March 2, 2015

The Honorable Fred Upton
Chairman
Energy and Commerce Committee
House of Representatives
Washington, DC 20515

The Honorable Frank Pallone
Ranking Member
Energy and Commerce Committee
House of Representatives
Washington, DC 20515

The Honorable Diana DeGette
Energy and Commerce Committee
House of Representatives
Washington, DC 20515

Dear Chairman Upton, Ranking Member Pallone, and Representative DeGette:

The Cystic Fibrosis Foundation applauds your efforts to focus attention on research and development of new treatments for those Americans who are suffering from diseases with inadequate treatment options. We appreciate your desire to ensure that the research, regulatory, and reimbursement systems are fully responsive to all Americans who need new medical treatments.

Representatives of the Cystic Fibrosis (CF) Foundation have participated in 21st Century Cures hearings and roundtable meetings in Washington, DC and around the country. We are pleased to have been included in the extensive fact-finding process undertaken by the committee and to have the opportunity to comment on the discussion draft recently released.

21st Century Regulatory Review

The Food and Drug Administration (FDA) must immediately be ready for regulatory review of the drugs of the 21st Century, including precision medicine drugs. As we make progress in classifying disease by

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genetic mutation, treatments will be targeted to those specific mutations. This discovery and development process will be complex and will raise regulatory challenges, as well. In order for FDA to be ready for this scientific and therapeutic development revolution, reviewers must be well-trained in the issues related to targeted, or precision medicine; they must be willing and able to reach across disciplines to obtain expertise related to a specific disease or therapy that they may lack; and they must be open to consultation with external experts who may possess that expertise.

The review of targeted therapies for small sub-populations of rare disease patients will raise many issues, including evaluation of "n of 1" trials, identification of appropriate endpoints for therapies that may provide significant benefit by preventing the progression of a chronic disease, and the evaluation of patient-reported outcomes for chronic disease patients.

The diseases themselves present complexities to regulatory review staffers. Each genetic mutation within a single disease may present specific disease traits, and reviewers will face obstacles to understanding and distinguishing the specific mutations and the appropriate targeting of drugs by mutation.

The ability of the agency to address the complexities of reviewing targeted therapies will rely significantly on the quality of the employees who are hired, trained, and retained by the agency. We also recommend strategies for consultation with outside experts to supplement and strengthen the expertise and skills of the agency staff.

We note that the current discussion draft does not yet include legislative language related to FDA hiring, travel, and training. In our opinion, successfully addressing the issues related to hiring and retention of quality FDA staff will determine the future of the agency and its ability to review precision medicines.

We recommend that the legislation address these issues in order to prepare an FDA workforce for the 21st century:

- Streamline the process for hiring FDA reviewers so that delays in hiring are eliminated and the leaders at FDA can promptly fill vacancies and hire reviewers with the skills and expertise necessary for complex product review.
- Address any obstacles – related to financial issues and conflicts of interest – that hinder the ability of review staffers to attend and participate in scientific and medical meetings.
- Provide resources for the training and mentoring of new reviewers, a process that may require additional agent FTEs so that experienced staffers can assume training responsibilities.
- Encourage flexibility in hiring, including placement of employees who will be employed part-time at FDA and part-time at the National Institutes of Health (NIH) so that FDA reviewers can continue research responsibilities or clinical care work that may inform their review work or provide them important background and knowledge related to new medicines.

The steps above are intended to provide flexibility to the agency to enhance its ability to hire and retain talented review staffers.

We also recommend a review of the regulatory science initiatives that have been undertaken by FDA and NIH to assess their effectiveness in the training and retention of reviewers. If those efforts have been useful, they should be continued and expanded. Such expansion may not require legislative action, but we recommend that this review be undertaken immediately and that the results inform the work of the committee.

Consultation with External Experts

During the debate on the Food and Drug Administration Safety and Innovation Act (FDASIA), the CF Foundation urged Congress to consider mechanisms for FDA review staffers to consult with experts outside the agency on topics related to the review of rare disease drugs. We have consistently maintained that the strength of the agency would be defined by its personnel, but we also thought that new drug review – including review of targeted therapies – would be strengthened if experts from outside the agency were consulted.

Section 903 of FDASIA -- Consultation with External Experts on Rare Diseases, Targeted Therapies, and Genetic Targeting of Treatments – requires the Secretary to maintain a list of external experts who might be consulted on review issues related to rare disease and genetically targeted treatments. These experts might be consulted if the Secretary "… lacks the specific scientific, medical, or technical expertise necessary for the performance of the Secretary's regulatory responsibilities and the necessary expertise can be provided by the external experts."

