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Dr. Richard Pazdur
Director
Oncology Center of Excellence
US Food and Drug Administration
Beltsville, MD 20705

Dr. Michelle Tarver
Acting Director
Center for Devices and Radiological Health
US Food and Drug Administration
Silver Spring, MD 20993

Dr. Patrizia Cavazzoni
Director
Center for Drug Evaluation and Research
US Food and Drug Administration
Silver Spring, MD 20993

Dr. Christine Lee
Acting Associate Commissioner
Office of Minority Health and Health Equity
US Food and Drug Administration
Beltsville, MD 20705

Dr. Peter Marks
Director
Center for Biologics Evaluation and Research
US Food and Drug Administration
Silver Spring, MD 20993

Dr. Kaveeta Vasisht
Associate Commissioner
Office of Women's Health
US Food and Drug Administration
Beltsville, MD 20705

Re: Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies [Docket No. FDA-2021-D-0789]

Dear Drs. Pazdur, Cavazzoni, Marks, Tarver, Lee, and Vasisht,

The FasterCures team at the Milken Institute is honored to provide its expert response to the Request for Comments on Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies [Docket No. FDA-2021-D-0789].

As a nonprofit, nonpartisan think tank, the Milken Institute believes in the power of capital markets to solve urgent social and economic challenges to improve lives. At the heart of the Institute's work is the idea that societies prosper with an educated, healthy workforce, open and efficient capital markets, and effective social institutions. FasterCures is driven by a singular goal: to save lives by speeding scientific advancements to all patients. For the last 15 years, FasterCures has advanced health equity by advocating for systemic patient engagement in biomedical research by bringing together diverse stakeholders to assess gaps, identify solutions, and develop the tools and resources to support decision-making.

FasterCures celebrates the significant advancements made by the US Food and Drug Administration (FDA) in establishing an updated plan for sponsors and clarifying the mechanism for delivering a federally mandated Diversity Action Plan (DAP) for clinical studies under the Food and Drug Omnibus Reform Act (FDORA). This guidance will be a vital step to ensure equitable and representative clinical studies considering demographic characteristics, such as race, ethnicity, sex, and age, in addition to encouraging sponsors to consider other factors, such as "geographic location, gender identity, sexual orientation, socioeconomic status, physical and mental disabilities, pregnancy status, lactation status, and co-morbidity."

FasterCures works to develop strategies and policies to increase diversity and inclusion in all stages of clinical research and thus commends the agency for releasing thorough draft guidance addressing the use of DAPs as a critical step toward addressing persistent health inequities. We welcome the opportunity to partner with the agency in strengthening the current draft guidance and providing additional recommendations on potential factors the FDA might consider for the successful implementation of DAPs:

1. Maintain the guidance language on "other factors," which include the impact of social and environmental factors on safety and efficacy and the consideration of different responses to the medical product based upon "pharmacokinetics (PK), pharmacodynamics (PD) or susceptibility to specific adverse events."
2. Clarify how the FDA can encourage and support sponsors to meet the DAP enrollment requirements when the enrollment goals cannot be met even with sponsors' best efforts.
3. Communicate the importance of ongoing investment in community-driven engagement to build trust in clinical studies and sustain long-term partnerships with historically underrepresented communities.
4. Identify and streamline regulations across FDA centers to support recruitment, retention, observation, and data collection with participants from underrepresented communities to accommodate seamless implementation of DAPs.

Recommendations to Maintain and Improve the Key Strengths of the Current Draft Guidance

1. Maintain language describing the factors sponsors should consider, which addresses different responses to medical products by certain demographic groups.

FasterCures fully supports the FDA's expansive thinking on how to address the potential differentiated effects of medical products on certain demographic groups, which could surface during the early phases of clinical trials. Therefore, we recommend retaining the language specified in lines 193-200 and 351-363 of the current draft guidance.

As one of the most mature regulatory agencies in the world, the FDA understands the implications of requiring sponsors to submit a DAP only for Phase 3 or pivotal trials. The agency clarified the confusion that this limited requirement for submitting DAPs might cause with sponsors if they only consider the representation of race, ethnicity, sex, and age at later stages of clinical studies.

