PERSONALIZED MEDICINE COALITION

September 26, 2024

The Honorable Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

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

Dear Commissioner Califf:

The Personalized Medicine Coalition (PMC), a multi-stakeholder group comprising more than 200 institutions from across the health care spectrum, thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on its draft guidance titled *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies*.[i] We understand that the draft guidance outlines FDA's expectations for Diversity Action Plans (DAPs), as mandated by the *Food and Drug Omnibus Reform Act of 2022*, to improve the participation of historically underrepresented populations in clinical trials and to improve the strength of evidence on the use of drugs and medical devices approved by the FDA for their intended use populations. According to the draft guidance, these plans must include enrollment goals disaggregated by race, ethnicity, sex, and age; a rationale for the enrollment goals; and an explanation of how the sponsor plans to meet these goals. PMC supports FDA's recognition of the critical role that diversity and representativeness play in clinical research and FDA's emphasis on community engagement measures to meet enrollment and retention goals. We also comment in this letter on the implications for DAPs on personalized medicine and identify opportunities for FDA to strengthen and clarify its draft guidance.

PMC defines personalized medicine as an evolving field in which physicians use diagnostic tests and individual details about a person's health to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms that impact health. By combining data from diagnostic tests with an individual's medical history, circumstances, and values, health care providers can develop targeted treatment and prevention plans with their patients.

Personalized medicine is helping to shift the patient and provider experiences away from trial-and-error toward a more streamlined process for making clinical decisions, which will lead to improved patient outcomes, a reduction in unnecessary treatment costs, and better patient and provider satisfaction. PMC and its members are leading the way in personalized medicine and in developing evidence showing how patients

and the health care system can benefit from the appropriate testing and tailored treatment of patients as soon as possible during their clinical experiences.

Delivering personalized medicine successfully depends on consideration of patients' biology, medical history, values, and circumstances. Unfortunately, systemic disparities and research participation barriers persist in clinical trials, even in disease areas characterized by elevated incidence and mortality counts among understudied patient populations. PMC and the FDA share the same goals of improving our understanding of the safety and efficacy of biomedical products within certain demographic subgroups and of facilitating equitable access to medical innovations to help patients, health care providers, caregivers, and other stakeholders make informed treatment decisions. Generating data for a broader and more representative population early in a medical product's clinical development can improve the generalizability of results across patient subgroups and inform the safe and effective use of a medical product for all patients.

Statement of Neutrality

Many of PMC's members will present their own responses to FDA's draft guidance on DAPs and will actively advocate for those positions. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance, and are not intended to adversely impact the ability of individual PMC members, alone or in combination, to pursue separate comments with respect to the draft guidance.

Support for Empowering Community Engagement in Clinical Trials

In 2024, PMC published recommendations for *Addressing Disparities in Research Informing Personalized Medicine* that were developed in collaboration with leaders from communities historically underrepresented in biomedical research.[ii] The group prioritized community engagement throughout the research enterprise. To ensure an appropriate and significant role for community representatives in planning and conducting research, recruiting participants, and making decisions related to collecting, handling, and sharing research data, the group recommended the following community-engagement strategies:

1. Provide resources for community-based organization (CBO) programs to enhance research participation.

2. Empower and provide necessary support to CBOs to deliver training in research competency to their communities and to deliver diversity and cultural competency training to researchers.

3. Increase funding for Federally Qualified Rural Health Centers (FQHCs), Urban Indian Health programs, and rural health clinics.

4. Rename Community Advisory Boards (CABs) as Community Impact Boards (CIBs); require a CIB to provide consultation within Institutional Review Board (IRB) deliberations; and include two community representatives on an IRB.

5. Foster the recruitment of investigators from diverse backgrounds to conduct personalized medicine research through research sponsor-based initiatives.

FDA's draft guidance identifies multiple clinical study enrollment and retention strategies that broadly align with these recommendations, including sustained community engagement through CABs, patient groups, and community organizations, among others; cultural competency training for investigators and research staff to facilitate trust; participant education on the clinical study; and selecting site locations that serve diverse populations. Building trust with underrepresented populations is essential for improving participation in clinical trials, and the draft guidance recognizes the importance of sustained engagement with communities in building this trust. By encouraging sponsors to partner with community organizations, engage with local leaders, and tailor their outreach efforts to the needs of specific populations, the draft guidance provides a roadmap for building stronger relationships with communities underrepresented in biomedical research. **PMC commends FDA's emphasis on community engagement, cultural competency training, and participant education in the draft guidance.**

Community leaders can help investigators and clinical trial staff understand the cultural and social factors that may influence a person's decision to participate in a clinical trial and educational initiatives that may be needed to build trust. **To help empower community voices throughout all aspects of study design and implementation, we encourage the FDA to provide recommendations for how sponsors can tailor their outreach and engagement efforts,** including on procuring necessary resources for enrollment sites and engaging community leaders and organizations that have the trust of target populations. FDA should also encourage long-term engagement between trial sponsors and underrepresented communities. PMC's report discusses a number of strategies and initiatives underway to support the inclusion of diverse communities in research that may be useful for the agency.[iii] By providing more detailed guidance and considering the recommendations from community leaders like those listed in PMC's report, FDA can help sponsors develop more effective strategies for recruiting and retaining diverse participants that meet the needs of underrepresented communities.

