

STATEMENT OF ROBERT BEALL, PHD

**SUBMITTED TO U.S. SENATE COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS (HELP)**

**TREATING RARE AND NEGLECTED PEDIATRIC DISEASES: PROMOTING
THE DEVELOPMENT OF NEW TREATMENTS AND CURES**

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Chairman Kohl and Ranking Member Brownback, it is my pleasure to submit this statement on behalf of the Cystic Fibrosis Foundation. We commend the Committee for convening this hearing to consider how to develop new treatments for rare and neglected pediatric diseases more efficiently and quickly. For all of those affected by rare and neglected diseases, an effective discovery, development and review system is absolutely critical. We applaud Congress for its continued attention and efforts to evaluate the best way to discover and develop therapies for the more than 7 million Americans with rare diseases.

The CF Foundation is recognized as a global leader in the area of drug development for rare disease. As Congress examines how best to foster new drug development for rare and neglected diseases, we urge you to extrapolate and build from our experience to benefit all Americans with rare disease. These lessons include:

- Supporting innovative funding models for drug development including the Therapeutics for Rare and Neglected Diseases (TRND) program and the Cures Acceleration Network (CAN) at new programs at the National Institutes of Health (NIH); and expanding and providing more flexibility to the Small Business Innovative Research program.
- Facilitating clinical research by encouraging the NIH to support the development of registries and clinical trials networks, or have demonstration projects for their support; and passing the Improving Access to Clinical Trials Act (S. 1674) to allow patients with rare diseases to participate in clinical drug studies without losing their eligibility for government health care coverage.
- Streamlining the drug approval process at the Food and Drug Administration (FDA) and providing adequate resources to the agency to execute its mission.

THE CHANGING FACE OF CF

Cystic fibrosis (CF) is a disease that affects only 30,000 Americans and 70,000 individuals worldwide. The effects of this disease are severe. The bodies of people with CF produce abnormally thick, sticky mucus that clogs the lungs, resulting in fatal lung infections and obstructing the pancreas, making it difficult for patients to absorb nutrients

from food and requiring hours of treatment per day. More than fifty percent of those with cystic fibrosis are under the age of 19.

There is no cure for CF despite significant therapeutic advances, outstanding management of the disease by patients and their physicians, and enhanced adherence to standards of clinical care. There is a pressing need for improved therapies for CF, and as new treatments are developed, efficient review is necessary.

CF is still a devastating disease; the median age of death is 27. But the story of CF is changing. It is a promising time full of hope and optimism for a disease where there once was none. The lessons the CF community has learned about developing drugs and other treatments for a rare disease offer an important and replicable road map for development strategies for rare disease, and the FDA's review process for rare disease drug development.

THE CF PIPELINE: A ROADMAP FOR RARE DISEASE DRUG DEVELOPMENT

Through aggressive investment in and management of the CF therapeutic development program, the Cystic Fibrosis Foundation is now managing a rich portfolio of potential new treatments with more than 30 drugs in the clinical development pipeline, including five already available to patients. The pipeline portfolio is diverse, with potential treatments targeting the range of symptoms of the disease including mucus alteration, anti-inflammatory, anti-infective, transplantation, and nutrition. The CF pipeline also includes drugs that may correct the genetic defects that cause CF. The CF Foundation is assuming an expansive role in research, supporting basic research, functioning as a venture philanthropist through investment in biotechnology companies for development of new CF therapies, and coordinating CF care quality improvement through a patient registry that includes most CF patients in the nation.

This vibrant portfolio of existing and potential treatments is due to the success of the CF Foundation's innovative "venture philanthropy" business model, to spur the development of new drugs. As the co-discoverer of the CF gene and our long-time friend Dr. Francis Collins has said, "What's been learned from CF can be extrapolated, generalized, to hundreds of other diseases." This testimony highlights some of these lessons.

