Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
"The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases"
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The Honorable Frank Pallone, Jr. (D-NJ)

1. Dr. Esham, what are some reasons why manufacturers choose not to participate in expanded access?

   Each clinical development program and each company have unique and multiple factors to evaluate the feasibility of establishing an expanded access program for an investigational medicine. For example, there may be ethical and resource capacity considerations relating to the establishment of criteria to make determinations about which requests would be granted and on what basis they would be denied. Complex medicines may have supply and differing abilities to scale up production during the investigational stages of development. Each investigational medicine may have differing levels of understanding about potential safety risks. There must also be consideration as to how difficult clinical trial enrollment is and whether expanded access would negatively impact ability to fully enroll clinical trials necessary for review and approval of an investigative medicine. Meeting the gold standard of FDA approval so the medicine is available to all patients as soon as possible must remain the primary goal.

2. What factors should developers consider when weighing whether to conduct an open label study, and how can we encourage their use when appropriate?

   In open-label trials, both the researcher and participants know which medicine is being given to patients. They are typically used when the controlled trial (Phase 3) has ended, and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational medicine until marketing approval is obtained. This also allows sponsors of investigational medicines to gain additional long-term safety and tolerability information or comparative information with other treatments. It does take a significant amount of additional work and resources. A sponsor has to develop a new study protocol and start-up process that includes obtaining Institutional Review Board approval, site contracts have to be executed that meet regulatory standards. This must occur on a timeline that ensures a patient's dosing schedule is not interrupted. While I

cannot speak directly to how each company makes a determination for conducting an open-label study for any given investigational product it likely includes an assessment of the evidentiary gain and ability to conduct the operations needed and ability to stay on track for timely approval of the medicine. Options such as open label studies and expanded access are tools available in the toolkit for companies to make decisions about how best to provide timely access of innovative medicines to approval but timely approval remains the best path to providing availability for all patients.

The Honorable Lisa Blunt Rochester (D-DE)

1. Dr. Esham, what are biopharma companies doing to support and partner with communities on education and engagement efforts? What can be done, from a legislative or regulatory perspective, to build a more inclusive, expansive, and sustainable clinical development ecosystem?

   There are a lot of individual and collective/collaborative efforts underway. We have seen some companies commit to expansion of clinical trial sites to places that serve historically underrepresented communities, some are deploying artificial intelligence capabilities to find patients across all subgroups and using that information to develop a more inclusive clinical trial design strategy, some are using approaches such as decentralized trials that make it easier for patients to participate in clinical trials and some provide extra services such as transportation that again lessen the burden of participation for patients.

   BIO is working with our member companies on several activities. One, we are developing a patient-friendly website for all patients to learn about clinical trials, how to evaluate opportunities and how to find a trial. This site contains information specifically designed to provide information to diverse patient populations and their families. We are and will be working with community organizations, community and religious leaders and patient organizations to improve how this information is provided to build a culturally competent and understandable information hub. We will be providing this content (at no cost) for use by any community or patient organization that would like to build their own information sites and materials. We are also working with organizations such as the Association of Clinical Research Organizations and Multi-Regional Clinical Trials Center of Harvard and Brigham and Women's Hospital to develop best practices for designing clinical trials that are representative of the patient population being treated. We are also developing legislative proposals we think would help advance clinical trial diversity efforts significantly over the next five years. We expect to have those proposals ready to share in November. In addition to our upcoming policy proposals, legislative efforts currently under discussion that advance utilization of decentralized trials, digital health technology tools and use of real-world evidence, provide funding streams for community organizations, efforts for NIH and other key governmental agencies to focus on building a diverse research and clinical trialist community, and funding and networking opportunities for clinical trialists that serve historically underrepresented communities are all important and beneficial ideas. As we collectively review these

concepts, we want to ensure that they will collectively work to build a sustainable and continuous clinical research infrastructure that enables diverse participation in clinical trials. This is an issue of paramount importance to BIO.

The Honorable Michael C. Burgess, M.D. (R-TX)

1. After years of work, in 2018 I was grateful that "Right to Try" was signed into law. This policy's intent was to open the door to innovative, experimental drugs for terminally ill patients, without compromising the work and mission of the FDA. Although I am grateful for the enactment of this policy, I still occasionally hear from patients who are not able to participate in expanded access. Can you explain the process for which companies may consider requests for expanded access, and why companies may choose not to participate?

