October 10, 2018

Scott Gottlieb, M.D.
Commissioner Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA-2018-D-2258, Human Gene Therapy for Rare Diseases; Draft Guidance for Industry

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

Dear Commissioner Gottlieb:

On behalf of the Cystic Fibrosis Foundation, we write to provide comments on FDA's draft guidance titled *Human Gene Therapy for Rare Diseases; Draft Guidance for Industry*. We appreciate the opportunity to share our thoughts on this document and commend the agency for taking steps to address the significant challenges associated with the development of gene therapy products for rare diseases.

Cystic fibrosis is a rare genetic disease that affects over 30,000 people in the United States. Although many people with CF now live into adulthood, approximately 47% of those with CF are still under the age of 18. As the Agency moves forward with finalizing this and other relevant guidance documents, it is important to reflect upon the unique needs of both adult and pediatric populations as well as special ethical considerations with regards to treating children with long-acting gene therapy products.

The Cystic Fibrosis Foundation is a national organization actively engaged in the research and development of new therapies for cystic fibrosis (CF), including new treatments to address the underlying genetic defect that causes the disease. The CF Foundation has been engaged in virtually every element of the research and development process, from preclinical discovery to identification of new therapeutics to conducting clinical trials as well as post-market surveillance and quality improvement studies.

While we have been fortunate as a community to have made great progress in the development of effective therapies for many people with CF, we are not yet done. The CF Foundation is dedicated to finding a cure that will benefit all individuals affected by CF. To this end, the Foundation is funding research into gene therapies, including editing and delivery technologies.

This comment letter is mainly directed towards the FDA's draft guidance titled *Human Gene Therapy for Rare Diseases*. However, our comments included in this letter broadly reflect our reading of the set of six gene therapy draft guidance documents released concurrently by the FDA in July 2018. We hope you will consider our remarks as you finalize each of the six guidance documents on gene therapy.

Flexibility in Trial Design and Endpoint Selection for Rare Disease Populations

We commend the FDA for recognizing the need for flexibility in trial designs and endpoint selection, particularly for rare diseases. Trial design and endpoint selection cannot be a one-size-fits-all approach for rare disease populations, or even within disease subpopulations. We appreciate the FDA's inclusion of considerations for the role genetic mutations may play in safety and efficacy as well. It may be important in some cases for FDA to distinguish between disease-specific studies and studies of mutation-specific disease subpopulations given that treatment approaches for subpopulations of genetic disorders can vary just as drastically as between different disease populations.

There is still a considerable amount of groundwork that must be done to determine effective pre-clinical and clinical trial approaches for gene therapy products addressing the underlying cause of CF. We do not yet know what endpoints or trial designs will be best suited to assess such products. FDA has previously shown flexibility for studies of drugs and biologics intended to treat rare disease populations, and the same approach is warranted for gene therapy products.

Considerations for Long Term Safety Measures

We request that the FDA address the need for more clarification on the level of uncertainty that it will accept with regard to long-term safety of gene therapy products. We are pleased to see that FDA will recommend long-term follow up of up to 15 years in some cases and believe that further guidance about long-term safety concerns with respect to both adult and pediatric populations would aid the development of gene therapy products.

Establishing Controls for Long Term Follow-Up

It is important to recognize the value of establishing peer comparators for the purposes of long term follow-up. We anticipate that linking the occurrence of long-term adverse events to gene therapy products and establishing frequency could be challenging. This process will be further complicated by the fact that we do not yet know what adverse events to anticipate in response to gene therapy products. Additional research is needed to understand what impacts these interventions may have in humans throughout a person's lifespan.

As the FDA notes, available natural history information for a given disease may not be sufficient to establish a historical comparator for the purpose of clinical trials. Within the CF community, advances in available treatments and standards of care have made some natural history data sets established through past control populations obsolete. In cases where natural history knowledge cannot inform the evaluation of patients who have been given gene therapy products, establishing controls for long term follow-up can aid in assessments of adverse events both prior to and following market entry of a gene therapy product.

