CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

October 15, 2015

Stephen Ostroff, M.D.
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA-2015-D-2818, Rare Diseases: Common Issues in Drug Development; Draft Guidance for Industry

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

Dear Commissioner Ostroff:

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 defect that causes the disease. The CF Foundation has been engaged in virtually every element of the research and development process, from investment to identification of new therapeutics to conducting clinical trials.

The CF Foundation appreciates the opportunity to comment on the Draft Guidance, Rare Diseases: Common Issues in Drug Development. We commend the agency for completing and publishing this draft guidance, which acknowledges that there are significant challenges associated with the development of drugs for rare diseases. There is a benefit for those who are engaged in rare disease R&D simply from the publication of the draft guidance document. However, we see the document as only a first step in providing basic guidance to rare disease research and development teams, and we look forward to additional guidance from the Food and Drug Administration (FDA) on this important topic.

There are two issues that we hope will be addressed in greater detail in a revision of this guidance document or in a follow-up guidance. First, we recommend that the guidance document recognize the diversity of rare diseases in terms of researchers' knowledge of the diseases' natural history, understanding of disease pathophysiology, and development of reliable endpoints, including surrogate endpoints. A document that reflects the diversity and complexity of rare diseases might offer more

National Office
6931 Arlington Road Bethesda, Maryland 20814
(301) 951-4422 (800) FIGHT CF Fax: (301) 951-6378 Internet: www.cff.org E-mail: info@cff.org

useful advice to drug developers. Second, we recommend that the section of the guidance document regarding "Evidence of Effectiveness and Safety" address the challenges of designing and conducting drug trials with greater specificity for rare diseases as opposed to more general drug development guidance.

Although we understand that the natural history of certain rare diseases is poorly understood, that is not the situation for all rare diseases. In the case of a number of diseases, there is a deep understanding of the "full range of disease manifestations and identification of important disease subtypes." The draft guidance notes the interest among researchers in the use of natural history data as a historical control and then identifies the challenges associated with historical comparators. We understand these obstacles, but we urge FDA to consider additional discussion related to this issue in a revised guidance so those rare diseases with well-defined natural history might consider the potential for using historical controls.

In the section of the draft guidance that addresses "Evidence of Effectiveness and Safety" the agency includes a solid discussion of the basics of clinical trial design. This portion of the guidance document also identifies the issues related to clinical trial design and conduct that may be especially difficult for rare disease R&D teams. For example, the guidance document states:

> There is no specific minimum number of patients that should be studied to establish effectiveness and safety of a treatment for any rare disease. The number of patients to establish effectiveness and safety is determined on a case-by-case basis, taking into consideration the persuasiveness of the data (e.g., comprehensiveness and quality), the nature of the benefit provided (or expected in the case of surrogate endpoints), the length of treatment or exposure, the patient population that would be treated after marketing approval, and the concern for potential harm from the treatment.

However, the draft guidance does not in fact offer rare disease drug sponsors any advice about how to address the difficulties of rare disease drug development. We read the guidance document as advice to rare disease drug sponsors to initiate conversations with FDA early in the development process to address issues of trial design and completion. Although we appreciate the willingness of the agency to engage in discussions with sponsors early in the development process, we encourage a revision of the guidance document so that sponsors can proactively initiate those meetings with development plans that are informed by the thinking and advice of the agency.

In the case of CF, for example, there are difficult questions about the design of trials to test therapies in especially rare CF mutations as well as issues related to appropriate endpoints. Trial design issues and patient accrual issues will also arise as the second or third therapy for a specific mutation is in development. In these instances it will be imperative that guidance include recommendations which appropriately balance study design recommendations with feasibility, particularly with respect to equipoise for the use of placebo and the cost associated

with active comparator studies. We trust that consultation with FDA will address these issues early in the development process, but more specific clinical trial design information in the guidance document would benefit sponsors in advance of those discussions. We encourage the agency to make revisions of this sort in the guidance document. We look forward to ongoing discussions with FDA regarding rare disease drug development. In addition, we look forward to learning in more detail the thinking of the agency about rare disease drug development through a revision of the draft guidance.

Sincerely,

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