June 13th, 2022

Robert M. Califf, M.D., MACC
Commissioner, Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA-2021-D-0789, Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry

Filed electronically at http://www.regulations.gov

Dear Commissioner Califf:

On behalf of the Cystic Fibrosis Foundation, we write to provide comments on the Food and Drug Administration (FDA) draft guidance on *Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials*. We commend the FDA's ongoing efforts to rectify the grave lack of adequate representation of diverse racial and ethnic groups in clinical research and appreciate the opportunity to offer feedback on this latest measure.

Background on Cystic Fibrosis and the Cystic Fibrosis Foundation

The Cystic Fibrosis Foundation is a national organization dedicated to improving the quality of life and standard of care for individuals with cystic fibrosis, a rare genetic disease that affects nearly 40,000 people in the United States. We are engaged in virtually every element of the research and development process—from preclinical discovery and identification of new therapeutics, to conducting clinical trials and post-marketing surveillance.

Historically, cystic fibrosis research and clinical trials have struggled with inclusion of underrepresented racial and ethnic minority populations, potentially due in part to the misconception that cystic fibrosis only affects white individuals. Achieving our mission of a cure for all people with cystic fibrosis will require broader, more diverse representation of people with cystic fibrosis of all races in research and clinical trials; for that reason, the Cystic Fibrosis Foundation is investing significant time, resources, and attention towards improving the diversity of participants in clinical trials for cystic fibrosis treatments. With that in mind, the following comments are informed by both our extensive experience with clinical trials and our ongoing efforts to ensure that clinical research is representative of the entire cystic fibrosis community.

Timeliness of Submitting Race and Ethnicity Diversity Plans:

The FDA recommends that sponsors submit a race and ethnicity diversity plan "no later than when a sponsor is seeking feedback regarding the applicable pivotal trial(s) for the drug," which is often at the End of Phase 2 (EOP2) meeting. We are concerned that this fails to reflect the need to take inclusion into account over the

entire life cycle of a drug product and recommend the FDA request submission of race and ethnicity diversity plans with sponsors' IND applications.

Setting the submission deadline for race and ethnicity diversity plans at the EOP2 meeting fails to capitalize on the opportunity to gather and analyze data from early clinical pharmacology studies that might identify critical race- or ethnicity-associated differences. The FDA discusses the collection of pharmacokinetic (PK), pharmacodynamic (PD), and pharmacogenomic data from diverse populations to inform analyses of drug exposure and response. However, these data are collected as early as Phase 1 trials and important differences related to genetic ancestry could be missed if sponsors do not implement race and ethnicity diversity plans until later in the drug development process. Enrollment and retention of diverse participants in clinical trials requires significant time, resources, and planning; earlier submission will ensure that sponsors lay the groundwork for the efforts described in the race and ethnicity diversity plans prior to initiating a clinical trial.

Additionally, the FDA should establish 'check-ins' at specific points in the drug development process—for instance, at the EOP2 meeting, if race and ethnicity diversity plans are submitted with INDs. This requirement would facilitate timely FDA review of data collected, sponsor adherence to the diversity plan, progress towards diversity plan goals, and necessary diversity plan updates.

Diversity and Ethnicity Plans for Rare and Ultra-Rare Diseases:

Improving enrollment of individuals from underrepresented racial and ethnic populations in clinical trials must be a universal priority across essentially every disease. With that in mind, we believe that all sponsors should be required to submit race and ethnicity diversity plans, regardless of the disease for which they're developing products. It should be noted, however, that sponsors recruiting for rare and ultra-rare disease trials often face significant recruitment challenges due to small patient populations. Despite this reality, discussion of rare diseases in this FDA document is limited to mentions of the increasing utilization of alternative study designs and potential difficulties of setting enrollment goals due to limited epidemiological data.