The safety and optimal dose data collected and determined in Phases 1 and 2 will be used for the Phase 3 studies, which then confirm the safety and efficacy with patients.[1] Numerous studies have provided evidence of how differences in race, ethnicity, sex, and age impact PK, PD, and safety. Inherent genetic polymorphism in different ethnicities and races, along with diet and weight differences, contribute to differences in PK.[2] The frequency of polymorphisms in genes encoding drug-metabolizing enzymes and drug transporters influences PK, optimal dose, and the safety of different medical products.[3] In addition, elevated blood concentrations and longer elimination times of drugs are consistently observed in women, which could cause significant adverse events if women are not properly represented in Phase I.[4] Children differ in PK and PD compared to adults,[5] and as we age, the inevitable physiological changes in cells and organs cause changes in PK and PD.[6]

The statute requires the submission of DAPs for Phase 3 and pivotal trials. However, to truly advance the appropriate representation of the US intended population of medical products, these differences in responses to medical products should be fully considered from the early phases of clinical trials, regardless of the submission requirement of DAPs in Phase 3 or pivotal trials.

2. Clarify the agency's intention if sponsors cannot meet recruitment goals according to the submitted DAP.

FasterCures would like the FDA to clarify how the agency plans to address events when sponsors cannot meet enrollment goals as agreed in their DAP. In the original draft guidance from 2022, one of the footnotes reads, "In the

event that recruitment goals are not met despite best efforts, sponsors should discuss with FDA a plan to collect this data in the post-marketing setting."[7]

The previous recommendation from 2022, as indicated, was not clear as to whether the agency plans to recommend collecting post-marketing data reflecting the original enrollment goals as part of post-marketing requirements and commitments. According to the Food and Drug Administration Amendments Act (FDAAA) of 2007, there are specific studies or clinical trials that the FDA can require from sponsors: when drugs were approved under the accelerated approval pathway, deferred pediatric studies under the Pediatric Research Equity Act, safety and efficacy studies in humans when the drugs were previously approved under the Animal Efficacy Rule, and assessment of a known, signals of, and unexpected serious risks.[8]

In the recent draft guidance, the FDA does not mention how the agency plans to handle cases in which sponsors cannot meet enrollment goals. Understanding that the FDAAA predates the FDORA and that adequate representation of diverse populations will impact the safety and efficacy of medical products, we believe there should be an appropriate level of enforcement mechanism from the FDA, such as requiring post-marketing studies with representative populations to further confirm the safety and efficacy of the approved medical products within intended populations.

In summary, FasterCures recommends the two points below to maintain and build upon the key strengths of the current draft guidance:

- **Maintain the language of factors sponsors should consider when they expect differential responses due to differences in PK, PD, safety, or effectiveness by sex, age, genetic variations by race and ethnicity, and other characteristics such as socioeconomic status, geographic location, and comorbidities.**
- **Clarify how the FDA intends to proceed if sponsors cannot meet recruitment goals according to the DAP and how the agency plans to enforce requirements in such cases, potentially through post-marketing studies.**

Recommendations to Ensure the Best Implementation of the Diversity Action Plan Requirement

The successful implementation of DAP is contingent on thoughtful strategies that integrate diverse perspectives at every level of clinical trial design and execution. To this end, FasterCures recommends that the FDA emphasize the following points, which will enhance the operationalization of the DAP guidance, lead to tailored implementation approaches, and ultimately improve the engagement of underrepresented populations in clinical studies.

3. Emphasize the importance of trust-building through community-driven engagement in DAP implementation.

FasterCures recommends that the FDA provide thought leadership with sponsors on the importance of community-driven engagement to build the foundation for executing DAPs, improving diversity in clinical trials, and building trust in clinical research.

