

SOPP 8212: Breakthrough Therapy Products - Designation and Management

Version: 6

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff “to expedite the development and review of a breakthrough therapy...” consistent with requirements described in section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and as explained in *Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics*.

II. Scope

A. This SOPP includes the procedures for:

- Review of requests for preliminary advice on whether it is appropriate to submit a formal request for breakthrough therapy designation,
- Review of a request for breakthrough therapy-designation submitted with an original Investigational New Drug Application (IND) or in an IND amendment,
- Breakthrough therapy related CBER-sponsor meetings and other communications,

- CBER periodic summary reviews of breakthrough therapy-designated biologic or drug product development programs,
 - Procedures for rescinding a breakthrough therapy designation under an Investigational New Drug (IND) submission (refer also to the draft *Guidance for Industry: Considerations for Rescinding Breakthrough Therapy Designation*), and
 - Review of requests to withdraw a breakthrough therapy designation or designation request.
- B.** This SOPP does not cover breakthrough device or device-led combination product designations. Please refer to the *Guidance for Industry and Food and Drug Administration Staff: Breakthrough Devices Program* for information specific to devices.
- C.** This SOPP does not cover general administrative procedures for INDs.
- D.** This SOPP does not address the specific content of scientific reviews.
- E.** This SOPP does not cover fast track or regenerative medicine advanced therapies (RMAT) designations.
- F.** This SOPP does not cover the review of biologics license applications (BLAs) or new drug applications (NDAs) submitted for breakthrough therapy-designated products.

III. Background

- A.** Section 506(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) as amended by section 902 of FDASIA, provides for designation of a drug as a breakthrough therapy "... if the product 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 product may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development." As part of FDASIA, the Food and Drug Administration (FDA) agreed to expedite the development and review of products designated as breakthrough therapy by:
1. Meeting frequently with the sponsor throughout the IND phase, in addition to the critical IND milestone meetings, to address important issues at different development phases;
 2. Providing timely advice to, and interactive communication with, the sponsor regarding the development of the product to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable;

3. Involving senior managers (in CBER, Division Directors and above) and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review;
 4. Assigning a cross-disciplinary project lead for the review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and
 5. Taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to potentially less efficacious treatment.
- B.** The *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* provides information regarding the qualifying criteria for a breakthrough therapy designation, and outlines at a high level, the features of a breakthrough therapy designation.
- C.** A breakthrough therapy designation is not the same as a biologic or drug approval and does not change the statutory standards for demonstrating the safety and effectiveness needed for product approval. A breakthrough therapy product development program must generate substantial evidence of effectiveness and sufficient evidence of safety to meet the statutory standard for approval.

IV. Definitions

N/A

V. Policy

- A.** Preliminary, non-binding advice on whether an official request for breakthrough therapy designation is appropriate may be requested when an IND is already in effect or in rare cases, when there is not an existing IND, for example, if completed clinical studies were not conducted in the United States. The intent is to alleviate CBER review of breakthrough therapy designation requests (BTDRs) which are premature or inadequate based on the breakthrough therapy designation criteria. Interactions between the requestor and CBER will be via teleconference. Official meeting minutes are not issued to the requestor following the teleconference.
- B.** Sponsors may make a request for breakthrough therapy designation with submission of an Investigational New Drug application (IND) or in an amendment to an existing IND, ideally no later than the end-of-phase 2 meeting. In general, it is anticipated that most requests for breakthrough therapy designation will be submitted as an IND amendment because clinical evidence is a requirement for this program.

