CYSTIC FIBROSIS FOUNDATION®

January 4th, 2023

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

Re: FDA-2022-D-0738, Ethical Considerations for Clinical Investigations of Medical Products Involving Children — Draft Guidance for Industry, Sponsors, and IRBs

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

Dear Commissioner Califf:

On behalf of the Cystic Fibrosis Foundation, we write to provide comments in response to the Food and Drug Administration draft guidance on *Ethical Considerations for Clinical Investigations of Medical Products Involving Children*. The Foundation greatly appreciates the FDA's commitment to protecting children in clinical trials and assuring the safety and effectiveness of medical products for children and we welcome the opportunity to comment on those efforts.

Background on Cystic Fibrosis and the Cystic Fibrosis Foundation

Cystic fibrosis (CF) is a rare genetic disease that affects nearly 40,000 adults and children 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. When the disease was first described in 1938, children with CF rarely lived past one year of age. In 2020, for the first time, the median predicted survival age for people with cystic fibrosis reached 50 years—a landmark development partially attributable to early pediatric access to modulator therapies, which are vital for halting or preventing the irreversible lung damage and pathogenic colonization seen in adults with CF. Early pediatric access to biological therapeutics, such as gene therapies, is expected to drive further improvements in morbidity and mortality for people with CF.

The Cystic Fibrosis Foundation is dedicated to ensuring that people with CF have the opportunity to lead long, fulfilling lives, with the ultimate goal of curing CF. Through our extensive involvement with the development of CF therapeutics, including modulators, the Cystic Fibrosis Foundation is profoundly aware of the urgent need to develop and enable access to therapeutics that are safe and efficacious for children while ensuring the safety of an extremely vulnerable population. With this in mind, we offer the following considerations for the FDA as it determines how to balance inclusion and protection of children in clinical investigations for medical products.

Specific Considerations for Clinical Investigations of Gene Therapy Products Involving Children

While there is a significant sense of urgency among patients and caregivers for pediatric access to gene therapy products, there remains uncertainty for sponsors regarding clinical investigations for gene therapy products involving children. This document represents a step forward in providing guidance to industry, sponsors, and

IRBs as they design and execute clinical investigations involving children; however, despite the fact that gene therapies differ markedly from traditional small-molecule therapeutics, discussion of gene therapy products within this draft guidance is limited to 1) the prospect of direct benefit as it relates to dosages planned for pediatric clinical investigations, and 2) the infeasibility of multiple-dose pharmacokinetic (PK) studies involving gene therapies.

With this in mind, we urge the FDA to specifically address clinical investigations of gene therapy products involving children in a separate guidance. Additional considerations might include the establishment of appropriate evidentiary standards for determining prospect of direct benefit for gene therapy products when many forms of approved supporting data (including nonclinical alternatives) may be unavailable, imperfectly applicable, or piecemeal; types of data specific to gene therapies that could be used to support clinical investigations (i.e., data derived from use of the same viral vector in other gene therapy products); the unique ethical concerns of placebo groups for clinical investigations of gene therapy products; and increased weighing of clinical durability in the risk/benefit assessment for pediatric clinical investigations of gene therapy products, which are designed to be long-lasting or permanent and can't be halted or reversed once administered.

Parental/Guardian Permission and Child Assent

Obtaining informed consent—or assent, in the case of pediatric subjects—is a fundamental requirement for ethical clinical investigations. Though we appreciate the role of parents and guardians in making the best possible decisions for their children, it is important to acknowledge that parental/guardian permission and child assent are interrelated yet distinct components of the decision to enroll a child in a clinical investigation. This concept is relevant to several scenarios articulated within the draft in which a child's assent is "unnecessary" or when the lack of assent can be overridden ("assent may be waived"). We encourage the FDA to emphasize the responsibility of IRBs to give appropriate consideration to the opinions of children capable of assenting when making decisions about clinical trial participation. Given the very serious ethical implications of waiving a child's assent to participate in a clinical trial, we also recommend the FDA consult with additional experts in pediatric medicine and bioethics, such as the FDA Pediatric Advisory Committee and the Clinical Research Ethics Consultation Collaborative, when revising and refining this guidance.

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Once again, the Cystic Fibrosis Foundation deeply appreciates the FDA's dedication to ensuring that sponsors obtain vital data on the safety and efficacy of medical products for pediatric populations while still providing appropriate safeguards for children participating in clinical investigations. We view these considerations as critical to the FDA's efforts and look forward to working with the Agency as it continues to refine its thinking.

Sincerely,

Mary Dwight

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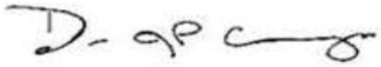

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