October 10, 2023

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

Re: FDA-2022-D-2629; Postmarketing Approaches to Obtain Data on Under-Represented Populations in Clinical Trials

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 **Postmarketing Approaches to Obtain Data on Under-Represented Populations in Clinical Trials**

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BIO appreciates the FDA developing this draft guidance, recognizing it is much needed to guide sponsors in complying with the requirements for ensuring the participation of underserved communities in postmarketing studies. The draft guidance allows sponsors and FDA flexibility to discuss what additional data, if any, is needed to sufficiently characterize the benefit-risk assessment of the medicinal product in the population(s) of intended use and how best to obtain those data on a case-by-case basis. We further appreciate how, through developing guidance on this topic, the FDA is elevating the need for clinical trial diversity and health equity.

We note that this draft guidance has been prepared by the Oncology Center of Excellence in cooperation with the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. We applaud the FDA's coordination between centers on addressing clinical trial diversity and the Agency's efforts to ensure the consistent application of this guidance across the Agency. The emphasis on inclusive research has been largely driven by FDA's Oncology Center of Excellence (OCE), with an increasing number of PMR/PMCs around evaluation of safety/efficacy data in underrepresented patient populations issued for oncology products. We would appreciate clarity on how the FDA will ensure that the issuance of PMRs/PMCs around diversity and hence the overall approach to inclusive research is consistent across oncology and non-oncology review divisions.

Early Engagement with FDA on Clinical Trial Diversity

BIO concurs that clinical trials should include patient populations that are historically underrepresented in clinical research. We request that the Agency describe how sponsor development teams can receive feedback from FDA reviewers on progress towards meeting enrollment goals throughout the development program. Such engagement will provide an

opportunity for sponsors to proactively address reviewer concerns with progress towards meeting diversity goals. In some cases, such engagement may avoid the need for postmarketing studies.

Foreign Clinical Data

Global clinical research is essential to ensure efficient drug development. The draft guideline notes that “FDA may approve a marketing application based solely on foreign clinical data” (lines 232-233). Applications based solely on data from studies performed outside the US would be exceptional, rather than standard practice. However, there may be circumstances where it is necessary and appropriate to consider the totality of global data, inclusive of US data when establishing and assessing diversity goals. The updated draft or final guidance should acknowledge the scientific principles outlined in ICH E5 and E17. It would be helpful for the Agency to provide more detail in the final guidance on how the inclusion of underrepresented groups outside the US can contribute to meeting the clinical trial diversity requirements. It would further be helpful for the Agency to share its perspective on the utility and acceptability of foreign real-world data.

Sexual Orientation, Gender Identity, and Intersectionality between Populations

As noted in the draft guidance, gender identity is one area where we there may be a lack of representation in clinical trials. The National Institute on Minority Health and Health Disparities has identified the sexual and gender minority, or LGBTQIA+, communities as a "health disparity population”. We recommend that the FDA, sponsors, and sites collaborate to explore considerations for the collection of Sexual Orientation and Gender Identity (SOGI) data. There are significant social challenges, methodological considerations (e.g., data privacy), and legal questions that could complicate this endeavor. Accordingly, we suggest the FDA consider soliciting broad stakeholder input, such as via a workshop or RFI, to gather best practices and considerations for the potential collection of SOGI data.

It is further important to recognize the intersectionality between many of these underserved and underrepresented patient populations, with significant intersectionality between race, gender identity, socioeconomic status, disability, and mental health. Health treatments and interventions and access to these, particularly in populations who have historically encountered stigma, discrimination, and mistreatment, also play an important factor in treatment outcomes. With regard to the LGBTQIA+ community, there is a lack of information on the outcomes of therapies in this population and the impact of other intersecting factors.