- C.** Fast track designation, breakthrough therapy designation, and regenerative medicine advanced therapy designation are distinct designation programs with different programmatic requirements. Sponsors may apply for and receive more than one designation for a given product, but sponsors should apply for each designation separately, in separate amendments to their IND. In addition, if a sponsor's development program is granted breakthrough therapy designation for one indication and has preliminary clinical evidence to support breakthrough therapy designation for another indication, the sponsor should submit a separate request, in a separate amendment to their IND.
- D.** CBER will notify the sponsor in writing, within 60 calendar days after receipt of the breakthrough therapy designation request, as to whether the product has received the breakthrough therapy designation. If CBER determines that the product does not meet the criteria for breakthrough therapy designation, CBER will include a written description of the rationale for the decision.
- E.** If a request for breakthrough therapy designation was denied because the preliminary clinical evidence did not demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, and a sponsor submits new/additional clinical data for review or corrects other faulty information that resulted in the denial, then that request will be considered a new designation request.
- F.** If a sponsor disagrees with CBER's rationale for denying the breakthrough therapy designation, then the sponsor may ask the division to reconsider based on the rationale stated in the denial letter. Such requests, without submission of new clinical data, generally will be reviewed within 60 days, but do not have a statutory review timeline. The sponsor will be notified in writing of CBER's decision.
- G.** CBER will not grant requests for breakthrough therapy designation for INDs that are inactive, on clinical hold or placed on clinical hold if submitted with the original application. If the IND is on partial hold at the time the breakthrough therapy designation request is received, the circumstances of the partial hold will be considered to determine how they may affect the review of the request for breakthrough therapy designation.
- H.** Sponsors of breakthrough therapy-designated products are eligible for earlier, expedited, and more frequent interactions with the FDA. As noted in the *Guidance for Industry and Review Staff; Best Practices for Communications Between IND Sponsors and FDA During Drug Development*, a formal communication plan should be established during the initial comprehensive multidisciplinary CBER-Sponsor meeting after breakthrough therapy has been granted. The plan should include the proposed timing and frequency of future meetings and teleconferences, information requests, and other submissions to the IND related to the breakthrough therapy product development program

- I. The regulatory project manager (RPM), review team members, their immediate supervisors (laboratory or branch chiefs), and senior managers will follow the processes and procedures outlined in the *Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants for PDUFA Products* and *SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products* when scheduling and conducting meetings for breakthrough therapy-designated products.
- J. The development program for a breakthrough therapy-designated product is expected to be expedited as compared to that of a non-breakthrough therapy-designated product; therefore, IND milestone meetings will likely take place in an accelerated timeframe relevant to the accelerated product development timeline. For example, the following topics should be discussed with the sponsor during the EOP2 milestone meeting if possible, or at an agreed upon time point prior to the pre-NDA/pre-BLA meeting:
 - Inspection and manufacturing facility(ies) considerations, and
 - Postmarketing study or clinical trial plans.
- K. The review team will solicit input from senior managers and experienced reviewers in all relevant disciplines when necessary.
- L. Review team members and supervisors will follow CBER's Managed Review Process when reviewing IND submissions for breakthrough therapy-designated products. These principles and practices include adhering to review timelines for IND amendments, documentation, and supervisory concurrence, when necessary, of written reviews.
- M. Review team members and supervisors will follow the principles set forth in the *Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development*.
- N. IND amendments related to the development of breakthrough therapy-designated products, e.g., clinical trial, chemistry, manufacturing, and controls (CMC), or pharmacology/toxicology information, will receive expedited review and a prompt response to the sponsor. The review timeline for these amendments will generally be 60 days, unless a different timeline is indicated by statute or regulation (e.g., response to clinical hold) or user fee agreements.
- O. Periodic reviews will be conducted at least annually to assess the continued adequacy of the proposed overall product development plan to facilitate an expedited development program.
- P. When the criteria for breakthrough therapy designation are no longer met CBER may choose to rescind the breakthrough therapy designation. CBER will notify the sponsor in writing of their intent to rescind the breakthrough

therapy designation. The Intent to Rescind Breakthrough Therapy Designation letter will include the criteria for making such a determination and provide the sponsor with an opportunity to submit additional data and justification to support the continuing breakthrough therapy designation and/or to request a meeting with CBER to discuss the breakthrough therapy designation for the product.

