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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA-2023-N-2462; Workshop to Enhance Clinical Study Diversity

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the **Workshop to Enhance Clinical Study Diversity.**

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO appreciates the FDA holding the workshop on November 29-30 to discuss approaches to enhance clinical trial diversity. BIO is committed to enhancing clinical trial diversity as part of the organization's BIOEquality Agenda. Ensuring that clinical trial cohorts are reflective of the prevalence of disease across populations is key to reducing health disparities and advancing health equity, ensuring that all patients benefit from innovative therapies and treatments.

Recognizing that some communities have been historically underrepresented in research, the biotechnology industry is leading change by deploying innovative strategies to ensure broader participation in clinical trials. BIO is facilitating further progress by convening stakeholders[1][2] to strategize overcoming the many challenges inherent in recruiting and retaining diverse clinical trial cohorts, and by engaging with the public on the value of, and need for, broad participation in clinical research.

Pursuant to Section 3602 of the Food and Drug Omnibus Reform Act of 2022 (FDORA), the Agency was required to issue draft guidance on the format and content of diversity action plans not later than 12 months after the law's enactment. BIO urges the Agency to issue this draft

[1] BIO Clinical Trial Diversity Summit Agenda 2021 - https://www.bio.org/events/bio-clinical-trial-diversity-summit/agenda
[2] Improving Diversity, Equity, and Inclusion in Clinical Trials, 2023 - https://www.ctpop.org/sites/ctpop/files/2023-10/2023.10.25_BIO_CTD%20White%20Paper_FINAL.pdf

guidance. We look forward to the opportunity to review and provide comments to the FDA when the Agency issues the draft guidance.

In 2022, BIO provided comments[3] to the FDA on its draft guidance on Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials. In responding, BIO made two overarching recommendations. First, recognizing that community engagement and building trust are essential aspects of improving clinical trial enrollment of participants from underrepresented populations, BIO recommended that FDA have the requisite expertise regarding approaches to facilitate community engagement and trust to provide useful feedback to sponsors regarding enrollment and retention challenges. Second, BIO proposed that the Agency work with sponsors to ensure that FDA-sponsor communications are streamlined and consistently implemented across the Agency, building from provisions described in the PDUFA VII Commitment Letter. To this end, we commend the Agency for establishing the Diversity Plan Implementation Committee (DPIC) to ensure consistency in providing advice to sponsors. BIO continues to believe that effective community engagement strategies and clear FDA-sponsor communications will be key for increasing diverse participation in clinical trials.

The different forms of diversity

In its regulatory approach to clinical trial diversity, BIO recommends that the Agency recognize the many different forms of diversity, including those that were discussed at the workshop, such as race, ethnicity, sex, pregnancy status, neurodiversity, geographic location and age. As noted during the workshop, additional considerations should incorporate the inclusion of people with a variety of disabilities or other characteristics, such as neurodivergence, chronic illness, physical and mobility differences. The term "disability" can be defined very broadly and for some conditions this information may be difficult to collect (e.g., no current standards for collection exist) and analyze. In addition to its 2020 Guidance on Enhancing the Diversity of Clinical Trial Populations, we urge the FDA to clarify how it defines specific disability categories and the agency's expectations regarding increased representation of people with disabilities or other differing characteristics in clinical trials.

As noted in FDA's 2023 draft guidance on Postmarketing Approaches to Obtain Data on Under-Represented Populations in Clinical Trials and as reflected in BIO's comments (add footnote link), sexual orientation and gender identity (SOGI) is another area where we there may be a lack of representation in clinical trials and accordingly a lack of information on the outcomes of therapies in LGBTQIA+ populations. The National Institute on Minority Health and Health

[3] BIO Comments on FDA Guidance on Improving Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials, 2022 - https://www.bio.org/letters-testimony-comments/bio-comments-fda-guidance-improving-enrollment-participants?mkt_tok=NDkwLUVIWi05OTkAAAGFQ9Myoa0anyj2U7Pm-W-8KmrmJ7DAQ7AgYknjqgj7miyc0MXtf3XqTvQ4SIkC8rcMzt-YcMpSLE2-MMPN4hk