PATIENT ADVOCACY & INVESTMENT TO "DE-RISK" EARLY-STAGE DRUG DEVELOPMENT

There was great excitement that a cure was just around the corner when Dr. Francis Collins, Dr. Lap Chee Tsui, and Dr. Jack Riordan of the University of Toronto discovered the cystic fibrosis gene in 1989. Yet ten years after that discovery, the CF Foundation was frustrated that although researchers were making great progress in understanding the biological defect, drugs for cystic fibrosis patients were not being developed. The problem was that it was too risky for drug companies to invest their resources in such a rare disease. In order to overcome this barrier, the Foundation decided to invest its own

funds in promising research and drug development conducted by private companies. The Foundation's financial investment "de-risked" pharmaceutical and biotech companies' involvement in research into cystic fibrosis therapies, accelerating the development of treatments. This patient involvement in financing potential therapies pioneered by the CF Foundation has since been dubbed "venture philanthropy."

Venture Philanthropy in Action

With the discovery of the defective gene in CF, the CF Foundation learned what went wrong in the cells of people with the disease – chloride did not move through airway cells in a normal manner. We needed a treatment that would restore the cell's ability to expel chloride. Our first significant foray into venture philanthropy was a \$40 million investment in a small California company that conducted high throughput screening to determine if there was an existing chemical compound that could restore the broken function – and open up the chloride channel - in a CF cell. The results were as we hoped. After screening tens of thousands of chemical compounds, two were shown to positively impact chloride transport. These drugs are now in clinical trials in CF patients.

In the past five years, the Cystic Fibrosis Foundation has invested over \$800 million in its medical programs of drug discovery, drug development, research, and care focused on life-sustaining treatments and a cure for CF, achieving exceptional results. In many cases, our initial funding for a therapy is magnified several times by our partners in the biotech and pharmaceutical industry. The CF Foundation's willingness to invest our own funds to demonstrate the scientific proof of concept "de-risks" industry's involvement in an orphan disease and is critical to their decision to invest in a potential therapy for CF.

FEDERAL FUNDS CAN FOSTER INVESTMENT IN RARE DISEASE DRUG DEVELOPMENT

Although we are fortunate to have so many therapeutic targets to pursue, we are still racing the clock to develop new CF therapies. Despite our successful fundraising efforts, we cannot pursue all of the promising research opportunities before us without help and without partners. What's more, not all rare or neglected disease communities have the financial resources needed to invest. To this end, we are pleased that the NIH and other health agencies pay special attention to advances in treatment methods and mechanisms for translating basic research across institutes into therapies that can benefit patients.

The NIH has increased its ability to facilitate investment in early stage proof of concept research through its TRND program, which builds upon the CF Foundation's drug development model. We are pleased to see growing support for TRND and urge Congress to significantly increase this program.

We also support CAN, an innovative therapeutics development model that will help meet the demand for testing promising new therapies for cystic fibrosis and other diseases. CAN will help coordinate the efforts of all stakeholders in the drug development process – including patient advocacy organizations and agencies outside of NIH – in order to

move discoveries forward. Including the FDA in the work that CAN will undertake provides a crucial link between NIH and the drug approval process.

It is also important to involve the private sector in rare disease drug development as early in the process as possible. As such, we encourage Congress to increase support SBIR grants. These grants in particular are important for companies pursuing the early discovery phase of drug development, the most difficult time to secure funding, often referred to as the “valley of death” for rare disease drug development because of the significant problems in connecting early start-up funding with later research funding. Programs like SBIR are also important to this mission because of the synergy between venture funding and SBIR funding. Small biotechnology companies are able to use SBIR funds in concert with funding from other sources, such as the CF Foundation, to overcome the most vulnerable stages of development. Likewise, biotechnology companies that use SBIR funds make themselves more attractive to outside investors by virtue of their previously funded successes.

The SBIR program has been a success, and the need for it has never been greater. We urge changes to the administration of the program to ensure that it meets its fundamental goals and supports research in fields that would otherwise be neglected because of small markets or obstacles to research. The current ownership rules for small businesses must be revised as start up biotech companies that are small businesses in every sense of the word continue to face challenges because they successfully secured funding from external investors. In addition, the program rules should be amended to dedicate a percentage of SBIR funds to research on orphan diseases, as early stage research on these diseases is understandably not an attractive target for pharmaceutical and biotechnology companies.

