December 15th, 2022

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

Re: FDA-2022-N-2394, FDA CBER OTAT Patient-Focused Drug Development Listening Meeting — Patient Perspectives on Gene Therapy Products

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

Dear Commissioner Califf:

On behalf of the Cystic Fibrosis Foundation (CFF), we write to provide comments in response to the Food and Drug Administration (FDA) *Patient-Focused Drug Development Listening Meeting on Patient Perspectives on Gene Therapy Products*. As a patient advocacy organization, the Cystic Fibrosis Foundation appreciates the FDA's ongoing commitment to understanding and incorporating the patient perspective into the drug development process and regulatory decision-making. We offer suggestions for the FDA as it considers how to improve the patient experience, facilitate patient education, and promote more extensive inclusion of patients and their perspectives into the development of gene therapy products.

Background on Cystic Fibrosis and the Cystic Fibrosis Foundation

Cystic fibrosis (CF) is a rare genetic disease that affects nearly 40,000 people in the United States. In people with CF, defects in the CFTR gene result in a buildup of thick mucus in multiple organ systems, leading to lung damage, life-threatening infections, and other complications. While modulator therapies can significantly reduce these symptoms, these therapies do not cure the underlying genetic defect that causes CF. For that reason, CF researchers have increasingly focused on gene therapies and their curative potential.

The CFF is dedicated to ensuring that people with CF have the opportunity to lead long, fulfilling lives, with the ultimate goal of curing CF. Since our founding, we have focused on ways to incorporate the patient voice into our programming and all aspects of CF care and research. One notable initiative is our Community Voice platform, which allows members of the CF community to partner with us, researchers, and other organizations to share their experiences and bring their insights and priorities to the forefront of CF research and care. The following suggestions are informed by the knowledge gleaned from this and other listening and outreach efforts aimed at better understanding the perspective of the CF community on gene therapies and gene therapy products.

Patient and Caregiver Understanding and Expectations of Gene Therapy Risks and Benefits

Language and Information Recommendations for Informed Consent Documents: In the 2020 *Guidance for Industry: Long-Term Follow-Up After Administration of Human Gene Therapy Products*, the FDA provides recommendations for information and language to be included in informed consent documents for clinical trials involving retroviral vectors. The guidance contains examples of specific, plain-language descriptions of the study agent (retroviral vector), mechanism of action for retroviral vectors, and the effect of DNA integration, in addition to suggestions for language addressing the risk of potential delayed adverse events and malignancy. We suggest that the FDA consider providing similar content and language recommendations for other components of the informed consent document for clinical trials for gene therapies. These may include eligibility for future gene therapy trials, patient rights, descriptions of the different phases of clinical trials (including combination phases), or explanations of sham or placebo groups in the context of gene therapies. Though we acknowledge the heterogeneity of clinical trials for gene therapies and how required information may differ with the disease and the type of gene therapy administered, we recommend working with patients and other critical stakeholders, such as caregivers, to identify and draft materials and language on important concepts that are broadly applicable across gene therapy products and could be used to improve understanding in the informed consent process. All language and materials used should be assessed to ensure they are accessible to laypeople and key concepts can be clearly understood.

Published Educational Materials: Much of the educational material regarding gene therapies available from the FDA is geared towards industry and regulatory professionals and not easy for the general public to find. We suggest that the FDA draft patient-oriented educational materials and compile them into an easily found, centralized location on its website. Alternatively, or additionally, the FDA should consider providing guidance for industry sponsors and patient advocacy groups on best practices for developing their own materials for educating patients and caregivers about gene therapies and clinical trials. As above, these educational materials should be drafted in consultation with patients and caregivers.

Comprehensive FDA Outreach for Patient-Focused Drug Development Efforts: We believe that the current FDA mechanisms for capturing the perspective of patients and other stakeholders (comment periods for draft guidances and FDA-led listening sessions, amongst others) may skew the agency's patient-focused drug development efforts toward the needs of patients and stakeholders most aware of and engaged with the regulatory process, which is not necessarily a representative sample. The FDA should develop and proactively implement a strategy for reaching out to broader and traditionally less-engaged or underrepresented patient and stakeholder populations for input over the course of such patient-focused drug development efforts. This effort may be aided by partnering with patient organizations and advocacy groups.

