June 14th, 2022

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

Re: FDA-2021-D-0398, Human Gene Therapy Products Incorporating Human Genome Editing: Draft Guidance for Industry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of the Cystic Fibrosis Foundation, we write to provide comments in response to the Food and Drug Administration (FDA) draft guidance on *Human Gene Therapy Products Incorporating Human Genome Editing*. We commend the FDA's ongoing efforts to navigate this rapidly developing field and appreciate the opportunity to contribute to the agency's regulatory deliberations.

Background on Cystic Fibrosis and the CF 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. Highly effective modulator therapies can ameliorate these symptoms—however, they are ineffective for treating patients with rare CFTR mutations and, ultimately, fail to correct underlying defects in the CFTR gene.

Through its Path to a Cure Program, the Cystic Fibrosis Foundation is 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. We believe that genome editing holds great promise for curing CF and are heavily invested in bringing this technology to the clinic. We therefore offer suggestions for clarification and revision of this document, with the goal of ensuring that genome editing products are safe and well-characterized without causing undue delays in the development process.

Off-Target Editing: Assessment Methods and Specificity Expectations

Given the recent development and relative lack of characterization of human genome editing products, we appreciate the FDA's emphasis on safety and risk management, particularly as it relates to off-target editing. With that said, we are concerned that the recommendations in this document are insufficient. The FDA suggests that sponsors establish what is, in essence, an efficiency threshold (the "therapeutic modification threshold," or the degree of genome modification needed for the desired therapeutic effect) for use in determining the

efficacy of a genome editing product; however, there is no discussion of a corresponding "safety threshold" linked to editing specificity. Though the risk tolerance for a genome editing product may vary based on disease severity and the type, location, and potential biological consequences of identified off-target editing events, it would be valuable for the FDA to articulate a comparable metric or threshold.

The FDA must also work toward establishing firm industry standards and best practices for assessing off-target editing. We acknowledge that the proliferation and rapid evolution of protocols for assessing off-target editing may complicate this endeavor, and that the FDA may need to update guidelines more frequently as technology advances. However, it is critical for establishing comparability between clinical trials, ensuring patient safety, bolstering public confidence in genome editing products, and preventing sponsors from spending time and resources developing and utilizing inadequate techniques.

Genome Editing Products with Modular Components:

Genome editing technologies are highly modular. Components of *in vivo* genome editing products include the enzyme responsible for the genomic alteration, a DNA targeting element, and, in some cases, a donor DNA template. Though the enzyme responsible for the genomic alteration and the delivery method utilized for *in vivo* administration are frequently kept consistent, the DNA targeting elements and donor DNA templates incorporated into a genome editing product may be substituted and replaced with relative ease.

While genome editing products must be appropriately characterized, simplification of the development and review process for near-identical products with previously validated components may reduce redundancies and allow sponsors to bring therapies to patients in a more timely manner. We therefore request that the FDA provide further detail regarding how the modularity of genome editing technologies will be incorporated into the development and review process, and whether near-identical genome editing products with varying DNA targeting elements or donor DNA templates could be considered different versions of the same drug product.

Preclinical Study Requirements for Genome Editing Products

The draft guidance states that the animal models selected for *in vivo* studies should demonstrate a biological response to the investigational genome editing (or species-specific surrogate) product, and analysis of this biological activity may be performed in a species-specific context, given potential differences in genomic sequences. However, when the pathophysiology of a disease or condition differs extensively between animals and humans, it might not be sufficiently informative to utilize animal models to demonstrate a biological response or therapeutic benefit, even with the use of a surrogate genome editing product.

The FDA further recommends that *in vitro* and *in vivo* preclinical studies interrogate editing specificity and off-target editing activity, including the type, frequency, and location of all off-target editing events. Such findings from *in vivo* animal models, however, cannot always be extrapolated to human subjects due to genomic differences. With these concerns in mind, we request that the FDA elaborate upon its expectations for the use of animal models in preclinical studies for genome editing products. This includes additional guidance regarding when, and if, it would be appropriate to utilize *in vitro* human cell-based models vs. *in vivo* animal models for various safety and efficacy assessments.

Usage of Clinical Cell Sources During Preclinical Studies:

The guidance states that definitive preclinical studies for *ex vivo*-modified genome editing products should utilize the clinical cell source. However, the *ex vivo*-modified cells directly administered to patients may not be

expected to manifest the biological consequences of the genomic alterations made—for instance, when the cells of direct therapeutic relevance are the progeny of *ex vivo*-modified stem cells used as a clinical cell source. As such, it may be difficult to fully assess the downstream biological consequences of editing, including expression and function of the corrected gene, without analyzing the differentiated cell populations that arise from them. The FDA should clarify the extent of analysis required of sponsors in these cases.

Adverse Event Monitoring and Long-Term Follow-Up

The FDA recommends a long-term follow-up (LTFU) period of at least fifteen years for products incorporating human genome editing (as detailed in the Long-Term Follow-Up After Administration of Human Gene Therapy: Guidance for Industry). However, though administration of a human genome editing product would ideally be a successful and singular occurrence for patients, it is important to acknowledge that these treatments might be deemed clinically ineffective. It is conceivable that patients who were treated with an ineffective genome editing product would want to enroll in a clinical trial for (or otherwise receive) another genome editing product during the LTFU period. While we acknowledge that this could confound safety and adverse event monitoring, there are significant ethical considerations for denying patients the opportunity to participate in subsequent clinical trials offering a potential curative treatment or addressing symptomatic aspects of the disease. The FDA must develop and articulate guidelines to address the possibility that LTFU study requirements will constrict patient opportunities and trial participation in rare disease populations, which could inhibit the development of future therapeutics.

****

Once again, the Cystic Fibrosis Foundation commends the FDA's commitment to providing guidance on the topic of human genome editing and appreciates the opportunity to offer feedback on this document. We will continue to monitor and engage in this evolving field, in conjunction with our industry and academic partners, and look forward to working with the agency on this endeavor in the future.

Sincerely,

Mary Dwight

Senior Vice President
Chief Policy and Advocacy Officer

Anthony Durmowicz

Vice President
Clinical Development