Even with the collective willingness to adequately implement the DAP, we must acknowledge one of the core challenges in recruiting underrepresented populations is the historical lack of trust between marginalized communities and biomedical research entities.[9] To bridge this gap, we recommend that the agency underscore the importance of robust and continuous community-directed engagement as a foundation for DAP implementation. The initial and continuous investment by sponsors and other clinical research organizations to build long-term partnerships with community organizations, patient advocacy groups, and local health-care providers is essential.[10] These organizations have strong relationships with underrepresented groups, which will accelerate and strengthen the relationships for the sustainable implementation of DAPs.

We want to share some notable examples for the FDA to consider for the agency's leadership on DAP implementation. The Equitable Breakthroughs in Medicine Development (EQBMED) initiative is a partnership among Yale School of Medicine, Morehouse School of Medicine, Vanderbilt University Medical Center, and the Research Centers in Minority Institutions Coordinating Center at Morehouse School of Medicine. The initiative is funded by the Pharmaceutical Research and Manufacturers of America (PhRMA).[11] Key features of the EQBMED model that could inform cross-industry initiatives include its approach to community-based clinical trial sites, mentorship, and training for investigators from diverse backgrounds, as well as the site maturity assessment model.[12]

The Yale Cultural Ambassadors Program through the Yale Center for Clinical Investigation is another unique partnership with the Connecticut African Methodist Episcopal Zion Churches and Junta, one of the first Latino community-based nonprofits in New Haven.[13] Key aspects of the Cultural Ambassadors program that have successfully increased minority participation in clinical research include partnership with trusted community leaders, educational outreach, and bidirectional communication.[14]

In addition, clinical research and site management organizations have started collaborating with pharmaceutical companies to enhance the representation of diverse populations in clinical trials.[15] Some key elements of these partnerships include built-in funding in a study budget for participants and site support for education and outreach, an emphasis on community-centric recruitment strategies, tailored engagement approaches, translation of materials to languages that represent the local community, and decentralized trial designs that mitigate logistical barriers to participation. These collaborative initiatives have made progress toward increasing diversity in clinical trials and overcoming traditional barriers, including limited access to trial sites, lack of diversity among research staff, financial and time burdens, and mistrust rooted in systemic bias.

4. Consider identifying and clarifying the rules and regulations surrounding clinical trials to facilitate adequate implementation of DAP requirements.

FasterCures believes that innovative technologies and clinical trial planning, design, and execution are crucial to improve the enrollment of underrepresented populations in clinical studies. Embracing digital health technologies (DHTs) and hybrid and decentralized trial designs will make trials more accessible, especially for participants who face geographic, financial, or logistical challenges to join site-based studies.[16] Artificial intelligence (AI), digital tools, and advanced analytics can also enhance participant recruitment and retention. However, sponsors should not replace direct engagement with patients and communities with AI tools that may perpetuate bias and are not developed with datasets that reflect diverse communities.

The FDA has created several guidance documents to provide a framework for the use of DHTs in drug and biological product development, consideration of remote data collection, and decentralized clinical trials for medical products.[17] We look forward to the FDA's continued leadership on AI as related to medical products and how it can aid DAP implementation.[18]

In summary, successful and sustainable implementation of the DAP will require several considerations from the FDA for communication and clarification:

- **Emphasize and communicate to sponsors and clinical research organizations about the upfront investment in building trust with marginalized and underrepresented communities through community-driven engagement to encourage participation in clinical trials.**
- **Identify and initiate processes to clarify rules and regulations, particularly surrounding the use of advanced tools and innovative clinical trial designs to support recruitment, retention, observation, and data collection.**
- **Ensure consistent FDA enforcement action in sponsor submissions of DAPs to reflect the intent of FDORA.**

FasterCures celebrates the revised draft guidance on DAPs and its comprehensive approaches for sponsors and clinical research organizations to adequately represent diversity in clinical trials. This is long-awaited progress in medical product research and development to ensure safety and efficacy to the intended US population and highlight the impacts of biological and social factors in medical product development. We want to emphasize that adequate implementation of DAPs requires commitments from all stakeholders to build foundational trust and infrastructure to sustain equitable and representative medical product development and access. FasterCures is committed to working with the FDA and other stakeholders to ensure that future.

Sincerely,

Esther Krofah
Executive Vice President, Health
Milken Institute

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