Patient and Caregiver Involvement in Clinical Study Design and Execution

Patient-Focused Drug Development Plans for Industry Sponsors: We applaud the FDA's growing efforts to increase the diversity of clinical trials, including the recently published *Draft Guidance for Industry: Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials* (2022). To ensure that industry sponsors actively incorporate patients and caregivers in the development process for gene therapy products, we suggest that the FDA issue an equivalent guidance focused on PFDD and calling for industry sponsors to submit a plan for patient involvement with their IND application. Contents of these plans may include both strategies to include the patient voice in the gene therapy development process and measures to protect patients over the course of clinical trials, such as embedding neutral, non-industry patient advocates into the clinical trial process.

Taking a Rigorous Approach to Sponsor Transparency: Patients and caregivers often learn about significant developments to clinical trials for gene therapies long after they occur, or not at all. With this in mind, the FDA

should take a more rigorous approach to sponsor transparency and communication with the gene therapy clinical trial participants and their caregivers. This may include mandating that sponsors contact and provide timely updates on events of importance, such as clinical trial results, serious adverse events, and other findings from long-term follow-up studies to trial participants and their caregivers.

Voluntary Incorporation of Proposed Patient-Focused Drug Development Legislative Provisions: We appreciate the adoption and promotion of a patient-focused drug development framework by the FDA, including the PFDD methodological guidance series for industry and PFDD listening meetings, as directed by the 21st Century Cures Act of 2016 and the FDA Reauthorization Act of 2017. In accordance with our prior suggestion regarding patient-focused drug development plans from sponsors, we recommend the FDA voluntarily incorporate the PFDD provisions proposed in Cures 2.0 Act, which would require sponsors to collect patient experience data during clinical trials and the agency to consider those data in regulatory decision-making; and the Food and Drug Amendments of 2022 (FDA22), which would direct United States and European regulatory agencies to work together in partial consultation with rare disease stakeholders to study processes for evaluating the safety and efficacy of available drugs for rare diseases and conditions, as well as require a study on the use of FDA mechanisms and tools to ensure that patient and physician perspectives are considered and incorporated throughout FDA processes. These provisions are not specific to gene therapy products, so we encourage the FDA to ensure that gene therapy products and the patients receiving them are considered throughout these efforts.

General Considerations

Pediatric Access to Clinical Trials for Gene Therapy Products: Though the FDA references the topic in its 2022 *Draft Guidance for Industry, Sponsors, and IRBs: Ethical Considerations for Clinical Investigations of Medical Products Involving Children*, and has touched upon it in others (*Draft Guidance for Industry: Human Gene Therapy Products Incorporating Human Genome Editing*, 2022; *Guidance for Industry: Human Gene Therapy for Neurodegenerative Diseases*, 2022), we urge the FDA to more explicitly address the fundamental tension between the need for early pediatric access for gene therapy products for certain conditions and the agency's discouragement of sponsors from performing early clinical trials for gene therapy products in pediatric subjects. We ask the FDA to directly, to the extent possible, articulate considerations for pediatric clinical trials for gene therapy products. This is particularly needed for diseases and conditions that do not result in pediatric mortality but do cause irreversible damage that accumulates with age and diminishes adult function and lifespan.

Heterogeneity within Diseases or Conditions: Even within the same disease or condition, there can exist significant heterogeneity in not only manifestation and severity, but also in the origin of the disease or condition (such as variance in causal genetic mutations). We encourage the FDA to consider this heterogeneity and how it may influence the goals of gene therapy, educational and programming needs, and risk tolerance of individual patients or subgroups of patients within the overall patient population into account as the agency continues it PFDD efforts. This may include better facilitating inclusion of multiple patient subpopulations in clinical trials for gene therapy products and incorporation of a more diverse set of patient experience metrics into regulatory decision-making to encompass the needs and perspectives of heterogeneous disease cohorts.

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Once again, the Cystic Fibrosis Foundation commends the FDA's commitment to soliciting input from patients and caregivers for developing and adopting a patient-focused drug development framework for gene therapy products. We believe that these suggestions may prove useful as the FDA continues its efforts to ensure that

patients are informed, consulted, and included throughout the entirety of the gene therapy product development lifecycle. We appreciate the opportunity to provide input on the subject and look forward to continuing this dialogue on behalf of the CF patient community.

Sincerely,

Mary Dwight

Senior Vice President
Chief Policy and Advocacy Officer