hurdles, and product risks which have no market incentive to overcome, despite potential improvements to manufacturing efficiency and product consistency and quality.

The FDA acknowledges this barrier and recognizes that adopting innovative approaches to manufacturing may present both technical and regulatory challenges. Biopharmaceutical companies may have concerns that using such technologies could result in delays while FDA reviewers familiarize

themselves with the new technologies and determine how they may be evaluated within the existing regulatory framework[5]. Until these innovative tools and technologies "graduate" to standard regulatory frameworks, the development and review of products that leverage them is resource and time-intensive for both sponsors and the Agency.

BIO supports FDA and Congressional efforts to facilitate the development and adoption of novel manufacturing technologies such as CDER's Emerging Technology Program. The ETP aims to "promote the adoption of innovative approaches to pharmaceutical product design and manufacturing. Through the program, industry representatives can meet with Emerging Technology Team (ETT) members to discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology prior to filing a regulatory submission." Additional support for the ETP program would help to facilitate the development and utilization of 21st Century manufacturing technologies. A comparable program in CBER, the CBER Advanced Technologies Team (CATT), provides similar support and engagement to sponsors developing CBER-regulated products that involve advanced manufacturing and testing technologies[6].

Recently, FDA requested that the National Academies of Sciences, Engineering, and Medicine (NASEM) research and publish a consensus study report on the existing and near-future manufacturing technologies that the Agency should prepare for and the barriers that stand in the way of their adoption. The final NASEM report, published in February 2021, recommended that the agency establish a review pathway to evaluate technologies independently from individual drug product applications[7]. BIO believes such a pathway would create confidence, establish regulatory structure and consistency, and facilitate the adoption of new technologies to produce new or existing drug products.

Closing Comments

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

[5] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program
[6] https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt
[7] https://www.nap.edu/catalog/26009/innovations-in-pharmaceutical-manufacturing-on-the-horizon-technical-challenges-regulatory

Congress to advance proposals that support the development and implementation of 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 improve the lives of patients and their families.