# Considerations for Rescinding Breakthrough Therapy Designation

## Guidance for Industry

***DRAFT GUIDANCE***

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For questions regarding this draft document, contact (CDER) Dat Doan, 240-402-8926, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**
**Oncology Center of Excellence (OCE)**

**June 2022**
**Procedural**

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*Contains Nonbinding Recommendations*

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# Considerations for Rescinding Breakthrough Therapy Designation Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

## I. INTRODUCTION

This guidance explains how, during its evaluation of a drug[2] development program, FDA may consider whether to rescind a breakthrough therapy designation (BTD). This guidance is consistent with, and supplements, the information on BTD contained in the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014)[3] and other BTD policies and procedures of the Center for Drug Evaluation and Research (CDER)[4] and the Center for Biologics Evaluation and Research (CBER).[5]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE) and the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See CDER's Manual of Policies and Procedures (MAPP) 6025.6 *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics.* CDER MAPPs are available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp.

[5] See CBER's Standard Operating Policy and Procedure (SOPP) 8212 Version 2 *Management of Breakthrough Therapy-Designated Products: Sponsor Interactions and Status Assessment Including Rescinding*. CBER SOPPs are available at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-procedures-sopps.

## II. BACKGROUND

Section 506(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356(a)) provides for the granting of BTD "if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development." The BTD program is intended to facilitate and expedite the development of those drugs that receive designation and involves a resource commitment from FDA to provide early and frequent advice, conduct multidisciplinary meetings involving senior managers, and when appropriate, expedite the review of resultant marketing applications. Thus, it is important that available evidence continues to fulfill the standards for BTD.

Breakthrough therapy designation applies to a drug (either alone or in combination with other drugs) and the specific use for which it is being studied. The information supporting the granting of BTD for a particular drug may change over time. Some drugs that appear promising in early development may not be shown to be safe or effective in later trials, or the magnitude of a treatment effect suggested by early development may not be observed in later stages of development. Accordingly, given the resource-intensive nature of the BTD program, and in keeping with the Agency's authority to grant BTD only to drugs that meet the legal criteria, FDA periodically assesses whether designated products continue to meet the criteria for BTD. If the designation is no longer supported by subsequent data, FDA may rescind the designation.[6]

## III. GENERAL CONSIDERATIONS FOR RESCINDING BREAKTHROUGH THERAPY DESIGNATION

Early clinical data, including evidence based upon robust pharmacodynamic endpoints, are typically used to support a BTD. Subsequent to granting BTD, information may become available such that the evidence no longer shows that the drug satisfies the BTD criteria. For example, a BTD may be rescinded for reasons such as:

1. A different drug is approved to treat the unmet need that informed the rationale for granting BTD. As a result of this new therapy, the BTD drug no longer meets the BTD criteria regarding substantial improvement over existing available therapies.[7] Note that

[6] FDA follows the processes described in MAPP 6025.6 and SOPP 8212 for rescinding BTD.

[7] *Available therapy* (and the terms *existing treatment* and *existing therapy*), as used herein, reflect the meaning of the term as discussed in the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014); those terms should generally be understood to refer to therapy that is approved or licensed in the United States for the same indication being considered for the new drug, and that is still relevant to the standard of care. In exceptional cases, a treatment that is not approved for the indicated use may be considered available therapy if the safety and effectiveness of the use is supported by compelling evidence, including extensive evidence in the published literature. For further discussion of *available therapy*, see the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics*, pp. 2–3.

another drug approved under accelerated approval generally will not be considered sufficient to lead to rescinding BTD.

2. Emerging data for the designated drug no longer support a finding that "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies."[8]

3. The designated drug's sponsor is no longer pursuing the drug's development program for the use that was the basis for BTD.

For example, rescinding a BTD may be warranted if a phase 3 trial intended to definitively show the designated drug's effect fails to meet its primary endpoint, or the extent of benefit is more modest such that the trial does not indicate that the drug may demonstrate a substantial improvement over available therapy. The emergence of additional safety information that alters the benefit-risk assessment of the designated product may also support a decision to rescind BTD.

In assessing whether the criteria for BTD continue to be met, FDA typically gives greater weight to trials that are conducted in larger populations, use a well-understood and widely accepted, well-constructed clinical endpoint, and incorporate certain design features (e.g., randomization, blinding). Thus, the quality of evidence available may impact FDA's decision-making.

In certain circumstances, FDA may decide not to rescind BTD designation, even if subsequent results appear not to support the evidence on which BTD was based. For example, if initial data were promising, and there are significant issues with the conduct and design of a subsequent study, the subsequent study may be given less weight in assessing whether the criteria for BTD are still met. However, if the evidence available from multiple well-designed studies reflect an inconsistent picture of clinical benefit, the assessment of whether the criteria for BTD continue to be met may become more challenging. For example, if a trial does not demonstrate statistically significant improvement in the primary endpoint being studied, but shows a favorable trend on a secondary clinical endpoint of interest, then the trial might still be consistent with FDA's determination that there is "preliminary clinical evidence"[9] to support BTD. In such circumstances, maintaining the drug's BTD may be warranted, especially if the "preliminary clinical evidence"[10] that led to the original BTD was strong. The decision whether to maintain or revoke BTD in such cases will depend on the facts specific to that drug development program.

This guidance document provides general considerations, and sponsors are encouraged to discuss specifics with FDA concerning evolving information and circumstances surrounding BTD for a particular drug.

[8] See section 506(a) of the FD&C Act.

[9] Ibid.

[10] Ibid.