We request that the FDA provide further guidance on the structure and contents of race and ethnicity diversity plans for sponsors developing drug products for rare and ultra-rare diseases. As an example, race and ethnicity diversity plans for rare and ultra-rare disease trials might include a "broadening eligibility criteria" section under the "Specific plan to enroll and recruit diverse participants" category. This section would describe actions to be taken if original enrollment targets, as determined by disease epidemiology, cannot be met due to participant ineligibility based on initial trial design and inclusion/exclusion criteria. The FDA has previously elaborated upon this topic (*Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry*) and could refer to those recommendations within the guidance text.

Clarification of Trial Enrollment and Retention Strategies & Operational Measures:

In its discussion of specific plans of action to enroll and retain diverse participants in clinical trials, the FDA distinguishes between "trial enrollment and retention strategies" and "operational measures." Though multiple examples of "trial enrollment and retention strategies" are described, it is unclear what the FDA would consider to be "operational measures." We request that the FDA clarify its intended definition of "operational measures" and how it differs from "trial enrollment and retention strategies." We would further recommend the inclusion, under either "trial enrollment and retention strategies" or "operational measures," of suggestions such as opening new research sites in locations with demographics that will facilitate enrichment of target populations; cross-center referral to match patients to appropriate studies; flexible timing for study visits; and easing of enrollment timeframes.

Absent from the "reducing burdens due to trial/study design/conduct" subsection of this guidance is financial reimbursement. Financial burdens can make participation in clinical trials prohibitively difficult; taking measures to ease them should be explicitly recommended as a strategy to improve trial enrollment and retention. With that in mind, the FDA should update and elaborate upon its prior guidance regarding ways to make trial participation less burdensome through financial reimbursement. The FDA has previously noted that reimbursement for "reasonable travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging" would not be considered unduly influential to trial participants. This list is overly narrow and does not include other identified cost burdens, such as meals and childcare. The FDA has also stated that "consideration may be given" to paying individuals for their trial participation. We believe that this language should be strengthened to actively recommend compensation for both trial participation and associated costs. It would be beneficial for the FDA to additionally provide guidance regarding the logistics of financial reimbursement, which may include sponsor support of research sites, proactive and same-day reimbursement, and criteria for determining the extent of financial reimbursement for trial participants.

We recognize that some aspects of these determinations are left to IRBs. However, further guidance on these topics would be beneficial for ensuring that sponsors can execute the strategies and achieve the goals set forth in their race and ethnicity diversity plans.

Diversity and Ethnicity Plan Data Collection and Publication:

Sponsors throughout industry are still working to determine how to best achieve better representation of individuals from historically marginalized groups in clinical research. Race and ethnicity diversity plans, as described, will contain a significant amount of information detailing different approaches, including post-implementation descriptions of the successes and challenges encountered by sponsors. Though there will be variability based on disease, target demographics, geographical location, and other factors, the FDA should consider compiling these data to use when determining and communicating further recommendations and best practices for improving clinical trial diversity. We emphasize that race and ethnicity information should be self-reported or provided by appropriate first-degree relatives or guardians, as the FDA has previously recommended. When reporting these data sponsors should describe the definitions used and choices offered to participants during the data collection process.

Demonstrations of Past Inclusion and Ongoing Improvement in Clinical Trial Diversity:

Improving the diversity of clinical trials is an ongoing process. For that reason, we believe that race and ethnicity diversity plans should include data describing the representation of racial and ethnic populations in sponsors' previous clinical trials for drug products treating that disease or condition, including the details and outcomes of prior race and ethnicity diversity plans, if applicable. This requirement would provide the FDA with a more comprehensive view of the progress sponsors are making towards increasing clinical trial diversity over time and allow the FDA to take both improvement and decline of appropriate representation into account when evaluating the sponsor's development program.

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Once again, the Cystic Fibrosis Foundation commends the FDA's commitment to providing guidance on improving clinical trial diversity and appreciates the opportunity to offer feedback on this document. We will

continue to strongly advocate for inclusion and representation and look forward to collaborating with the agency on this matter in the future.

Sincerely,

Mary Dwight

Senior Vice President
Chief Policy and Advocacy Officer

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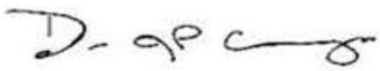

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