February 5, 2018

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

Re: FDA-2017-N-6476, Pediatric Rare Diseases- A Collaborative Approach for Drug Development Using Gaucher Disease as a Model

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Dear Commissioner Gottlieb:

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. 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.

We appreciate the opportunity to comment on this draft guidance and commend the agency for taking steps to address the significant challenges associated with the development of drugs for rare diseases, especially those prevalent in pediatric age groups. We see great potential for the use of master protocols and innovative trial designs to help mitigate enrollment burden, eliminate unnecessary duplication of research infrastructure, and to efficiently test multiple therapies.

Though Gaucher disease and cystic fibrosis are symptomatically dissimilar, this guidance, directed towards pediatric rare disease, outlines a number of useful parallels as we consider how to further develop and expand the use of innovative trial designs for CF treatments and therapies. We also see potential for future application of these guidelines to adult rare disease populations.

Previously CF has been considered primarily a pediatric rare disease, but with improvements in treatment and clinical care, this is no longer the case. Many people with CF are living into their 30’s, 40’s and beyond, and more than 50% of the current CF population is over the age of 18. As such, we are considering how to apply master protocols and innovative trial designs to both pediatric and adult CF populations.
We will address below some of the specific areas where our views are aligned and where we feel deeper consideration is critical to facilitate a successful, collaborative approach to drug development.

**Disease Characteristics and Response to Treatment**

Cystic fibrosis is a rare genetic disease that affects about 30,000 people in the United States and 70,000 worldwide. Similar to Gaucher disease, the underlying biology of cystic fibrosis is the same in adults and children, but clinical manifestations may differ between the two groups. Children with cystic fibrosis tend to have less severe symptoms, which become more severe with age as a result of the progressive nature of the disease. However, as similarly noted with Gaucher disease, there are a number of disease-modifying factors such as genetic mutations and epigenetic factors that may further influence disease presentation and rates of clinical progression in CF.

There are currently 12 commercially approved therapies available to treat cystic fibrosis, including two disease modifying therapies that target the underlying cause of the disease for those with certain genetic mutations. Roughly 50% of the CF population may benefit from one of these currently approved treatments, and we expect to see this number increase as additional treatments are developed. However, targeting especially rare mutations is particularly difficult. 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. Such genetic segmentation of the CF population creates additional 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. The FDA has been a great partner in developing ways to evaluate the safety and efficacy of treatments in situations where 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.

Further, developing additional similar disease modifying therapies for CF patients presents similar challenges of sample size. As the number of patients who benefit from modulator therapies increases, there is a dwindling number of treatment-naïve patients who are able to serve in a placebo group. We note similarities here to developing additional therapies for Gaucher disease.

We see great value and potential in master protocols as a way to help facilitate the development of modulators to treat new mutations as well as next-generation modulator therapies. For modulators as well as other high priority therapeutic areas such as anti-inflammatories, harmonized studies would reduce the number of individuals needed in the study by allowing the use of a shared placebo group for multiple drug candidates.
**Endpoint Assessments**

We agree that developing age-specific endpoints may be necessary for drug development in rare pediatric diseases like Gaucher disease and CF. Previous approval of lung treatments for CF in adult patients has largely been based on measurements of FEV1 as a primary endpoint. However, because CF is a progressive disease, children with CF tend to have higher FEV1 measurements than adults with the disease, and it is difficult to demonstrate improvement in FEV1 in pediatric populations.

Further, though the CF Foundation hopes to use new biomarkers to measure efficacy in patients with cystic fibrosis more effectively, current options are insufficient. The CF Foundation is working to develop new, more effective biomarkers to examine efficacy in both children and adults with CF.

