Alliance for Regenerative Medicine

October 9, 2023

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

Re: Docket No. FDA-2022-D-2629 for Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products

Dear Sir/Ms.:

The Alliance for Regenerative Medicine (ARM) is pleased to submit comments to the US Food and Drug Administration (FDA) in response to recently released guidance titled, *Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products.*

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

Representation in clinical trials of patient populations that are historically underrepresented in clinical research is highly important to ARM. We therefore appreciate FDA's initiative in developing guidance on this topic.

ARM agrees that instances may occur in which this information may be limited and, despite sponsors' best efforts, these populations are not adequately represented in premarket clinical trials. We appreciate that under these circumstances, when additional information is needed, the FDA is providing flexibility in allowing the collection of such data in the postmarket setting.

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Considerations for rare diseases

ARM agrees that in certain circumstances, information from a diverse, representative patient population may be limited, and premarket requirements must be balanced within the benefit-risk framework. We recommend stating that these circumstances include trials for rare diseases, which may face challenges to timely enrollment.

In addition to moving some requirements to the postmarket period, ARM recommends allowing flexibility within postmarketing requirements for rare diseases. For example, the guidance indicates (lines 99-100) that for products granted accelerated approval, the confirmatory trial should represent the diversity of patients expected to use the drug in the United States. While ARM supports this concept in principle, identifying the total prevalence of some rare diseases can be challenging. In such cases, sponsors may have even less available data on the demographic breakdown within a rare disease.

Given the complexity of recruiting for cell and gene therapy trials for rare diseases, ARM underscores the need to strike an appropriate balance between adequate US population representation and timely completion of trials. We appreciate the Agency acknowledging that foreign clinical data can support a marketing application should it be reflective of the intended US patient population (Lines 232 – 234). We recommend clarification that when PMRs/PMCs are required, these commitments may be satisfied with data from both US and ex-US patients, provided the overall demographics are representative of the US patient population. Because sponsors have received inconsistent advice on requirements for US data, ARM requests the Agency to identify what circumstances, if any, would require additional US data (in general or for a specific underrepresented population). Additionally, ARM suggests that foreign clinical data should be acceptable in trials that may face US recruitment challenges due to a small worldwide patient population.

Postmarket study design flexibility

ARM supports the flexibility identified in postmarket study design to enable greater representation of historically underrepresented populations. We encourage FDA to apply these principles more broadly to rare diseases in general. We specifically support allowing the use of the following approaches:

- Use of subjects from pre-approval studies to obtain a larger sample size of the subpopulation of interest (Lines 148 – 150).
- Pooling of data across trials when methodologically appropriate and when the studies contain an adequate number of patients and data from each subpopulation (lines 196 – 199).
- Enrollment and analysis of subpopulations underrepresented in the main analysis population in single arm trials in a separate cohort (lines 154 – 157).

ARM also supports the use of real-world data (RWD), including electronic health records and registries, to provide postmarket data when appropriate (lines 182-184). Doing so may assist with the challenges of recruitment of additional patients

in the postmarket setting for rare diseases—small population size and the availability of the product commercially, especially if a competing commercial product is also available. We suggest the Agency add language to assist sponsors in assessing the compatibility of the RWD source and to enable sponsors to contextualize the differences in baseline characteristics between the clinical study and the RWD groups. We recommend FDA provide an example of the complex issues that should be considered in using RWD to obtain postmarket information on traditionally underrepresented populations (lines 186-187), such as missing data in RWD sources. We understand that patients may wish to opt out of providing data on optional demographic fields.

Other considerations

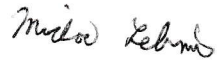
ARM appreciates the examples provided of circumstances under which postmarketing requirements (PMRs) may be needed (e.g., when adverse events seem to occur at a higher rate in an underrepresented population, but insufficient participants from this populations participated in the pivotal trial).

The FDA should offer flexibility in postmarket studies for novel therapies such as CGTs that can only be offered in a limited number of clinical sites. The complexity and novelty of many CGTs often results in only large academic medical centers being equipped to offer them, especially initially after approval. Geographic distance and transportation limitations may contribute to barriers to participation in clinical trials generally, including in postmarket follow-up requirements, that may disproportionately impact underrepresented subpopulations. We believe these issues merit short-term flexibility combined with long-term systemic attention from multiple stakeholders, including sponsors.

Moreover, to address these challenges, the Agency should provide examples of ways local providers could record critical data for patients unable or unwilling to travel long distances to these academic centers for follow-up evaluations. The FDA should also indicate that remote data collection, e.g., through the use of digital health technologies, may be useful in obtaining required confirmatory data.

To conclude, we support an approach that balances early patient access to needed treatments with the crucial need for representation in clinical trials of historically underrepresented populations to ensure safety and efficacy in all subpopulations treated by a therapy. We appreciate the FDA's efforts to do so within this guidance document, and we look forward to collaborative efforts with the Agency and other stakeholders in achieving these aims.

Sincerely,



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