Disparities has identified the sexual and gender minority communities as a "health disparity population". However, there are significant social challenges, methodological considerations (e.g., data privacy), and legal questions that would complicate this endeavor. Accordingly, we suggest the FDA consider soliciting broad stakeholder input via workshop or RFI to gather best practices and considerations for potential collection of SOGI data, including the intersectionality of SOGI with other key demographic identities such as race and ethnicity. Such a cross-functional effort should also reflect a strong intersection of patient preferences for the collection of this data – including whether sponsors and sites should consider cultural competency training and additional security measures to protect this highly sensitive information. Finally, in considering diversity enrollment goals for these distinct categories, we ask that the Agency avoid using sex or sex assigned at birth interchangeably with gender identity, as these two identities are distinctly different and can refer to different demographic populations.

Diverse clinical trial participation and rare diseases

There are some disease contexts where deploying effective strategies to ensure diverse participation is especially challenging. This is the case for the development of treatments for rare diseases; challenges include the small size of the patient population, disease heterogeneity within the patient population, and the lack of robust natural history data. Companies developing therapies development for small patient populations often encounter difficulties with clinical trial recruitment; in the case of gene therapies, the patient population is further narrowed due to the need to screen participants for preexisting immunity to components of the therapy itself. For advanced therapies, many of which are indicated for rare diseases, administration requires specific knowledge and experience which may be limited to a small number of clinical trial sites at specific locations. As any delay in clinical development for rare disease therapies threatens to further exacerbate racial, ethnic, geographic, and socio-economic disparities related to treatment access, BIO urges the FDA to recognize and consider these challenges pertaining to rare diseases in its approach to encouraging greater diversity in clinical trials. BIO acknowledges that FDORA provides for the clinical trial diversity requirements to be waived depending on the rarity of the condition, and asks for more guidance about considerations for requesting/receiving such waivers.

Considerations for international studies

We appreciate that the November 2023 workshop focused on establishing US enrollment goals, and therefore the discussion centered on potential sources of disease prevalence/incidence data within the US. However, drug development is a global endeavor and sponsors routinely conduct multi-regional clinical trials (MRCTs) to meet the needs of patients within and beyond the United States. We appreciate that the Agency has expressed support for MRCTs, and specifically encouraged enrollment of patients from African and Latin American countries. To

support this, we encourage the Agency to elaborate on existing ICH E5[4] and E17[5] principles regarding what evidence can be provided to justify data from MRCTs to demonstrate the applicability of foreign data to US demographics. We urge FDA to clarify in which circumstances the agency will ask for global information on diversity and how it intends to interpret and use that data (e.g., whether a Black person in the U.S. is considered the same race as a Black person from South Africa; how to interpret "White" as a default when race is not collected in other countries or when multi-racial participants with African ancestry check "other"; the inaccuracy of race as a proxy for underrepresented groups ex-U.S. compared to U.S., and differences across countries in defining underrepresented groups and associated disparities). We also encourage FDA to consider and describe how study enrollment demographic data will be disseminated post-approval in the case of multi-regional clinical trials given that US OMB categories for race and ethnicity cannot be applied to ex-US data.[6]

Some aspects of FDORA requirements and FDA's related guidance are difficult to reconcile with ICH E17, which provides general principles for planning and design of MRCTs with the aim of increasing acceptability in global regulatory submissions. The Diversity Action Plan is a US-only requirement, and other health authorities have expectations for studies conducted in local populations, limiting (or outright prohibiting) the collection of individual patient-level data on race and ethnicity or other demographics, and/or have different interpretations about subgroups. We recommend the FDA address these considerations in guidance and consider raising the topic at ICH to enhance global harmonization.

With regards to the collection and presentation of disease prevalence and incidence data by demographic group, a number of uncertainties remain that BIO urges FDA to consider and address. These include how the agency is intending to assess demographic data and a whether a request for data from "other regions" refers to within the US or ex-US, what data can best inform program diversity plans, and how FDA intends to measure success with regards to disability groups in the absence of an accurate baseline (given the lack of an industry data collection standard).