RESEARCH DEVELOPMENT

Not only does the CF Foundation provide financial support for groundbreaking research, but we also bring expert knowledge of the disease, research protocols and trial design, and patients to move the trials forward swiftly. In doing so, the Foundation improves collaboration and data sharing among researchers, care-givers, and patients. The CF Foundation supports 112 care centers throughout the country that provide specialized care to 95 percent of the CF population. This integrated network of clinical care is essential to the drug development pipeline.

RESEARCH COLLABORATION SPEEDS INNOVATION

For nearly 25 years, the CF Foundation has promoted translational medicine through its Research Development Program (RDP) in major academic medical institutions across the country. Participating institutions have expertise in CF basic research and strong ties to local CF Foundation-accredited care centers. The frequent interactions between basic “bench” scientists and frontline caregivers encouraged by the RDP have led to the scientific foundation for several promising drug candidates in the CF Foundation’s drug

development pipeline. Many of the RDP sites have leveraged support from the CF Foundation to successfully compete for additional funding from the NIH to further their CF research. Many of these academic investigators have provided highly valued tools for the drug discovery process, including cell lines, assays, and antibodies.

The CF Foundation also brings academic investigators together with consultants from industry to shape industry collaborations and regularly review project progress. The exchange of ideas fostered through this process benefits all parties and advances the shared goal of discovering drugs for CF.

SHARING BEST PRACTICE IN CLINICAL TRIAL DESIGN

Nearly 80 of the CF Foundation-accredited care centers participate in our Therapeutics Development Network (TDN), a nationwide network conducting clinical trials to evaluate the safety and effectiveness of new CF therapies. The TDN centers work together to promote quality, safety and best practices in CF clinical trials by centralizing and standardizing the research process. Thirteen of the centers provide specific expertise in conducting early-phase trials that often involve complex protocols to measure the activity of new compounds. Other members of the TDN provide expertise in CF-related outcome measures in areas such as microbiology, inflammation, and lung function. Providing this expertise ensures that individual drug companies investigating a potential CF therapy do not have to “reinvent the wheel” when developing trial protocols.

The TDN centers carry out a broad range of studies and, in particular, support Phase III trials that can involve hundreds of patients over several months or years. Since 2003, the TDN has participated in more than 50 clinical studies with more than 3150 subjects from the CF population. Heralded as an exemplary clinical trials network, the TDN helps shorten the timeline of the drug development process.

Through our care centers nationwide, the CF Foundation supports a robust patient registry that is another key component of our ability to foster drug development for the disease. The broad collection of patient data provided by the registry is a valuable tool for companies considering development of a CF therapy because of the detailed patient information it offers. We encourage additional funding to enable the NIH to foster the development of patient registries for pediatric and rare diseases, as well as clinical trials networks such as our TDN. We urge the NIH to support demonstration projects to enable existing registries and clinical trial networks to expand into new areas of drug development, including Phase IV safety and effectiveness monitoring, and comparative effectiveness studies of drugs.

PATIENT INVOLVEMENT IN RESEARCH

As promising compounds are discovered, researchers face a real challenge in recruiting people to help test new drugs. As with all rare diseases, a significant percent of the CF patient population is needed to participate in clinical trials. However, people with CF –

and many other rare diseases – are experiencing a very real disincentive to participating in the clinical trials that could produce new therapies to treat their condition.

Current rules dictate that when a Supplemental Security Income (SSI) beneficiary receives compensation for participating in a clinical drug trial, this compensation counts toward their income eligibility for SSI and Medicaid. This serves as a disincentive to participation by those with low incomes, slowing down the clinical trial process and hindering the development of sorely needed treatments. The Improving Access to Clinical Trials Act, S. 1674, would solve this problem by allowing patients with rare diseases to participate in clinical drug studies without losing their eligibility for government health care coverage. S. 1674 will help potential new therapies for CF and other diseases to move swiftly from the research stage through FDA approval, ensuring that life-saving drugs get into the hands of the patients who need them most, and we urge you to swiftly pass this legislation into law.

