



August 23, 2022

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

Re: FDA-2021-D-1152, Considerations for Rescinding Breakthrough Therapy Designation: Draft Guidance for Industry

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of the Cystic Fibrosis Foundation, we write to provide comments in response to the Food and Drug Administration (FDA) draft guidance on *Considerations for Rescinding Breakthrough Therapy Designation*. We appreciate the FDA's ongoing willingness to revisit critical regulatory programs to provide additional clarity and more effectively meet the needs of sponsors and patients.

### **Background on Cystic Fibrosis and the Cystic Fibrosis Foundation**

Cystic fibrosis (CF) is a rare genetic disease that affects nearly 40,000 people in the United States. In people with CF, defects in the CFTR gene result in a buildup of thick mucus in multiple organ systems, resulting in lung damage, life-threatening infections, and other complications. Through its Path to the Cure Program, the Cystic Fibrosis 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. Numerous treatments for cystic fibrosis—including the CFTR modulators Kalydeco, Orkambi, Symdeko, and Trikafta—have benefited from Breakthrough Therapy Designation (BTD) for various indications. The following suggestions are informed by the knowledge gleaned from our experience with those and other approval processes.

### **Rescinding Breakthrough Therapy Designation for Drugs Addressing Similar Unmet Needs**

As established in the *Expedited Programs for Serious Conditions—Drugs and Biologics* Guidance for Industry (May 2014) and reiterated here, a drug product may no longer meet the FDA's "substantial improvement over existing available therapies" criteria following approval of an alternative drug that addresses the need that informed the original BTD rationale. Should this occur, the FDA may revoke BTD.

We recognize that the BTD program is resource-intensive. However, we believe that the FDA's policy of rescinding BTD under this "alternative drug" provision undervalues the legitimate benefits of rapidly bringing multiple drug products for underserved conditions to market. The FDA should therefore explicitly take into consideration the following factors when determining whether to continue BTD in these situations.

*Varying patient response profiles:* A drug awarded BTM and subsequently approved may offer substantial improvement over existing available therapies to wide proportions of a patient population. Current BTM policies, however, do not account for patients whose condition may not respond to the approved drug, patients who may not tolerate the approved drug, or patients for whom the approved drug is not an appropriate option for other reasons such as drug-drug interactions. The regulations governing BTM should be modified to give FDA the flexibility to allow multiple drugs for the same unmet need to maintain BTM if they elicit different patient response profiles (resulting from distinct mechanisms of action or other pharmacological characteristics) and otherwise continue to meet the criteria for BTM.

*Serious adverse events:* The FDA has previously stated that a new drug may receive BTM by virtue of demonstrating important safety advantages related to serious adverse events compared with available therapies, as long as it is similarly efficacious to available therapies. This allowance should also be reflected in the guidelines for rescinding BTM during the development process.

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Once again, the Cystic Fibrosis Foundation commends the FDA's commitment to updating its guidance on expedited programs to accommodate shifts in the therapeutic development landscape. We believe that these changes will provide the FDA with the flexibility required to use BTM in a manner that appropriately addresses the needs of all patients. We appreciate the opportunity to provide input on the subject and look forward to working with the FDA on future revisions.

Sincerely,

Mary Dwight



Senior Vice President  
Chief Policy and Advocacy Officer

Anthony Durmowicz



Vice President  
Clinical Development