In addition, **PMC supports FDA's consideration of decentralized clinical trials as a measure for meeting Diversity Action Plans' enrollment and retention goals.** Conducted at the point of care, decentralized trials can help make trials more agile and efficient and can allow patients to receive treatments from community providers when they are unable to travel to a trial site. PMC has been supportive of FDA's ongoing efforts to advance these and other novel clinical trial designs that may help facilitate clinical trial participation among patients representing diverse populations, those living in difficult geographic regions, and those with a limited capacity for travel.[iv,v]

Opportunities to Strengthen and Clarify the Draft Guidance

Global Alignment on Definitions for Race and Ethnicity

As mandated by the *Food and Drug Omnibus Reform Act of 2022*, DAPs are required to disaggregate enrollment goals by race, ethnicity, sex, and age group. The draft guidance indicates that FDA intends to update its categories for capturing race and ethnicity to be consistent with recent revisions published by the U.S. Office of Management and Budget (OMB) through its *Statistical Policy Directive No. 15*.[vi] FDA's definitions for the terms "race" and "ethnicity" will have global implications for data collection and reporting under clinical trials, FDA should work with global partners to help drive global harmonization of relevant demographic data that should be captured to uncover potential differences in response to treatment and to capture the molecular and social variables that can help drive a personalized medicine approach. These definitions also should account for individuals who are multi-racial, multi-

ethnic, or whose race and ethnicity is unknown. **PMC encourages FDA to work with global partners to harmonize, as much as is feasible, the collection and consideration of relevant demographic data.**

Use of Non-US Trial Data From Global Studies

FDA's draft guidance provides recommendations on how to design a DAP and set enrollment goals using data about the incidence and/or prevalence of a disease in the U.S. population. The draft guidance appears to set forth the expectation that DAPs can describe global study plans broadly, but that the race and ethnicity goals themselves are based on U.S. prevalence and incidence. The draft guidance also implies that international data can be leveraged to support U.S.-based enrollment goals for the FDA. While intrinsic factors like genetics may be similar across nations, extrinsic factors in such data, like diet, lifestyle, comorbidities, and access to health care, would not reflect those of the U.S. population. Differential outcomes may be more related to these extrinsic factors. **FDA should provide clarity on how data collected from non-U.S. trial sites can augment data from U.S. sites to inform its assessment of safety and efficacy for new medical products.**

Setting Enrollment Goals and Powering Subpopulation Analyses

PMC appreciates that the draft guidance considers the impact of genetic variation that can define subsets of a disease as well as pharmacogenetic variants on drug metabolism and adverse reactions. Certain genetic variants may be more prevalent in certain racial and ethnic populations. While the guidance provides a general framework for setting enrollment goals based on prevalence data, it is unclear how to calibrate these goals to accurately reflect genetic variation and disease prevalence across different demographic groups. Clear, data-driven methods are needed to ensure that enrollment goals are realistic, achievable, and aligned with the overall objectives of promoting diversity in clinical trials. **FDA should provide more detail on determining prevalence to set enrollment goals and how the agency will evaluate these enrollment goals.**

In addition, enrollment of racial and ethnic populations based on prevalence alone may not be sufficient to power studies that accurately detect differences in safety and effectiveness in small populations. In order to accurately assess subgroup differences, clinical trials must be explicitly designed for that purpose and have an adequate number of participants to detect any difference between subgroups. **DAPs should specify study design features that will support accurate subgroup analyses to inform the safety and effectiveness of medical products in relevant subpopulations.**

Flexibility for Rare Diseases and Small Patient Populations

PMC appreciates the draft guidance's recognition of the unique challenges involved in enrolling diverse populations for rare disease trials. Rare diseases often have small and geographically dispersed patient populations, which can make achieving diversity in clinical trials especially difficult. Although the draft guidance acknowledges these challenges, it offers limited specific solutions for addressing this growing area for personalized medicine, which accounted for a record 61 percent of new personalized medicines approved by the FDA in 2023.[vii] **FDA should provide more detailed guidance on conducting representative trials in rare disease that allows for appropriate flexibility in setting and achieving diversity goals in small patient populations.** This could include:

- Alternative methods for estimating disease prevalence and setting enrollment goals when traditional methods of calculating prevalence may not be applicable due to small population size;

- Strategies for recruiting diverse participants from small and dispersed populations, such as by leveraging patient registries, collaborating with rare disease patient organizations, or using innovative trial designs;
- Strategies to preserve the integrity of small studies where sharing patient demographics may risk participant anonymity and/or unblinding the study, with such strategies possibly involving high-level diversity goals and high-level reporting on progress; and
- Options for adjusting enrollment goals, including mechanisms to request waivers or modifications to DAPs when needed.