STREAMLINING THE DRUG APPROVAL PROCESS

The venture philanthropy effort has yielded a number of potential CF treatments. Our efforts to date have focused on translating basic research findings into agents for clinical testing, coordinating the clinical trials network for testing CF treatments, and removing barriers to participation in trials by CF patients. As more promising treatments begin to emerge from the development pipeline, our attention is increasingly focused on guaranteeing an efficient FDA review process. It is essential that this final step be as well coordinated as the steps that come before it so that promising drugs are in the hands of people with CF as soon as possible.

We urge Congress to significantly increase funding for the FDA to ensure that it can meet its statutory obligations to review drugs for safety and efficacy in a timely manner. This is particularly important for rare diseases, many of which are life-threatening. While some have called on Congress to isolate rare disease drug review in a stand-alone division, we believe rare disease drug review will be better served by bolstering support for the multiple divisions that must review rare disease drug candidates and enabling these divisions to consult experts in particular rare diseases more readily. To use CF as an example, the 30 potential therapies in our drug development pipeline could be reviewed by one of five different divisions within the Office of New Drugs at the Center for Drug Evaluation and Research (CDER). To silo each of these complex and very different drugs into a rare disease drug review division is more likely to slow down the review process than speed it up because one small underfunded division must review multiple drugs treating widely different biological systems. It would be extraordinarily difficult to have the expertise needed with the proposed funds for such a rare drug division. We encourage Congress to adequately fund CDER so that it has the scientific expertise in each of its existing divisions to review new drugs.

We commend the FDA for encouraging drug developers to utilize expert advisors through the drug development process, and urge these consultations to begin in the pre-Investigational New Drug (IND) Application process. We also encourage the Agency to

consult with such experts itself throughout the drug development process to supplement the review offices' knowledge of rare diseases. Such consultation can help determine the most appropriate and efficient IND and New Drug Application (NDA) package. By tapping experts, such as those participating in clinical trials for CF through our TDN, the FDA will have access to the most up-to-date clinical trial design and outcomes measurements. This will ensure that the trials are appropriate to determine a drug's safety and effectiveness but also that the scope of the trial is feasible within a rare disease patient population.

We are encouraged by initiatives that the agency has undertaken to enhance its scientific expertise for review of rare diseases and more generally by the willingness of FDA leaders and review staff to engage in constructive dialogue to address the problems of rare disease review that we have identified.

The joint regulatory science initiative of FDA and the National Institutes of Health (NIH) signals the firm commitment of the agencies to enhance the scientific expertise of FDA review staff. This effort, still a relatively new one, promises to provide special benefits in strengthening the scientific knowledge and experience for rare disease treatment review. In addition, the agency directed important resources and attention to rare disease treatments by naming a lead reviewer on rare diseases. We have also found the agency to be willing to engage in constructive dialogue to address other problems posed by rare disease review and those issues that are specific to CF product review.

In addition, we have identified a number of key issues related to the efficient conduct of clinical trials supporting registration of INDs that should be addressed to improve FDA review of CF therapies. We believe that FDA action on these issues would benefit review of all rare disease treatments. These issues include: 1) identification of and regulatory agreement regarding endpoints for approval of rare disease treatments; 2) making widely and readily known the process for validation of biomarkers to identify subpopulations of CF patients who might benefit from therapies approved for other populations; 3) consistency between FDA and the European Medicines Agency, to eliminate difficulties associated with conducting parallel and duplicative trials in orphan populations; and 4) regulatory guidance regarding methods for evaluating supplemental uses of devices, including nebulizers, without undertaking trials that are prohibitive for cost and other reasons.

We applaud the Committee for turning its attention to fostering the development of treatments for rare and neglected diseases and to evaluating initiatives or programs that might enhance such review. We believe the experience of the CF Foundation in clinical research can serve as a model of drug discovery and development for research on other orphan diseases and we stand ready to work with Congressional leaders, disease advocacy organizations, and others to make this a reality. On behalf of the Cystic Fibrosis Foundation, we thank the Committee for its consideration.

Thank you again for this opportunity to submit this statement.