February 16, 2018

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

Re: FDA-2017-D-6617, Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease- Guidance for Industry

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

Dear Commissioner Gottlieb:

On behalf of the Cystic Fibrosis Foundation, we write to provide comment on FDA’s draft guidance, Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease, and offer our support for the approach outlined in the document. 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 that address the gene defect that causes the disease, and the guidance provided in this document is very relevant for our work and cystic fibrosis drug development overall. 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.

Cystic fibrosis is a rare genetic disease that affects about 30,000 people in the United States and 70,000 worldwide. Scientists have found more than 1,700 different CF-causing mutations, many of which are extremely rare and may only be found in a handful of people with CF across the globe. In fact, nearly one-third of U.S. CF patients have one mutation which less than 50 living CF adults in the U.S. carry, and there are over 1000 CFTR mutations that less than 5 patients have. Such genetic segmentation of the CF population creates challenges to developing new therapies because in many instances it may be prohibitively difficult or outright impossible to recruit enough patients with a specific mutation to run a traditional clinical trial.

We commend the agency for taking steps to address the significant challenges associated with the development of drugs for rare genetic diseases, especially those with low-frequency molecular subsets. The FDA has been a great partner is developing ways to evaluate the safety and efficacy of treatments in
these situations, and we appreciate FDA’s attention on this matter and the opportunity to comment on specific aspects of this draft guidance.

**Grouping Strategies for Inclusion of Patients With Low-Frequency Molecular Alterations in Clinical Trials**

We appreciate the agency’s openness to exploring strategies for grouping patients with low-frequency molecular alterations for inclusion in clinical trials. Overall we agree with the FDA’s guidance on this issue and commend the agency for including its views on the types of evidence to support a grouping strategy in order of strength. We expect this information will be helpful for industry and others to understand what data the FDA prefers in developing grouping strategies for inclusion of patients with especially rare mutations in clinical trials.

**Generalizability of Findings Across Molecular Subsets**

We are pleased that FDA has provided information on generalizing study findings to molecular subsets that may not have been represented in clinical trials and agree with the FDA’s views on this issue. We are aligned with FDA in its assessment that the results of a trial should apply to a population as defined rather than being limited to the population that was studied. As mentioned above, some CF-causing mutations are so rare that it might not be possible to examine a specific molecular alteration in a clinical trial. However, if there is a strong understanding of the molecular function of certain rare mutations, and we may reasonably predict how they will respond to new therapies, then the findings of a trial should be extrapolated accordingly. We feel the FDA’s guidance on this issue is reasonable and beneficial for making drugs available to the greatest number of CF patients.

**Refining the Target Population/Indication After Initial Approval**

The FDA has provided helpful guidance as we work to find ways of extrapolating information around the safety and efficacy of treatments in situations where not all relevant molecular subsets may be represented in a clinical trial or when running a traditional clinical trial is not feasible. Recently the agency developed a novel approach to approve an expansion of the indication for the drug Kalydeco (ivacaftor) to patients with rare mutations that are more difficult to study. In addition to existing clinical study and CF patient registry data, this approach used in-vitro data to assess the potential for efficacy, and we congratulate the FDA on this innovative and thoughtful approach.

We agree that in instances where it is prohibitively difficult or not possible to illicit sufficient efficacy data specific to individuals with especially rare mutations, it may be appropriate to require additional data collection and analysis in the postmarket setting. As FDA is aware, CFF is equipped to conduct these studies using our therapeutics development network sites and robust registry of CF patients. We further agree that the FDA should have the power to narrow the target population or indication for a drug after initial approval if additional data identifies safety concerns that were previously undetected or inconclusive.

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Once again, we commend the FDA for its request for comments on this draft guidance. We see important opportunities for collaboration and discussion regarding the development of targeted therapies for rare genetic diseases, and we look forward to working alongside the FDA in the future in this endeavor.

Sincerely,

Mary Dwight
SVP for Policy and Advocacy