1. If the sponsor does not submit additional justification or supportive data or request a meeting within 60 days of receipt of the *Intent to Rescind Breakthrough Therapy Designation* letter, CBER may rescind the breakthrough therapy designation.
 2. After review of additional information and meeting with the sponsor (if applicable), if CBER decides to rescind the breakthrough therapy designation, CBER will notify the sponsor in writing and will provide the rationale for this decision in the *Rescind Breakthrough Therapy Designation* letter. The rescinding of a breakthrough therapy designation does not mean that the product is not promising or that the product may not receive marketing approval. It means that the criteria for breakthrough therapy designation are no longer met.
- Q.** Marketing applications for breakthrough therapy-designated products may be eligible for priority review, accelerated approval and/or rolling review as described in the Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics. As stated in Appendix A of the guidance, rolling review should be discussed at the pre-BLA/NDA meeting (or sooner). Generally, a complete portion (i.e., an eCTD module), such as the entire CMC section, toxicology section or clinical section should be submitted, unless submission of an incomplete module was agreed upon. If rolling review is agreed upon, ideally, all portions of the application should be submitted no more than one year after the initial portion. Any review of portions already submitted may be suspended because our ability to conduct a meaningful review may be inhibited without the missing information. Efficacy supplements submitted for products with an indication that has breakthrough therapy designation are eligible for rolling review.

VI. Responsibilities

Note: Refer also to *SOPP 8217: Administrative Processing and Review Management Procedures for Investigational New Drug Applications* for additional general responsibilities for IND review.

A. Review Team Members

1. Participates in all review team meetings
2. Participates in the CBER-sponsor initial comprehensive meeting after breakthrough therapy has been granted, and subsequent CBER-sponsor

meetings when issues regarding their assigned areas of responsibility are being discussed

3. Performs periodic summary reviews of the breakthrough therapy product development program related to their assigned areas of responsibility
4. Consults with subject matter experts outside of the assigned review team, when necessary
5. Meets regularly with their supervisor to provide updates on the status and progress of the breakthrough therapy product development program
6. Identifies issues with the breakthrough therapy product development program, proposes potential solutions when appropriate, and communicates issues to their supervisor, and the RPM as soon as possible

B. RPM

1. Stays up-to-date on the status of the breakthrough therapy product development program, including planned and on-going clinical trials, product development plans, and discipline-specific information requests, meetings, and teleconferences with the sponsor to facilitate an efficient review of the development program.
2. Serves as the primary point of contact (scientific liaison) between the review team and the sponsor.
3. Ensures the review team is kept up to date on all aspects of the product development program.
4. Schedules and facilitates all review team and CBER-sponsor meetings (or designates a qualified staff member to facilitate, if unable to attend), working to ensure that review team and CBER-sponsor meetings for breakthrough therapy-designated products are prioritized on the calendar.
5. Communicates with the appropriate point of contact (e.g., RPMs) in other CBER offices and FDA Centers to exchange information, coordinate efforts, and request consults when the review team requires additional scientific expertise

C. Discipline Branch and Laboratory Chiefs

1. Meets with the discipline reviewer to stay up-to-date on the status and progress of the breakthrough therapy product development program
2. Ensures the quality and consistency of discipline reviews

3. Attends the initial CBER-sponsor comprehensive multidisciplinary breakthrough therapy meeting, critical IND milestone meetings, and subsequent review team and CBER-sponsor meetings when issues regarding their areas of responsibility are being discussed
4. Keeps the discipline Division Director up-to-date regarding the status of the breakthrough therapy product development program

D. Discipline Division Director

1. Attends (or designates the Deputy Division Director to attend, if unable to attend) the initial CBER-sponsor comprehensive multidisciplinary breakthrough therapy meeting, critical IND milestone meetings, and, any subsequent CBER-sponsor meetings, e.g., Intent to Rescind meetings, when issues regarding their areas of responsibility are being discussed
2. Meets regularly with the discipline-specific branch or laboratory chief to keep apprised of the breakthrough therapy product development status
3. Keeps their Office Director up-to-date on the status of breakthrough therapy product development programs within the division
4. Resolves differences in scientific opinions between disciplines, as needed