Considerations for Gene Therapy Products and Potential for Adverse Immune Responses

We appreciate the FDA's inclusion of considerations on potential immune response to gene therapy products and vectors throughout the series of guidance documents. However, we wanted to raise additional concerns over potential immune responses related to the bioactivity of gene therapy products.

For individuals with CF who have nonsense mutations and therefore have never produced the CFTR protein at all, we do not know if the novel production of that protein in the body will elicit an immune response. A similar concern likely extends beyond the CF community to other genetic disease populations. There may need to be special considerations for gene therapy interventions that result in the production of particular proteins where none were present before.

The FDA should seriously consider what safety measures will be needed to protect such patient populations during clinical trials and beyond. We ask that the FDA identify potential steps to address dangers posed by latent immunogenicity to bioactivity resulting from gene therapy products, such as requiring preclinical testing to define the risk and frequency of such reactions in a given population and mandating drug sponsors to develop companion diagnostics to evaluate the potential for immune response to product bioactivity prior to treatment administration.

Considerations on Benefits and Risks of Gene Therapy Products for Patients with Available Therapies

We commend the FDA for presenting a drug development path for patient populations with existing prophylactic treatments in the Agency's *Human Gene Therapy for Hemophilia; Draft Guidance for Industry.* Trial designs that allow patients to stay on some or all of their current therapies while participating in investigational gene therapy product assessments will be critical for CF patients, many of whom will be on effective therapies by that point.

For rare disease populations with access to effective non-gene therapies, there has to be a path forward to test and show the benefit of a gene therapy product in comparison with existing alternative therapies. While we would like to see advancements in treatment options for patients both with and without available therapies, we believe it is important to proceed with caution in moving patients from effective conventional treatments to gene therapy products given unknowns in long-term safety and efficacy. We ask that the FDA provide some further considerations on risk-benefit assessments for testing gene therapy products in such populations as the Agency finalizes these guidance documents.

The CF Foundation has extensive experience with regard to this issue. There are more than 1,700 genetic mutations that result in cystic fibrosis. Effective treatments, called CFTR modulators, are available for patients with certain mutations. Although not a cure, these disease modifying treatments greatly improve the health of many patients who have eligible gene mutations.

Subpopulations in CF affected by mutations that are more challenging to address, such as those with nonsense mutations, will have very different therapeutic development needs compared with subpopulations that have effective modulators already available to address the underlying genetic mutation. While this may not be applicable to all rare disease populations, it is important to note that disease subpopulations may have important differences from one another that warrant consideration

during the trial design process. We ask the FDA to keep these needs in mind throughout the drug development process.

Special Considerations for Pediatric Populations

The CF Foundation commends the FDA for acknowledging that more nonclinical studies may be required to address concerns over developmental toxicity for gene therapy products. The FDA also cites special ethical considerations for pediatric populations with regard to administration of investigational drug products. We note that the concern over the long-term safety of any drug intervention is heightened in these populations. We believe special attention is further warranted with regards to gene therapy products.

While early intervention for pediatric patients can result in marked improvements in an individual's health outlook, effective early life interventions may result in serious adverse events during critical developmental years and beyond. It is crucial that therapeutic benefits of a gene therapy product are weighed appropriately against potential long-term adverse effects. Given the uncertainty of early interventions with gene therapy products, caution should prevail in risk-benefit assessments of pediatric products. We ask the FDA to consider how the long-acting nature of gene therapy products may impact standard risk-benefit assessments used by the Agency for pediatric populations throughout the drug development process.

We would like to raise further ethical concerns with regard to the use of gene therapy products in pediatric populations who have access to effective therapies. The FDA should thoroughly consider the value of early life interventions using gene therapy products for such populations given the potential for serious delayed adverse events and the uncertainty of long-term benefits over existing treatments.

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Once again, we commend the FDA for its request for comments on this series of draft guidance documents. The CF community is still at a relatively early stage with regard to the development of gene therapy products, but we hope that our comments will contribute positively to further conversation at the Agency on safeguards for the use of gene therapy products in humans. We are watching this field closely and look forward to working alongside the FDA in the future on this endeavor.

Sincerely,

Mary Dwight

Senior Vice President of Policy and Advocacy
Cystic Fibrosis Foundation