CYSTIC FIBROSIS FOUNDATION®

April 28th, 2023

Robert M. Califf, M.D., MACC
Commissioner, Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA-2022-D-2983, Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

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

Dear Commissioner Califf:

On behalf of the Cystic Fibrosis Foundation, we write to provide comments in response to the Food and Drug Administration (FDA) draft guidance on *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products*. We greatly appreciate the FDA's commitment to facilitating the development and execution of alternative trial designs, including the utilization of external control data for clinical investigations, and welcome the opportunity to provide input on such efforts.

Background on Cystic Fibrosis and the Cystic Fibrosis Foundation

Cystic fibrosis (CF) is a rare genetic disease that affects nearly 40,000 adults and children in the United States. In people with CF, mutations in the CFTR gene result in a buildup of thick mucus in multiple organ systems, leading to lung damage, life-threatening infections, and other complications. CFTR modulators, which directly target defects in the processing, trafficking, and function of the CFTR protein, have drastically altered the CF therapeutic landscape and the lives of modulator-eligible people with CF, who constitute over 90% of the CF population. However, the development of these therapeutics has resulted in a significant decrease in the number of people with CF eligible for clinical trials based on key inclusion and exclusion criteria, including CFTR variant, active treatment status, and lung function. This depletion of an already limited pool of potential research participants, in combination with a therapeutic pipeline that remains robust, has necessitated a re-imaging of clinical trial design in the CF space.

The CF Foundation is engaged in virtually every element of the research and development process—from preclinical discovery and identification of new therapeutics to conducting clinical trials and post-marketing surveillance. Our research and investment portfolio includes CFTR modulators, symptomatic treatments, and a growing array of biologics, such as mRNA and gene therapies. Because the emergence and widespread clinical use of CFTR modulators has effectively resulted in a new, ultra-orphan population consisting of people with CF who are either modulator-ineligible or -intolerant, companies developing these critical products are finding it increasingly difficult to perform right-sized, placebo-controlled randomized clinical trials. With this in mind, the utilization of external control data, such as the real-world data contained in the CF Foundation Patient Registry and high-quality datasets derived from numerous current or previously completed clinical trials run through the

CF Therapeutic Development Network, may mitigate the logistical difficulties of executing CF clinical trials in a post-CFTR modulator era. We therefore offer the following considerations for the FDA as it continues to develop its guidelines for the design and conduct of externally controlled trials for drug and biological trials.

Data Considerations for External Control Arm Data from Clinical Trials

General selection of an external control arm from previously completed trials:

While we agree that significant comparability between trial arms is necessary for the use of external control data in clinical trials, we are concerned that this draft guidance may place too much emphasis on potential bias in selecting external control arms from previously completed trials whose outcomes are already known. As articulated in this draft guidance, the use of data from clinical trials for external control arms can be highly advantageous due to the inherent rigor of protocol-based data collection. However, the language used in the *Data from Clinical Trials* section suggests that the FDA prefers that sponsors utilize external control data from concurrent clinical trials and may even consider the use of such data from previously completed clinical trials to be largely nonviable, even if the results of such trials are consistent with prior experience and reflect contemporaneous standard of care.

Concurrent clinical trials may serve as valuable sources of external control data, particularly in terms of the considerations for data comparability described in this draft guidance. However, those datasets are unlikely to be readily available in circumstances in which sponsors would need to rely on external control data to properly execute clinical trials (e.g., drug development programs for rare diseases). For such cases, we believe that it may be detrimental to discourage or set an unrealistic standard for the utilization of external control data from previously completed clinical trials when its use may be appropriate and justifiable. Furthermore, this position is at odds with the historical use of external controls in the FDA's regulatory decision making; there are numerous examples of using external control data from previously completed clinical trials for regulatory purposes[1], including to support the approval of medical products.[2] We therefore ask that the FDA clarify its guidance regarding the use of external control data from both concurrent and previously completed clinical trials.

Use of external control data derived from the treatment arm of a previously completed clinical trial:

In general, when selecting a dataset from a previously completed clinical trial for use in an externally controlled trial, sponsors will likely choose to use the control arm from that trial. However, for previously completed clinical trials in which the active treatment was not found to differ clinically or statistically from the control arm, it may be possible to derive useful external control data from both the experimental and control arms of that trial. We therefore ask the FDA to address the potential use of experimental arms that have proven safe but not efficacious in previously completed clinical trials for externally controlled trials.

Shared use of external control datasets across different sponsors for multiple therapeutic comparisons:

Based on our experience with the acquisition and utilization of external control data, we believe that it would be extremely valuable to have the option of using the same external control datasets for multiple externally controlled trials from different sponsors. External control data suitable for use in clinical trials is frequently scarce in the context of rare diseases; even the considerable amount of real-world data contained within the CF

[1] Mishra-Kalyani PS, Amiri Kordestani L, Rivera DR, et al. External control arms in oncology: current use and future directions. Ann Oncol. 2022;33(4):376-383. doi:10.1016/j.annonc.2021.12.015

[2] Jahanshahi M, Gregg K, Davis G, et al. The Use of External Controls in FDA Regulatory Decision Making. Ther Innov Regul Sci. 2021;55(5):1019-1035. doi:10.1007/s43441-021-00302-y

Foundation Patient Registry and the datasets available from previously conducted CF clinical trials represent a relatively limited pool of potential external control data when compared to the number of current and anticipated clinical investigations within the CF research and development ecosystem. The concept of a shared control group is well-established for clinical trials that utilize master protocols; however, given the significant variance in study designs, investigational products, and data needs across clinical trials from different sponsors, even within the same research space (e.g., gene therapy products for cystic fibrosis), master protocols are not always feasible. It would therefore be useful to employ a similar concept outside of traditional master protocols. We urge the FDA to provide guidance on the use of the same external control dataset for multiple clinical trials from different sponsors.

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Once again, the Cystic Fibrosis Foundation appreciates the FDA's dedication to working with sponsors and other organizations involved in drug development to advance innovative clinical trial designs in an increasingly complex biological and regulatory environment. We view these considerations as critical to the FDA's efforts and look forward to working with the Agency as it continues to refine its thinking.

Sincerely,

Mary Dwight

Senior Vice President
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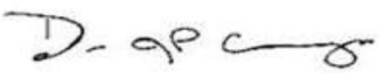

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