Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "
February 3, 2022

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The Honorable Lisa Blunt Rochester (D-DE)

1. **What more can the industry do to expand clinical trial diversity, and what more can the FDA do to support biotechnology companies, academic institutions, and related organizations seeking to increase clinical trial diversity?**

Response:

To drive the industry's efforts to create a more expansive, inclusive, and sustainable clinical development ecosystem, BIO along with our Industry members developed a policy strategy to focus on the removal of regulatory barriers and enhance and develop lagging data sources and infrastructure. We acknowledge that even with improvements to these technical components, many barriers to inclusive clinical trial participations still exist, including language and health literacy differences and historical mistrust of clinical ethics. BIO is committed to working with stakeholders across the spectrum to address these critical components.

The barriers to a clinical development paradigm that are more effective, efficient, and patient centric within FDAs purview are:

1. **Lack of reliable data sources** and alignment on how to set representative targets- U.S. demographic data is incomplete or lacking for many disease areas. This leads to poorly or inaccurately informed enrollment targets and actions plans during drug development. While FDA regulations require sponsors to present a summary of safety and effectiveness data by demographic subgroups their trials, it is difficult to compare this data to epidemiology data to understand whether enrollment targets are representative of the disease population. Additionally, the FDA and industry need to discuss and establish acceptable methodologies to set enrollment targets that are representative of the disease population as we work to improve data sources.
2. **Lack of certainty regarding clinical trial parameters** - There is lack information for drug sponsors regarding how the FDA views clinical trial parameters that are essential to patient recruitment, such as how to support and establish demographic enrollment targets and inclusion/exclusion criteria.

3. **Lack of certainly regarding innovative clinical trial designs.** Clinical trial designs with regulatory certainty are often geographically centralized around academic medical centers and burdensome to participate in (multiple mandatory visits to the clinic). This makes it difficult to recruit individuals from different geographic localities and individuals who aren't economically able to travel or take time off from a job. Modern trial designs that embrace 21st Century technologies (i.e., use of digital technologies, decentralized clinical trials, RWE) that have been shown to be successful in facilitating trials and driving diverse enrollment during the COVID-19 pandemic[1] lack regulatory direction and certainty from the FDA.

BIO appreciates FDA's ongoing efforts to delineate clinical trial diversity expectations, including the April 2022 *Draft Guidance Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials*. We look forward to working with FDA to ensure that this and future guidance documents adequately address the needs of patients, industry, and other relevant stakeholders. However, there are other potential solutions that would support FDA's ongoing efforts that are outlined below.

Potential Solution to support FDA's ongoing efforts

- ***Create and Share Reliable Epidemiological Data Sources***
  Modeled from Patient Informed Drug Development meetings and information sharing, FDA should hold public meetings with comment periods on followed by issuing guidance on:
    - How and when drug sponsors should collect and present disease prevalence and demographic data, the methodologies sponsors should use to conduct diversity assessments, and the criteria FDA considers when accepting various epidemiological data sources data in Investigational New Drugs Application (INDs).
    - How to create more reliable data sources for more diseases, and make data readily and publicly available to all sponsors.

- ***Create Certainty in Clinical Trial Parameters***
  Require FDA to establish an FDA-Sponsor Diversity Engagement Strategy Framework and plan for pivotal trials:
    - The Goals of the Diversity Engagement Strategy would be to enable timely engagement for sponsors and FDA to meet and discuss demographic and/or disease prevalence data and target enrollment during drug development, for approval and any post-approval commitments for continued collection of such data.

- ***Develop Robust Guidance and internal process documents***

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

While not legally binding, guidance documents serve as de facto parameters for FDAs expectations which drug sponsors closely follow. FDA, after holding public meetings with comment periods should issue guidance to address the following issues

- The type, timing, and requirements for meetings between FDA and drug sponsors to engage on developing demographic and/or disease prevalence targets for investigational new drug applications (INDs), New Molecular Entity New Drug Applications/Biologics Licensing Application (NME NDAs/BLAs).
- Criteria and rationale for establishing clinical trial demographic and/or disease prevalence targets in INDs and in NME NDAs/BLAs needed to support FDA approval, including special considerations for small or genetically targeted patient populations.
- Criteria and rational for post marketing commitments for demographic and disease prevalence data including utilization of RWD/RWE.
- Approaches for inclusion and exclusion criteria, study/trial designs, clinical endpoints, biomarker selection, study analysis to better enable inclusion of underrepresented communities.
- Reporting requirements and inclusion of demographic and disease prevalence data in prescription drug labeling and processes for updating information.
- Develop internal process document (SOPP, MAPPs, templates) to train and educate review teams on the criteria and rationale established above.

- ***Advance Innovative Trial Design and Digital Health Technologies***
  Providing sponsors with clarity regarding the FDAs view of decentralized trials, use of RWD/RWE, use of digital health tools to collect endpoints, such as remote monitoring devices, cell phones, smart watches, and non-traditional clinical trial locations will help drive the uptake of these tools. While not legally binding, guidance documents serve as de facto parameters for FDAs expectations which drug sponsors closely follow. FDA, after holding public meetings with comment periods should issue guidance to address the following issues

  - The use of DHTs in traditional and decentralized trials, including addressing the validation of measurements made by DHTs, the use of DHTs to measure existing endpoints, and usability considerations by diverse populations.
  - Approaches for generating real world evidence capturing diverse communities that can meet regulatory requirements in support of labeling.