Considerations Unique to Diagnostic Tests

Diagnostic tests can help guide treatment decisions and determine which treatments will be safe and effective for any given patient. Diagnostic testing is a crucial element of personalized medicine. Under FDA's draft guidance, DAPs would be required for companion diagnostics with either an investigational device exemption (IDE) or pre-market approval (PMA) application. For companion diagnostics, which help define subpopulations of patients who may or may not benefit from a certain treatment, the enrollment population for the diagnostic clinical study would be determined by the registration population for the clinical study of the corresponding therapeutic. **For companion diagnostic IDEs or PMAs, FDA should allow sponsors to leverage the DAP submitted by the drug sponsor for the corresponding drug clinical study.**

In addition, FDA recommends that DAPs for medical devices consider data on relevant factors for device performance in determining enrollment goals and characterize any differential effects across a diverse population. While there are possible genetic differences that could impact a diagnostic test's clinical performance, this would not affect its analytical performance. **In its discussion of information a medical device sponsor should include in its rationale for enrollment goals, FDA should clarify it is referring to a device's "clinical" performance.**

Ensuring Successful and Responsible Collection of Post-Market, Real-World Data

Both accountability and transparency are needed to build community trust in the personalized medicine research enterprise. While FDA's draft guidance strongly encourages sponsors to share key information from their DAPs with the public, the draft guidance does not discuss how the agency would enforce adherence to these plans. Community leaders involved in PMC's disparities project emphasized the importance of fostering shared accountability to achieve meaningful community engagement and inclusion in personalized medicine research. **To ensure the success of DAPs, FDA should incorporate a structured mechanism, including regular reporting requirements, to track and assess the progress of sponsors in meeting diversity goals.**

Real-world data (RWD) provides an important method to supplement trial data and enhance understanding of a product's effect in diverse patient populations. Community leaders in PMC's disparities project also recommended the intentional and responsible collection of RWD on patients from underrepresented communities to fill gaps in existing RWD sources. It is important to evaluate disparities between pre-approval demographic breakdowns and post-marketing real-world use data and associated outcomes. **FDA should encourage opportunities for post-marketing studies that leverage RWD and support efforts by sponsors to collaborate with communities in closing any RWD gaps, including incomplete race and ethnicity data.**

Conclusion

PMC appreciates FDA's commitment to improving clinical trial diversity. We look forward to working with you and your colleagues to improve the participation of historically underrepresented populations in clinical trials. If you have any questions about the content of this letter, please contact me at 202-580-5080 or dpritchard@personalizedmedicinecoalition.org, or David Davenport, PMC's Manager of Public and Science Policy, at ddavenport@personalizedmedicinecoalition.org or 804-291-8572.

Sincerely,

Daryl Pritchard, Ph.D.
Senior Vice President, Science Policy

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[i] Food and Drug Administration. *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies* [Docket No. FDA-2021-D-0789]. https://www.fda.gov/media/179593/download. (Accessed September 18, 2024)

[ii] Personalized Medicine Coalition. *Addressing Disparities in Research Informing Personalized Medicine*. March 13, 2024. https://www.personalizedmedicinecoalition.org/research/disparities-in-research. (Accessed September 4, 2024.)

[iii] Personalized Medicine Coalition. *Addressing Disparities in Research Informing Personalized Medicine*. March 13, 2024. https://www.personalizedmedicinecoalition.org/research/disparities-in-research. (Accessed September 4, 2024.)

[iv] Personalized Medicine Coalition. *Comment Letter on Cures 2.0 Request for Information (RFI).* August 2, 2024. https://www.personalizedmedicinecoalition.org/wp-content/uploads/2024/08/response-letter.pdf. (Accessed September 4, 2024.)

[v] Personalized Medicine Coalition. *Remarks on Public Stakeholder Panel: FDA's Public Workshop on the Seventh Reauthorization of the Prescription Drug User Fee Act.* September 28, 2021. https://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PDUFA_VII_Goals_Letter_Comments_Docket_Submission_10.28.21.pdf. (Accessed September 24, 2024.)

[vi] Office of Management and Budget (OMB). *Revisions to OMB's Statistical Policy Directive No. 15: Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity*. Federal Register Vol. 89, No. 62: 22182. March 29, 2024. https://www.federalregister.gov/d/2024-06469. (Accessed September 24, 2024.)

[vii] Personalized Medicine Coalition. *Personalized Medicine at FDA: The Scope & Significance of Progress in 2023.* February 29, 2024. https://www.personalizedmedicinecoalition.org/wp-content/uploads/2024/02/report-3.pdf. (Accessed July 2, 2024.)