   Each clinical development program and each company have unique and multiple factors to evaluate the feasibility of establishing an expanded access program or "Right to Try" program for an investigational medicine. For example, there may ethical and resource capacity considerations relating to the establishment of criteria to make determinations about which requests would be granted and on what basis they would be denied. Complex medicines may have supply and differing abilities to scale up production during the investigational stages of development. Each investigational medicine may have differing levels of understanding about potential risks. There must also be consideration as to how difficult clinical trial enrollment is and whether expanded access would negatively impact ability to fully enroll clinical trials necessary for review and approval of an investigative medicine. Meeting the gold standard of FDA approval so the medicine is available to all patients as soon as possible must remain the primary goal.

   As you know, The Right to Try Program is different in that FDA permission is not required and allows individual patients with their physicians to apply for access to an investigational drug. The same considerations described above apply to this pathway as well with the additional considerations regarding not needing FDA permission.

2. How can real-world data and evidence be used to help understand the safety and efficacy of products under consideration for approval by FDA?
   a. Could real-world data and evidence help expedite the approval process for innovative drugs?

   Label Expansion: In 2019, BIO published a paper about how Real-World Evidence (RWE) can used for label expansion. Here is an excerpt from that paper.

   > "BIO believes that RWE studies can augment insights gained from traditional randomized clinical trials (RCTs) about the effectiveness of therapeutics. This application of RWE builds on the long-standing FDA use of RWD in safety assessments, including Sentinel. RCT designs and their associated statistical models have evolved over the past century to control for most known sources of

bias and confounding when making statistical inferences about the efficacy of tested interventions. By contrast, RWE reflects how patients are treated in routine clinical practice and how they take their medicines in everyday use (i.e., the real world).

RWE studies can provide meaningful insights about the therapeutic impact of a product in the real-world population that will be exposed, across variables that may not be included in RCTs—for example, the performance of a therapeutic intervention as a function of age, underlying conditions/co-morbidities, real-world medication-taking behaviors, quality of life improvements, or in comparison to other available therapies not studied in RCTs. The external generalizability contributed by RWE can be used to understand the risks and benefits to the range of populations and patients who use the therapeutic, to target new patient populations, account for regional and global variations in healthcare practice, and provide further information than that afforded by RCTs alone.

RWE can also provide critical insights in cases where RCTs are unethical or impractical. For example, in rare disease, pediatrics, and other limited populations, RWE studies can mitigate challenges often faced by RCTs such as ethical constraints or limited trial enrollment, providing historical controls where appropriate control populations do not exist or are not feasible. While traditional RCTs will remain important, the number and size of those trials might be reduced with growing acceptance of new research approaches including RWE. RWE provides additional context and greater external generalizability to the benefit-risk regulatory assessment. The use of RWE—introduced by this broader generalizability—may allow for improved regulatory decision making as evidence may become more readily available.

BIO Members believe that RWE studies, including high quality observational studies, that are conducted in accordance with best practices articulated by expert groups, such as International Society for Pharmacoeconomics and Outcomes Research/International Society for Pharmacoepidemiology (ISPOR/ISPE), may be sufficient to inform specific regulatory decision-making for label expansion without the need for additional RCTs. Decisions about an individual regulatory question are made on a case-by-case basis, and the totality of the evidence must be considered. Depending on the specific details of any given situation, the additional evidence provided by a high-quality observational study may be sufficient to answer the question at hand. Although some recently published thought papers suggest that observational studies are not yet appropriate for label expansion, BIO believes that the necessary tools are actively being developed and in some specific contexts are already sufficient to generate meaningful evidence and should form the basis of future FDA guidances. “

Full paper can be viewed here:
https://www.bio.org/sites/default/files/legacy/bioorg/docs/BIO%20White%20pap

er%20%20-%20Incorporating%20RWE%20Within%20the%20Label_FINAL%202019.pdf

Additional Uses of RWE: In 2021 BIO and PhRMA presented to the FDA with additional case studies about how RWE can be utilized, and challenges encountered with the goal of informing FDA guidance efforts and improve the ability to utilize RWD/RWE for regulatory decision making. The discussions focused on how RWD/RWE can be utilized for the following purposes: 1) External controls that are part of the totality of evidence that meets the regulatory threshold for substantial evidence; 2) High-quality prospectively collected registry data that could be used for regulatory decision-making; 3) Data and analytics to support labeling revision, 4) Validated real-world endpoints, and: 5) Registry-based randomize trial designs for registration purposes. These efforts align with the resources and commitment provided under the PDUFA VI legislation and current PDUFA VII Commitment Letter that will be considered by Congress in 2022. It is also important to note that BIO believes the use of RWD/RWE for products on the market has tremendous potential in advancing our understanding of health outcomes across genders, races, ethnicities, ages, and other subpopulations.

We do believe that the use of RWD/RWE may enable expedited development and review processes when possible and appropriate. We also believe it can serve to provide more timely and informative data for medicines that are on the market and expedite expanded or changed label claim.