March 9, 2020

Stephen Hahn, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA-2019-D-4964, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Draft Guidance for Industry

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

Dear Commissioner Hahn:

On behalf of the Cystic Fibrosis Foundation, I write to provide comments on the draft guidance entitled Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Draft Guidance for Industry. We appreciate that the FDA has signaled the importance of clinical trials that work for rare disease communities in this fundamental document.

Background on Cystic Fibrosis and the CF Foundation
The Cystic Fibrosis Foundation is a national organization actively engaged in the research and development of new therapies for cystic fibrosis (CF) – a rare genetic disease that affects over 30,000 people in the United States. 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.

The CF Foundation has significant experience with the process of rare disease drug research and development. When the Foundation was formed in 1955, no CF-specific drugs existed. However, by raising and directing funds needed to fuel CF drug development programs, the Foundation has encouraged pharmaceutical companies to invest in rare disease research. Additionally, with the Foundation’s CF Therapeutics Development Network (TDN) – the largest CF clinical trials network in the world – we have been able to advance clinical drug development through the design and implementation of clinical trials that are both feasible and informative for the CF community.

This is a transformative moment for the CF community. With the recent FDA approval of a drug called Trikafta®, we anticipate that approximately 90 percent of the CF community will eventually benefit from available disease-modifying modulator therapies. This new therapy represents the achievement of a milestone inconceivable even just a decade ago, and we are now preparing for the impacts that the potential introduction of this new treatment will have on the research landscape for current and future...
CF therapies. However, we recognize that not all people with CF will benefit from this new therapy or other disease-modifying treatments already on the market, and many people will still struggle with serious complications related to advanced disease. From our perspective, the most important and challenging work in CF is still ahead.

**Special Considerations for Rare Disease Populations**

We applaud the FDA for acknowledging the need for flexibility in trial designs and endpoint selection for rare diseases in this key guidance. FDA’s ongoing efforts to provide updated advice to sponsors on the unique challenges inherent in rare disease drug development is a crucial signal of the importance of getting treatments to patients with serious conditions and major unmet needs. This guidance takes important steps to directly address the distinct characteristics and needs of rare disease populations and how such factors may impact the design of clinical trials for generating evidence of efficacy.

Rare disease communities often face unique challenges such as small patient populations, poor disease characterization, and a wide range of disease presentation that make it more difficult to carry out traditional clinical trials. FDA innovations in regulatory science, modernization of clinical trial designs, and increasing emphasis on the importance of patient input have all been critical in addressing the many challenges rare disease drug development programs face.

The Agency’s flexibility with regard to how these innovations can be applied has played a vital role in advancing new therapies for rare diseases like CF. Today, there are 14 therapeutic products available in the United States to treat people with CF, four of which treat the underlying cause of the disease. The revisions in this guidance reflect important regulatory flexibilities the FDA has at hand to support the development of safe and effective therapies for rare disease populations, and we have seen the therapeutic pipeline continue to grow for CF as well as for a number of other rare diseases as a result.

The FDA’s regulatory flexibility will become even more essential for CF therapeutic development in the future. We expect that CF clinical trials will be impacted by a changing CF patient population, as those without effective modulators or with established disease will likely have different treatment needs and priorities compared with those who are healthier thanks to early intervention with modulator therapies. These subpopulations will likely have important differences from one another that warrant consideration during the clinical trial design and enrollment process. In particular, more traditional clinical trial designs may not work for reaching the shrinking CF population with the highest unmet treatment need. Traditional designs for the evaluation of new therapies may also be more difficult and in some cases unethical even in the population with access to disease modifying therapies, in particular if these designs require periods of withdraw from standard of care therapies to incorporate a placebo-control arm.

We also appreciate the FDA’s recognition of special considerations for pediatric patient populations in this guidance. For many rare disease communities like CF, it is especially important that regulatory agencies support drug development efforts for pediatric patients. Although many people with CF now live into adulthood, approximately 45% of those with CF are still under the age of 18. We know early intervention for pediatric patients can result in marked improvements in an individual’s health outlook. In CF therapeutic development, we’ve seen several products with trials starting in CF patients who are
age 12 years and up with additional trials sequentially including younger and younger patients. We appreciate that we have seen a successful approach that accelerates access to important therapeutic advances for pediatric CF patients. We hope the FDA will continue to encourage drug development approaches that ensure therapeutic advances reach pediatric patients with orphan diseases that are not subject to the Pediatric Research Equity Act (P.L. 108-155) in a timely manner.

**********

Once again, we thank the FDA for its request for comments on revisions to this core guidance document. The FDA’s application of regulatory flexibility has been critical for advancing much needed treatments for rare disease communities. This has also helped to codify the Agency’s existing practices and expectations for evidence of effectiveness, which is an important step for continuing the progress we have seen to date for communities like ours. We look forward to working alongside the FDA in the future on this endeavor.

Sincerely,

Mary Dwight
Chief Policy and Advocacy Officer
Cystic Fibrosis Foundation