On behalf of the Cystic Fibrosis Foundation and the approximately 30,000 people living with cystic fibrosis (CF) in the United States, we are pleased to submit the following testimony to the Senate Appropriations Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies for Fiscal Year 2019. In order to encourage efficient review of drugs for cystic fibrosis and other rare diseases, we urge the committee to prioritize the Food and Drug Administration (FDA) by providing at least $3.3 billion for the agency in Fiscal Year (FY) 2019.

We appreciate that the President’s Budget for FY 2019 proposes an increase of $473 million in appropriated funding to support new innovation, activity, and efficiency at the agency. The FDA approved a record-high 46 new drugs in 2017, and more than 400 rare disease drugs and biologics have been approved in the last 30 years. The FDA must have the necessary resources to accommodate for the growing complexity of drug development and continue serving its critical mission of ensuring new treatments are safe and effective for patients.

Cystic Fibrosis Drug Development

Progress in CF Drug Development
Cystic fibrosis is a rare, progressive genetic disease that causes the body to produce thick mucus that clogs the lungs and other bodily systems, resulting in life-threatening infections and other complications. Most approved CF treatments target the symptoms of the disease such as therapies to help thin and clear mucus that builds up in the lungs; treat lung infections and inflammation; and aid with food digestion and nutrient absorption.

There are also three FDA-approved therapies now available to target the underlying cause of CF, Kalydeco® (ivacaftor), Orkambi® (ivacaftor/lumacaftor), and Symdeko™ (tezacaftor/ivacaftor). However, each of these therapies is only approved to treat a subset of the CF population whose disease is caused by specific genetic mutations. Overall the three targeted treatments that are available today could benefit more than 60 percent of people with CF based on genotype, and trials are underway to determine the effectiveness and safety of these drugs in children as young as six months old.

Though incredible progress has been made in CF drug development over the last several decades, there is still a long way to go before we have a cure for everyone living with cystic fibrosis. Over the last few years, the CF Foundation has significantly expanded its research investments with both large and small biotech firms and leading companies to accelerate the discovery and development of new CF treatments. In 2017, we supported a number of large, multi-center studies, including 45 ongoing trials and 23 new trials. This includes therapies
tailored to an individual’s specific CF-causing mutation as well as mutation agnostic therapies that treat the symptoms or underlying cause of CF regardless of an individual’s genetic makeup.

**Correcting the Underlying Cause of CF**

All three targeted therapies that are approved to treat cystic fibrosis restore the function of the defective cystic fibrosis transmembrane conductance regulator (CFTR) protein in the lungs and other organs and allow it to function more normally. Studies show these treatments are very effective for many patients and can slow disease progression and subsequent tissue damage. The FDA has been a critical partner in the development of targeted therapies, and additional funding for the agency is critical to ensure FDA can continue this great work.

Most recently, Symdeko was approved by the FDA in 2018 based on its demonstration of significant improvements in lung function and other key measures of the disease for those with two copies of the most common cystic fibrosis-causing mutation. Much like the other targeted therapies, Kalydeco and Orkambi, Symdeko’s approval is a testament to what can be achieved when well-staffed, collaborative review teams have the resources to ensure a swift review of new drugs for patients. We urge the Committee to provide increased resources for the agency to help ensure new, ground-breaking treatments for CF and other diseases can receive a robust and efficient review.

The FDA also plays an important role in helping to develop therapies for patients with especially rare mutations when traditional clinical trials may not be possible. There are over 1,700 known mutations of the CF gene, of which more than 1,000 affect 50 or fewer individuals in the US. The FDA has made great strides in this area, and we commend them for their willingness to collaborate with external partners on this issue and develop creative solutions while maintaining important safety and efficacy standards.

Recently, Kalydeco’s label was expanded to include people with CF ages two and older who have one of 23 rare, residual function mutations. The approval was made using a novel approach developed by the FDA based on a combination of in-vitro laboratory results, data from CFF’s patient registry, and the drug’s established safety record. Novel approaches such as this are an exciting advancement in drug development for unique cases where the patient population is not large enough to carry out a full clinical trial. We encourage the Committee to provide increased funding for the agency to continue and expand these efforts.

**Developing Treatments for CF Complications**

In addition to therapies targeting the underlying cause of the disease, the CF Foundation continues to develop new and better treatments for CF symptoms and complications such as infections, inflammation, excessive mucus, and GI issues. The goal of these treatments is to preserve lung function and maintain the health of those with CF so they will eventually be able to benefit from new therapies that treat the underlying cause of the disease as they become more widely available. In 2017 the CF Foundation spent $40 million on research in these areas to fund more than 200 different research projects. There are also more than 15 potential therapies currently in the drug development pipeline to treat complications of CF.
Due to the prevalence of antimicrobial resistance, the development of new anti-infective treatments is particularly critical for the CF community. Those with CF frequently experience chronic lung infections that can cause permanent damage and progressive loss of lung function. Many people with CF experience a steady decline in lung function throughout the course of their lives due to complications associated with the disease. In 2017 the CF Foundation dedicated roughly $17 million to research related to new anti-infective agents.

While the CF Foundation is committed to advancing anti-infective treatments, multi-drug resistant bacteria make treating infections more difficult. Because of this, the CF Foundation also supports the development of new therapeutic agents with novel approaches to fighting infection. It is our hope that the agency will prioritize the great public health need for new, effective antibiotics and will be able to collaborate with sponsors and researchers to support the development of these therapies. In that light we applaud the announcement of the upcoming June 2018 FDA workshop on the development of inhaled antibiotics for individuals with CF and non-CF bronchiectasis.

As CF drug development continues to advance at a rapid and exciting pace, the FDA needs adequate resources to support a sufficient number of reviewers and retain those with appropriate levels of experience and expertise to provide rigorous, data-driven review within the timelines laid out in the User Fee Agreements. FDA also needs sufficient funding to allow for early meetings with sponsors, issuing guidance that helps industry better understand FDA’s thinking on novel issues, and other activities that have proven critical in assisting industry and researchers in the early stages of drug development.

**Present and Anticipated Challenges in Drug Review Process at FDA**

A number of clinical trial design issues have been identified that may arise in the review of treatments for rare diseases and precision medicine therapies. As therapeutic targeting becomes more common and more advanced personalized treatments like Kalydeco and Symdeko move through the pipeline, FDA will need robust resources to support modern review processes and navigate unprecedented challenges in drug development and review.

In response to these complexities, CF researchers are exploring innovative ways to provide adequate data on safety and efficacy of targeted treatments for individuals with especially rare CF-causing mutations. In particular, scientists are looking at establishing a system of grouping both rare and common CF mutations that we could reasonably expect would react similarly to targeted therapies. It is our hope that substantiating these groups for use in clinical trials, we will be able to more adequately assess new, targeted treatments that we would otherwise not be able to examine in those with very rare CF mutations. As we work to ensure that every person with cystic fibrosis has access to treatment and ultimately a cure, the FDA needs adequate funding to develop new approaches to handling variations in trial design that maintain safety and efficacy standards while facilitating the timely development of treatments for patients with rare diseases.

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We look forward to continuing our work with the FDA to establish innovative solutions to these and other critical challenges in the years ahead. Once again, we urge the Committee to make
funding for the Food and Drug Administration a priority in Fiscal Year 2019 by providing at least $3.3 billion in funding for the agency through the appropriations process. The CF Foundation stands ready to work with the Committee, FDA, and Congressional leaders on the challenges ahead. Thank you for your consideration.

Sincerely,

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