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[4] International Council for Harmonisation (ICH), E5 Ethnic Factors in the Acceptability of Foreign Clinical Data, Guidance for Industry (June 1998). Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e5-ethnic-factors-acceptability-foreign-clinical-data.

[5] ICH, E17 General Principles for Planning and Design of Multiregional Clinical Trials, Guidance for Industry (July 2018). Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e17-general-principles-planning-and-design-multi-regional-clinical-trials.

[6] United Nations Statistics Division. Ethnicity: A Review of Data Collection and Dissemination Social and Housing Statistics Section Demographic and Social Statistics Branch United Nations Statistics Division August 2003

Goals vs Targets

FDORA uses the term “goals” in describing the objectives for recruitment and enrollment to be set out in Diversity Action Plans. FDA also has used the term “target” to describe these goals. We urge the agency to assess progress against “goals” to avoid unintended implications that all effort except hitting a hard “target” is a failure. For example, where a sponsor is diligent in setting Diversity Action Plan goals and in its recruitment and retention efforts, but the actual numbers of voluntary study participants fall short of a goal, efforts should be recognized as positive progress against a “goal,” rather than failure to hit a hard “target,” particularly given that clinical trial participation is affected by many aspects of the overarching societal context and broader healthcare ecosystem unrelated to (and outside the control of) sponsors.

Defining recruitment goals and monitoring the composition of a study

During the November workshop session on the establishment of clinical study enrollment goals, panelist Scott Halpern proposed the use of the Participation-to-Prevalence ratio (PPR) for defining recruitment goals. Panelist Tom Fleming recommended the use of the Data Monitoring Committee (DMC) to enhance engagement via the DMC membership and monitor composition of a study. It would be helpful for the FDA could provide their perspective on these recommendations.

Providing aggregate demographic data

BIO appreciates FDA’s sharing data from the oncology review divisions' first year of experience with Diversity Action Plans, and we encourage the agency to continue to do so, including regarding how plans are used and implemented across programs. In addition, although it is important to maintain as commercial confidential information the specific targets set forth in individual Diversity Action Plans, aggregated, de-identified data on targets set for multiple programs in a single indication or narrow therapeutic area could be helpful for stakeholders. We encourage FDA to consider providing aggregate demographic data by therapeutic area in the Drug Trials Snapshots (as was done previously).

Considerations for decentralized trials

As the FDA suggests in the *Decentralized Clinical Trials for Drugs, Biological Products, and Devices* 2023 FDA draft guidance, data obtained in a decentralized clinical trial may differ from the (historical) data obtained in a traditional site-based clinical trial. This may present challenges in interpreting clinical trial results that include a very diverse patient population via the use of decentralized elements. BIO believes it would be helpful to have the FDA clarify their perspective on this distinction and measures a sponsor may take to ensure the acceptability of data collected in a novel or decentralized setting.

Enriched patient populations

Including a very diverse patient population under diverse treatment conditions in the study and evaluating the entire study population combined carries the risk that efficacy of a beneficial new drug cannot be established. We suggest that the FDA emphasizes the approach where an enriched patient population under strict treatment conditions, as referred to in the 2020 guidance, supports efficacy evaluation for registration, and that other patients are evaluated separately.

Financial burden of clinical trial participation

Finally, financial burden (beyond travel expenses and other out of pocket costs) continues to be a hurdle for many clinical trial participants, and can disproportionately affect clinical trials in some therapeutic areas, e.g., those requiring very frequent, lengthy, or complex assessments, indications that require extended research timelines, and/ or treatment areas where even the standard of care is not adequately covered for patients who have insurance or are participants in government healthcare programs, such as Medicaid. Sponsors are limited in their ability to ease these burdens due to rules enforced not only by FDA, but by sister agencies like CMS and the HHS OIG. Medicaid patients also can be subject to additional tax burden due to stipends or reimbursement they receive for participating in clinical trials. BIO urges the FDA to work with HHS and other agencies to ensure that these roadblocks are addressed in a way that allows sponsors to provide the support needed to help ensure that clinical research is a realistic option across different communities.

Sincerely,

/s/
Derek Scholes
Sr. Director, Science & Regulatory Affairs
Biotechnology Innovation Organization