The draft guidance notes that quality of Clinical Outcome Assessment (COA) tools can vary and recommends standardizing COAs and working with FDA and relevant stakeholders to standardize their development. The CF Foundation is very interested in exploring clinical outcome assessments (COAs) and their viability for measuring efficacy in cystic fibrosis trials. To this end, CF researchers have developed the Cystic Fibrosis Respiratory Symptom Diary – Chronic Respiratory Infection Symptom Score (CFRSD-CRISS), an 8-item patient-reported outcome (PRO) designed to evaluate the effect of treatment on the severity of respiratory infection symptoms in adults and adolescents with cystic fibrosis. The CFRSD-CRISS is a self-administered diary that respondents are asked to complete nightly in one sitting. In April 2014, the CFRSD-CRISS was submitted to the FDA for qualification, but the process has not yet been completed. We look forward to continuing our work with the agency on this issue and providing any additional information that may be helpful.

We also anticipate several challenges arising with the use of endpoints in harmonized trials. First, we expect significant barriers to having multiple sponsors come to consensus on a single protocol. Though not impossible to overcome, asking sponsors to compromise on study design and endpoints is a relatively new frontier in drug development and a stark contrast to current levels of engagement that sponsors typically have with one another. It’s important to consider that this will be a heavy burden at the outset. Second, we also anticipate a desire to change aspects of the study design and protocol over the course of running a successful, continuous master protocol. We feel that this issue could be mitigated through a representative steering committee and using a traditional protocol amendment, but it is important to determine the process for doing so prior to starting the master protocol. It will be imperative for groups successfully conducting master protocols to share operational aspects of their studies to facilitate contractual agreements, funding models, and regulatory strategies for future programs.

**Long-Term Clinical Aspects**

Facilitating coordinated, specialized care and treatment through our accredited CF care center network is a critical component of the CF Foundation’s work. The CF care center network consists of more than 120 centers with dedicated health care professionals who partner with people living with CF and their families to provide expert cystic fibrosis care and specialized disease management. Many of these care center sites are also part of our CF Foundation Therapeutics Development Network, enrolling and
managing clinical trials and CF studies. Similar to the Gaucher population, most individuals with CF receive care and treatment through a specialized care center, allowing for routine follow-up of patients to evaluate long-term safety and long-term maintenance dosing. We agree that long-term, post-market evaluations should be encouraged through these care and research centers, especially for pediatric trials.

Further, we agree that robust patient registries should work as an adjunctive tool for efficient monitoring of efficacy and safety. The Cystic Fibrosis Foundation maintains a 28,000-patient registry, including genetic data, demographic information, and health status data. The CF Foundation makes data from the registry available for research, and it has been an invaluable tool in facilitating harmonized trials, supporting label expansion of certain drugs for those with rare mutations, supporting industry post-marketing commitments/requirements, and examining trends in CF care over time. As mentioned above, we shared data with the FDA to support the expanded approved use of Kalydeco to treat additional, rare mutations of CF. In addition to several other supporting data sources and in vitro studies, this information allowed FDA to develop a novel approach to expand the indication for this critical treatment to more than 900 additional people with CF.

**The Use of Extrapolation of Efficacy for Pediatric Gaucher Disease**

We also commend the FDA for addressing extrapolation of efficacy in this draft guidance. We see many parallels to the cystic fibrosis population here and agree that the use of extrapolation of efficacy in pediatric populations, as FDA is currently doing in cystic fibrosis programs, can help avoid unnecessary studies, increase efficiency, reduce testing burden to patients, and better allocate resources to address relevant questions. In the future, we hope that additional biomarkers can be developed to further streamline the drug development and approval process with the use of longer-term clinical data acquired post-marketing (lacking significant safety concerns pre-marketing) used to support safety. Overall we appreciate FDA’s handling of extrapolation of adult outcomes to pediatric populations and are largely aligned in our views. We are aware that some regulatory bodies outside of the United States, including the European Medicines Agency, have moved toward requiring confirmation of efficacy in pediatric trials. We commend the FDA’s current approach. It is critical that pediatric populations have access to effective treatments, but as you know the additional challenges inherent in pediatric clinical trials make efficacy especially difficult to measure in younger cohorts. As addressed above, the progressive nature of CF creates significant barriers to proving efficacy in pediatric CF populations, and we have not yet developed biomarkers sensitive enough to meet efficacy standards for this population. We agree that additional clinical studies should be used to determine efficacy across all age groups, but we feel that these studies are usually most appropriate in post-market surveillance settings.