E. Product Office Director

1. Stays informed of the status of breakthrough therapy product development programs within the Office through the Division Directors
2. Attends the initial comprehensive multidisciplinary breakthrough therapy meeting, critical IND milestone meetings, and review team and CBER-sponsor Intent to Rescind meetings, as appropriate
3. Addresses specific issues or policy questions brought to his or her attention through the discipline, or division management chain
4. Consults with the Discipline Office Directors, the Associate Director for Review Management (ADRM), the Center Director and appropriate groups as necessary regarding breakthrough therapy product development issues, including rescinding breakthrough therapy designation

F. Office of Regulatory Operations (ORO), Division of Informatics (DI), Regulatory Information Branch (RIB)

1. Characterizes amendments as received.
2. Prepares Performance Reports

VII. Procedures

A. Request for Preliminary Advice of Whether a Request for Breakthrough Therapy Designation is Appropriate (Refer to internal CBER Job Aid *JA 851.01: Preliminary Breakthrough Therapy Designation Request Advice* for detailed procedures.)

1. Receive request for preliminary breakthrough therapy designation advice **[RPM]** and characterize request in the appropriate regulatory system **[RIB, RPM]**.
2. Provide requestor with Template *T 815.05: Preliminary Breakthrough Therapy Designation Request Advice Template*. **[RPM]**
3. Upon receipt of information, characterize request in the appropriate regulatory system **[RIB and/or RPM]** and ensure review team receives the information. **[RPM]**
4. Schedule a brief (e.g., 15 to 30 minutes) teleconference with the sponsor as quickly as resources allow. **[RPM]**
Note: There is no statutory review clock associated with this submission
5. Review information and determine whether: **[Discipline Reviewer(s)]**
 - It is appropriate for the sponsor to submit a Breakthrough Therapy Designation Request;
 - It is premature for a Breakthrough Therapy Designation Request;
 - The Product/Indication does not meet breakthrough criteria; or
 - A decision regarding the Breakthrough Therapy Designation Request cannot be made as additional information is necessary.
 - a. If additional information is needed, contact sponsor as needed
 - b. Participate in internal meeting, if needed prior to teleconference with sponsor.
6. Participate in teleconference with the requestor. **[RPM, Clinical Reviewer, Clinical Branch/Laboratory Chief]**
7. Document discussion using template *T 815.06: Memorandum of Teleconference -Preliminary Breakthrough Therapy Designation Request Advice*, enter into the appropriate regulatory system, and upload to CBER's Electronic Repository (CER). **[RPM]**

B. Request for Breakthrough Therapy Designation (Refer to CBER Internal Job Aid, *JA 851.03: Management of Breakthrough Therapy: Review of and Response to Requests for Breakthrough Therapy Designation, Reconsideration, and Withdrawal* for detailed procedures.)

1. Receive, digitally image (if applicable), process and load into the CER. Notify the appropriate Office through the load notification. **[DCC]**
2. Characterize the request in the appropriate regulatory system. **[RIB]**
3. Check to ensure that the request is not submitted to a pre-IND file, to an IND on clinical hold, or to an inactive IND. **[RPM]**
 - a. If submitted to a pre-IND file, inform sponsor via telecon that a request for breakthrough therapy designation cannot be made prior to the submission of an IND.
 - b. If the IND is on clinical hold, deny the designation request using the appropriate letter template.
 - c. If the IND is inactive, deny the designation request using the appropriate letter template.
 - d. If the IND is on partial hold the review team will consider the specific circumstances of the partial hold and whether this affects the review of the request.
4. Notify upper management including Center Director, Center Deputy Director, Associate Director for Review Management (ADRM) and Product Office RPM Director (if applicable) by email (weekly report) that a request for breakthrough therapy designation has been received. **[RIB]**
5. Verify that the designation request is:
 - a. Specific to a single indication of a single product; if multiple, inform sponsor that additional designation requests would be needed, and/or
 - b. Specific to a single type of designation. If sponsor requested another type of designation (i.e., RMAT, fast track) within the same amendment, inform sponsor that additional designation requests would be needed, and
 - c. Document communication in the appropriate regulatory system and ensure the amendment characterization only reflects the single request. **[RPM]**
6. Verify that the request has been characterized accurately in the appropriate system, update, if necessary, and inform RIB of any changes that have been made. **[RPM]**