<u>Other Policy Solutions for Consideration</u>

- ***Communication plan for information sharing***
  Require FDA to reform and expand on Drug Trials
  - Require transparent tracking of demographics in premarket clinical trials of drugs and reported as part of the Drug Trials Snapshot at the time of FDA approval.

- Enable sponsors to submit contextual information for individual snapshots that can be updated as information evolves

Build a more Expansive, Inclusive, and Sustainable Clinical Trial Network Infrastructure

- Require that HHS conduct a series of public roundtable discussions between NIH, FDA, CDC, community organizations, Industry, and CROs to meet regularly to discuss and report on advances in diverse recruitment and develop new strategies in a collaborative way. Potential topics for roundtable:
  - Establishing a publicly available database of active clinical trialists identifiable by facility and area of experience including where should it be house, reporting requirements by medical facility and/or clinical trialists.
  - Establishing clinical trialists training programs and mentoring networks for investigators, trialists and facilities serving underrepresented communities.
  - Establishing a publicly available database of community engagement organizations supported by NIH
- No later than 90 days after each public roundtable discussion, HHS should make available on their website a report and recommendations on the topics discussed at the roundtable discussion.
- No later than 180 days after each public roundtable discussion, HHS should make available on their website an implementation plan and actionable activities on the topics discussed at the roundtable discussion.
- Require HHS to establish or leverage existing programs for a federally funded clinical trial investigator fellowship pilot program for women, LGBTQIA+, racial and ethnic minorities to help increase representation of underrepresented population.

- ***Diversity and Inclusion for workforce development***
  Require FDA and NIH to improve transparency around hiring, retention and promotion practices within their organizational leadership and scientific workforce.
  - Establish clear objectives to diversity organizational leadership and scientific workforce.
  - Provide regular reports to Congress on metrics around hiring, retention and promotion of diverse leadership and scientific workforce.

The Honorable Gus Bilirakis (R-FL)

1. As Co-Chair of the Rare Disease Caucus, I'm particularly interested in the work FDA and Congress can do to facilitate and improve regulatory pathways for rare disease R&D. Can you tell me more about the proposed pilot programs for Split Real Time Application Review in the PDUFA agreement and what that means for rare disease patients? Dr. Esham, can you elaborate on this and explain what this means for companies conducting clinical trials for these rare disease treatments and cures?

Response:
BIO appreciates the opportunity to provide additional comments about strategies to bring medications to patients who need them as safely and quickly as possible, especially for those suffering from rare diseases who often lack other treatment options. As noted in my testimony, there are at least 7,000 known rare diseases collectively impacting over 25 million Americans with new rare diseases identified each year. The PDUFA VII Commitment Letter contains several provisions that will build upon the efforts of previous agreements to address this critical issue that remains a priority of BIO and our member companies.

The Split Real Time Application Review (STAR) pilot program aims to shorten review timelines for certain drug and biological products that are intended to treat serious conditions with unmet medical needs. It builds on innovative review concepts that have proven successful for FDA's Real Time Oncology Review (RTOR) program by expanding them to all disease areas outside of oncology, enabling more timely reviews and availability of these medicines to vulnerable patient populations. More specifically, STAR's scope includes efficacy supplements across all therapeutic areas and review disciplines that meet certain criteria described in the Commitment Letter. For applications accepted into the STAR pilot program, review activities and workload will be streamlined for both FDA and sponsors by allowing the sponsor to submit an application in two parts rather than the traditional single part, enabling FDA to begin review of key application components as much as 2-3 months earlier than usual. The goal for applications reviewed under STAR is to allow FDA to provide a regulatory decision at least one month earlier than the priority 6-month PDUFA action date.

Rare disease patients in particular stand to benefit from STAR significantly due to the pilot program's eligibility criteria. The medical product must have clinical evidence indicating that it could demonstrate substantial and quantifiable improvement on a clinically relevant endpoint compared to currently available therapies. Also, the product must be intended to treat a serious condition with an unmet medical need. As a result of these criteria, products reviewed under STAR could directly benefit those suffering from rare diseases by expediting patient access to innovative and novel uses for existing therapies by allowing FDA to initiate review earlier than would otherwise occur, enabling earlier approval of these products. For these patients without other viable options, getting treatments potentially months earlier can be the difference between relief, disability, or even death.

Companies with applications accepted into STAR who are conducting clinical trials for these rare disease treatments and cures benefit directly through increased workload and pipeline management efficiency. The requirements for each of the two submissions, as clearly defined in the Commitment Letter, allow the sponsor to prioritize clinical data collection, analysis, and submission in a way that provides FDA review teams with information essential to beginning their evaluation while the company continues to compile the second submission requirements. This could prevent workload and resource-related delays in the submission of applications that are not only the focus of STAR but also for other products in the company's pipeline with potential to help more patients. With more regulatory flexibility, the company can optimize resource allocation to bring as many new treatments to FDA for review as possible.

The Commitment Letter also includes training requirements for FDA staff to ensure review teams are prepared to execute on earlier and faster evaluations as soon as the pilot program begins. In addition, FDA will conduct a public workshop by the end of Q2 in FY 2026 to discuss the potential value and feasibility of expanding the scope of the pilot program from efficacy supplements only to certain new drugs and biologics, potentially increasing the impact of the program to even more patients, including those suffering from rare diseases.

With respect to advancing science related to rare disease treatment generally, the STAR pilot program will be well-complemented by another pilot program described in the Commitment Letter, the Rare Disease Endpoint Advancement (RDEA) pilot program. 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 have 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 RDEA pilot program 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.