The "external expert consultation" provision of FDASIA also identifies specific issues on which external experts might advise the agency, including rare diseases, the severity of rare diseases, the unmet medical need associated with rare diseases, the willingness and ability of individuals with a rare disease to participate in clinical trials, an assessment of the benefits and risks of therapies to treat rare diseases, the general design of clinical trials for rare disease populations and subpopulations, and the demographics and the clinical description of patient populations.

External experts who would provide advice under Section 903 would do so as special government employees.

To our knowledge, the agency has not moved to develop and maintain the list of external experts and has not chosen to consult external experts on the subjects identified in FDASIA Section 903.

We believe that the need for external expert consultation of the sort we identified and articulated during the FDASIA debate still exists. As included by Congress in the user fee reauthorization, the agency controls the development and maintenance of a list of experts and also controls the decision to take advantage of external expert advice. We recommend that the committee reconsider the external expert consultation provision of the law and evaluate whether parties outside the agency should be permitted to request that the agency obtain external expert advice.

We recommend that product sponsors and patients be allowed to request that the agency consult with outside experts. The final decision to seek such advice would still be at the discretion of the agency, but other parties could make a recommendation that advice be obtained. In our experience, the topics related to rare diseases and rare disease therapies that are identified in the law are still topics on which FDA often needs additional information and advice. However, the agency does not typically seek that information and advice.

Patient-Focused Drug Development

We are pleased that the committee wishes to emphasize patient-focused drug development strategies. The discussion draft raises questions for us about how patient experience data will be used in regulatory review. The draft indicates that these data will inform the risk and benefit consideration, but it is not clear to us in concrete terms how that will be accomplished.

We recommend three ways in which patient input regarding disease burden, unmet medical need, management of a complex chronic condition, and quality of life considerations can inform the regulatory review process.

First, the patient-focused drug development meetings that were authorized by FDASIA should be refined and continued. Although there has been no meeting focused on cystic fibrosis and we realize the meetings are ongoing, we can offer some advice about the meetings. We believe that the meetings should be structured so that they address issues of disease burden, unmet medical need, and the burden of chronic care management. In the case of CF, we believe that conveying the ongoing daily therapy burden and the progressive nature of the disease will serve to educate drug developers and regulatory reviewers about ongoing therapy needs and how discovery and development efforts may address those therapeutic needs. We also advise that review staff be involved in these meetings, from planning through attendance and consideration of recommendations from the meetings. This is the optimal means for ensuring that the meetings have a connection to and inform the drug review process. We would also note that patient quality of life data, if collected and analyzed appropriately, might also be used in the regulatory review process. These data may be especially useful in assessment of therapies for progressive chronic diseases, including cystic fibrosis. We discuss this issue below.

Second, we recommend that the external expert consultation provision that we discuss above be utilized to obtain advice about drug development and review from patients and patient advocates.

Finally, we urge that patient-reported outcomes be considered during the drug review process. To make this a viable option, the agency must move to approve patient-reported outcome instruments. We urge that they do so without delay so that PRO data can be responsibly considered during drug review.

Real-World Evidence

We note with interest the inclusion of a provision in the discussion document that would permit sponsors to submit so called “real-world evidence” to support a new indication of an approved drug or to satisfy post-approval study requirements. The CF Foundation has for many decades supported a patient registry that collects important data about CF patients, their disease, and the treatments they receive. The data in this registry might be the type and quality that the discussion draft anticipates would be utilized in the regulatory review process.

We also note that the terms for utilizing real-world data will be established through a guidance developed by FDA. We urge that the legislation make clear that real world evidence shall be utilized in a review process that is data-driven and that the agency be encouraged to set standards for real-world evidence that will reassure patients that FDA-approved products are safe and effective.

Sharing, Accessing, and Using Health Data

The CF Foundation is enthusiastic about the potential for clinical trials, clinical care, claims, and other health care-related data to be utilized to improve drug discovery, development, and delivery. As discussed above, the Foundation has been a pioneer in the development and utilization of a CF patient registry.

As the committee looks at ways to improve the sharing and utilization of health data, we urge that your work be guided by a few simple principles: 1) patient privacy should be protected and patient and family trust in the use of their data should be maintained, 2) privacy protections should be commonsense approaches and should not be unreasonably bureaucratic, and 3) current systems and experiments in data collection and sharing should not be undermined by well-intentioned efforts to improve such sharing. We are aware of many entities – research foundations, academic health centers, medical professional societies, and pharmaceutical companies and consortia of companies – that are designing and executing "big data" projects. We urge that committee efforts to regularize and capitalize on these efforts not thwart their progress and creativity. We urge this caution on behalf of the Foundation and its patient registry efforts as well as others who are innovators in this area.