**Proposed Multi-Arm, Multi-Company Trial for Pediatric Gaucher Disease**

We appreciate the proposal provided in this guidance for a multi-arm, multi-company trial and agree this is an exciting area to explore with great potential for saving valuable time and resources in drug development. We note that the example provided in this guidance for Gaucher disease maintains a traditional study design and commend the agency for starting with a straightforward approach. We look
forward to working with the agency on strategies to mitigate existing barriers and see potential for incorporating master protocols in more complex study designs in the future.

The CF Foundation is also considering how to develop master protocols to make CF clinical trials more time efficient and less costly. Though our work has largely focused on adult CF trials, we see a great number of parallels to the pediatric Gaucher trial in this proposal.

The CF Foundation is currently using a harmonized protocol to conduct a prospective, observational, population-based cohort study in US cystic fibrosis patients to assess the incidence of and risk factors for fibrosing colonopathy. The study examines six pancreatic enzyme replacement therapies, and the protocol reflects equal sponsorship by the registering sponsor as well as several collaborators, all of whom have agreed to common inclusion criteria and outcomes measures. Data routinely collected via the standard CF registry will be used to determine exposure to any specific pancreatic enzyme replacement therapy and to assess potential risk factors for the outcome of confirmed fibrosing colonopathy. An independent adjudication panel will be utilized to validate the diagnosis of fibrosing colonopathy based on a prospective case definition as well as decision rules. Though the CF Foundation has already experienced some proof of concept for master protocols through this study, we have also identified unresolved barriers and lessons learned that we believe are critical to consider before harmonized trials can be scaled up and used more widely.

As we mentioned above, one challenge that remains before the master protocols are ready for mainstream implementation is how to incentivize and foster collaboration among industry competitors. To mitigate some of this conflict, it is critical for master protocols to be developed and managed by a neutral, third-party broker. Though efficient for the drug development process overall, master protocols mandate a shift for industry partners because they are required to collaborate and compromise on study design. This was a notable hurdle in our harmonized trial to examine fibrosing colonopathy. Though the study itself is relatively simple, it took significant time and effort to bring industry partners to consensus. We expect harmonized protocols in the pre-approval space will appeal more to smaller sponsor groups who benefit greatly from the cost and efficiency savings, and we expect they would not be as attractive for larger, more established sponsors.

Further, companies must be assured that protocols will be set up only to compare each drug to the shared control and that products under development will not be compared to each other. We expect it would be nearly impossible to facilitate a harmonized, collaborative approach if manufacturers have concerns that the protocol is biased or puts their development process at increased risk. That being said, we feel strongly that drugs should be studied further after approval to better understand which therapies are most effective in real world settings. The CF Foundation is a leader in examining comparative effectiveness in CF drugs, and we believe that master protocols may also be an effective tool for comparison studies and other post-market data collection.

We also believe that the development of open-concept platform designs that allow companies to enter a protocol at different times will be critical to the successful implementation of harmonized trials. For
rare disease clinical trials especially, it is unlikely that several companies would be prepared to start
trials at the same time. Though they create additional logistics concerns, open-concept designs are most
appropriate for the current drug development landscape. Successful implementation would create more
flexibility and incentivize adoption of master protocols.

Looking forward, we are excited at the potential for master protocols to bring much needed efficiency
and collaboration to drug development. Several areas of CF research are ripe for such innovative trial
designs including anti-inflammatories, antibiotics, and the next-generation of CFTR modulators, all of
which present challenges in enrollment and trial length that could be mitigated through harmonized
protocols.

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Once again, we commend the FDA for its request for comments on this draft guidance. There are
important opportunities for collaboration and discussion regarding master protocols, and we look
forward to working alongside the FDA in the future in this endeavor.

Sincerely,

Preston W. Campbell, III, MD
President and Chief Executive Officer