Sincerely,

/s/
Derek T. Scholes, Ph.D.
Senior Director,
Science and Regulatory Affairs
Biotechnology Innovation Organization

LINE-BY-LINE RECOMMENDED EDITS

SECTION/ LINE	ISSUE	PROPOSED CHANGE
I.	**Introduction**	
18-19	Original text: "FDA regulations require sponsors to present information from premarket clinical trials on the safety and effectiveness of drugs in terms of gender, age, and racial subgroups." The terms gender and sex are used interchangeably in the document introduction. Underrepresentation is historically known to exist for both sex (female persons) as well as gender identity, whereas safety and efficacy data have been required by sex (not gender), age and racial groups.	Recommended revision: "…in terms of sex ~~gender~~, age, and racial subgroups."
II.	**Background**	
60-63	"FDA encourages efforts to include underrepresented populations in clinical trials, including populations based on race, ethnicity, sex, age, geographic location, gender identity, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity."	Consider adding sexual orientation to this list.
III.	**Mechanisms for Obtaining Postmarketing Data on Underrepresented Populations**	
80-83	"FDA may require an applicant to conduct postapproval studies or clinical trials as a postmarketing requirement (PMR) where the statutory criteria are met, or FDA may enter into a written agreement with the applicant to collect these data as a postmarketing commitment (PMC)."	FDA may want to consider the hurdles/challenges of having under-representative samples in the pivotal trials before requiring an applicant to conduct any post-approval trials (e.g., phase 4). There might be cases where the inherent hurdles in pivotal trials are the same that occur in post-approval studies and require special consideration by the FDA and sponsor.

94-95	"…before requiring a postmarketing clinical trial, FDA must find that a postmarketing study or studies will not be sufficient to meet those purposes."	It would be useful to specify which type of study is meant here, as opposed to a clinical trial: does it mean observational study?
A. PMRs		
113-117	"For example, FDA may require an applicant to evaluate the incidence rates of certain serious adverse events among U.S. racial and ethnic minorities or older patients **when there are data to suggest that those adverse events may occur at a higher rate in these populations** but an insufficient number of participants from these populations participated in the pivotal trial to adequately evaluate the signal."	It would be helpful to have more clarity on FDA's thinking around the 'data' that may be obtained during the course of a development program that would necessitate a PMR. For example, does this include emerging data from publications or clinical trials suggesting disparities in different populations? Does data mean evidence from within the pivotal trial or development plan for the molecule that is not sufficiently addressed with the filing package? Or any of the above?
B. PMCs		
130	To provide further clarifications, we recommend the Agency discuss the spectrum of missing/lacking data. For example, there could be a scenario where approval is based solely on clinical data that does not reflect the US disease population (e.g. minimal African American, Asian/Pacific Islander or Hispanic participation) to a scenario where the data is largely reflective of the US population aside from falling slightly below representative for a particular race or ethnicity category. Accordingly, we believe there should be considerations for this spectrum of available data.	
IV. Study Design and Statistical Considerations		
A. Considerations for Single-Arm Trials		
ENTIRE SECTION IV.		We acknowledge that design considerations for different types of studies have been provided. However, specific guidance around