Single IRB Review

The CF Foundation supports a Therapeutic Development Network, or TDN, that links clinical research sites across the country and provides centralized data analysis services. The TDN has been a critical element in the success of the CF Foundation in therapeutic development. We are proud that we have brought efficiencies to many aspects of the clinical trials process, from patient accrual to data analysis at the end of trials. Duplicative institutional review board (IRB) review of trials has persisted as an inefficiency in our trials process.

We are pleased that the committee is directing attention to the issue of IRB review. In general, we support the movement toward single IRB review in multi-site trials. We urge that a single IRB used in this situation have the capacity to consider so-called "local issues" as well as the special needs of vulnerable populations.

ACE Kids Act

We commend the committee for attempting to meet the needs of children with complex medical conditions through inclusion of the Advancing Care for Exceptional (ACE) Kids Act in the discussion draft. We understand the pressing health care needs of children with complex medical needs, as many individuals with CF fit in this category. We are also well aware of the obstacles to quality care that these

children may encounter, including restrictive coverage and payment rules and limitations on care networks.

We are concerned that the solution of the ACE Kids Act, which would rely on children's hospital-based networks of care, would have the unintended consequence of creating new and different barriers to care for certain children with complex medical needs. For example, children with CF depend on a CF care network that includes hospitals, academic health centers, and other providers across the country. The networks that are anticipated by the ACE Kids Act are not consistent with the outstanding system of care that already exists for CF care. We encourage the committee to remain focused on addressing the access issues confronted by these children.

The FDA Review Process

We understand the interest in eliminating inefficiencies and streamlining the timeframe for regulatory review so that new products reach consumers at the earliest possible time. However, the drive to speed the regulatory process must be accompanied by efforts to protect the quality of regulatory review. It is critically important that individuals with CF and others with serious and life-threatening diseases can trust that the drugs they are prescribed are safe and effective and that FDA has reviewed data that support such findings.

It is most important that patients and their health care providers are assured that FDA review is rigorous and is based on thorough evaluation of safety and efficacy data. However, it is also important that third-party payers trust the FDA review process. We are concerned that third-party payers are considering determinations related to the "reasonable and necessary" use of a new drug that veer toward a full-fledged evaluation of the safety and efficacy of a new product. This approach will at the very least serve to slow patient access to new therapies, if payers undertake to effectively repeat an FDA review process they consider inadequate. There are also risks that such payer reviews will result in coverage standards that will seriously hinder patient access to new therapies, if such payers believe that FDA review is inadequate and that they must reconsider safety and efficacy data.

Resources to Support a 21st Century Drug Development and Review Process

We urge that the Congress make available the resources that FDA will require to be a 21st century regulatory agency. We have been mindful in our recommendations not to layer significant new responsibilities on the agency. However, we note that the hiring, training, and travel recommendations we have made will be accompanied by some additional cost to FDA. To make these recommendations meaningful, they must be resourced. The same is true for other new responsibilities that the committee would propose for FDA.

There are some situations in which the National Institutes of Health has provided certain core facilities and processes to foster translational research, and those successful efforts might be considered and expanded. For example, NIH has brought together diverse parties – foundations, academic researchers, and industry – to screen compounds in multiple libraries and identify targets for drug development. This

has occurred in the case of nontuberculous mycobacteria and other "superbugs" as well as in other disease areas.

These are important models in which NIH has leveraged its central role in biomedical research to improve efficiencies and address duplication in translational research, bring important resources and leadership to under-resourced areas, and foster collaboration.

We recommend that existing programs, including but not limited to the National Center for Accelerating Translational Science, the Cures Acceleration Network, the Reagan-Udall Institute, and others (some established by legislative action and some by administrative action), be evaluated carefully to ensure that they meet the standards of fostering collaboration, accelerating research, and addressing inefficiencies and duplication in the research process. Existing programs should meet those high standards, and new efforts should be designed to meet them, too.

We offer a caution about the number of reports, commissions, and panels that are included in the discussion draft. FDA would be challenged to honor the reporting and advisory panel requirements in the discussion draft without new resources. Even if Congress determines that it will provide adequate resources for the agency to meet all of these new reporting requirements, we question if that is the best investment of new resources. As the legislative drafting process moves forward, we urge that all of the reports, commissions, and panels be rigorously evaluated before being included in a final legislative draft.

We appreciate the opportunity to comment on the discussion draft and look forward to additional discussions regarding 21st century cures.

Sincerely,

Robert J. Beall, Ph.D.
President and Chief Executive Officer