STUDY DESIGN AND STATISTICAL CONSIDERATIONS		statistical considerations regarding subpopulation analysis of under-represented populations by the Agency would be helpful. We also would appreciate examples of where different types of trials may be recommended by the FDA. Finally, we ask that the FDA specify or provide examples of what types of trial design modification and trial enrichment (e.g., extension cohort for the population of interest) might be warranted based on under-representation of certain subgroups.
138-140	"The sections below describe …"	We suggest that the Agency consider adding an additional statement at the beginning of this section to further emphasize that differences in treatment response, disease occurrence, or safety concerns in under-represented populations (e.g., between racial/ethnic groups) could be studied carefully when such data is readily available or easily ascertainable. This could be of particular importance in the context of extrinsic ethnic factors (e.g., social, environmental and behavioral factors), and the resulting confounding which requires the use of matched, adjusted or stratified analyses on these variables.
B. Consideration for Randomized Trials		
173-177	"Sponsors could also stratify based on the subpopulation(s) of interest if there are potential prognostic implications associated with the subpopulation. For example, a trial can stratify based on race, ethnicity, sex, age, or a hypothesized difference in efficacy in the population of interest versus the general population, so that analyses can focus on benefits and risks in the underrepresented population." It is unclear whether the sentence is referring to "stratified randomization" or "stratified analysis" (or both). In addition, we note that the concepts of prognostic effect vs. predictive effect could be	Suggested revision: "Sponsors could also ~~stratify~~ conduct stratified randomization and/or stratified analysis based on the subpopulation(s) of interest if there are potential prognostic implications associated with the subpopulation. For example, a trial can stratify based on race, ethnicity, sex, age, or a hypothesized difference in ~~efficacy~~ prognosis in the population of interest versus the general population. In addition, if there is a hypothesized difference in efficacy (i.e., a predictive effect) in the population of interest versus the general population, additional subgroup analysis could be conducted so that analyses can focus on benefits and risks in the underrepresented population."

	further clarified. If there is "a hypothesized difference in efficacy", this is a predictive effect (not prognostic). Conducting stratified analysis or stratified randomization will not mitigate the problem. Instead, conducting subgroup analysis will allow the evaluation of the effect in the subgroup of interest.	
C. Real-World Data (RWD) Sources		
182-183	"Real world data, including electronic health records and registries, can be used to provide postmarketing data **when appropriate…"** We would further welcome guidance on assessing the compatibility of real-world and clinical trial data. The difference in efficacy or safety between sub-population and the overall population may not be applicable if the RWD data is not compatible with clinical trial data.	We would welcome examples illustrating when use of different types of real-world data would or would not be appropriate. Suggest addition of this text regarding compatibility of real-world and clinical trial data: "Sponsors should carefully assess the adequacy of the RWD to appropriately answer the questions relevant to the subpopulation(s) of interest (e.g., ensuring the RWD source is fit for purpose by contextualizing and understanding differences in baseline characteristics between the clinical study and the RWD study population)."
D. Pooled Studies		
192	"Meta-analyses of randomized trials can be conducted to obtain postmarketing data…"	Could the agency clarify whether meta-analysis would also be relevant for single-arm trials. If so, then further details should be also added for pooling of single arm trials.
196-198	"Pooling data across trials, **if methodologically appropriate,** may allow for a meaningful evaluation of the drug in patients from different clinically relevant subpopulations"	We would welcome more clarity on when pooling data across trials would or would not be considered by the Agency to be methodologically appropriate.
V. Postmarketing Approaches to Obtain Data on Underrepresented Populations and Other Considerations		
A. Development Recruitment Strategies Tailored to the Intended Population		
213-215	"If during the course of the clinical development program, the strategies implemented to recruit and retain a representative population appear unlikely to accomplish the intended objective despite	We would appreciate more clarity on how to engage with FDA to provide updates during enrollment phase (timing and content) in real time, ideally in a streamlined and agile way that is not overly burdensome for sponsors or FDA.

	best efforts, the sponsor and FDA should discuss next steps."	
B. Foreign Clinical Data		
227-228	"These consideration would be applicable to trials conducted in the post-marketing setting." We recommend a minor typographical revision.	Suggested revision: "These considerations would be applicable to trials conducted in the postmarketing setting."
232-234	"FDA may approve a marketing application based solely on foreign clinical data if, among other factors, the data are applicable to the U.S. population and U.S. medical practice. If a sponsor submits a marketing application comprised of patients enrolled predominantly outside of the United States, data and rationale should be submitted to support applicability to the U.S. population and medical practice…"	Consider providing examples of the type of data that would demonstrate applicability of foreign clinical data to the US population and US medical practice. For example, when it would or would not be appropriate to pool patients from the same race subgroups for analyses, and how to determine the equivalency of foreign and U.S. racial subgroup data.