7. Route the request to the IND review team members and alert office leadership that breakthrough therapy designation request has been received and provide the review timeline. **[RPM]**
8. Send acknowledgement of receipt of breakthrough therapy designation request letter to sponsor no later than 14 calendar days after CBER receipt. **[RPM]**
9. Brief Office Director (OD) or designee, schedule a meeting if necessary. **[RPM]**
10. Confirm with clinical team if an Oncology Center of Excellence (OCE) presentation is needed (only for oncology or hematology oncology indications). **[OTAT RPM]**
11. Review the request for designation and make a decision based on the criteria in the *Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics* and the available reviewer template *T843.03 CBER Breakthrough Therapy Designation Determination Review*. **[Review Team members]**
 - a. Determine if consults are needed and if inter-center, follow *SOPP 8001.5: Inter-Center Consultative Review Process*.
12. Send letter to sponsor denying or granting designation within 60 days of receipt of request and upload the communication into the CER. **[RPM]**
13. If breakthrough therapy designation is granted, provide guidance to the sponsor describing content of initial comprehensive meeting as described in [Appendix A](#).

C. Initial Comprehensive Multidisciplinary Meeting with Sponsor

1. Receive and route sponsor request for initial comprehensive multidisciplinary meeting to all review team members. **[RPM]**
 - a. The sponsor should be encouraged to hold the meeting as soon as possible; however, the timing of the meeting may depend on where the sponsor is in their product development program when breakthrough therapy-designation is granted.
 - b. Contact the sponsor to follow-up on their proposed timing for the meeting if the meeting has not been held within six months of the breakthrough therapy designation to determine status.
2. Schedule pre-meeting and sponsor meeting. **[RPM]**

- a. The initial comprehensive meeting may be an IND milestone meeting, e.g., End of Phase (EOP) 2, or pre-BLA/pre-NDA meeting.
 - b. A combined milestone/initial comprehensive multidisciplinary meeting should use the procedures and processes for the milestone meeting. The attendees for a combined meeting must include all required participants for the initial comprehensive meeting.
3. Receive and route meeting package. **[RPM]** The meeting package should include an overall high-level coordinated product development plan including, as a minimum:
 - a. Regulatory issues, such as expanded access plans, and plans for submission of a proprietary name request
 - b. Current and planned clinical trials and data analysis, including early plans to mitigate or minimize risk, and the proposed pediatric development plan
 - c. Nonclinical pharmacology, pharmacokinetics, and toxicology information
 - d. CMC and facility information
4. Attend the pre-meeting for the initial comprehensive meeting with the sponsor. **[RPM, Review Team Members, Branch/Laboratory Chiefs, Division Directors, Office Director]**
5. Attend initial comprehensive multidisciplinary meeting. **[RPM, Review Team Members, Branch/Laboratory Chiefs, Division Directors, Office Director]**
 - a. Provide guidance and advice specific to the product and reach agreement on a planned development program.
 - b. Discussion topics will depend on the therapeutic area, development phase, and specific development program issues of the proposed product and indication, and could include:
 - General and/or regulatory plans
 - Planned clinical trials and endpoints
 - Plans for expediting the manufacturing development strategy
 - Studies that potentially could be completed after approval

Refer to Appendix A: Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting for a detailed list of possible discussion topics

- c. Discuss a communication plan with the sponsor. The plan should include the proposed timing and frequency of future meetings and teleconferences, information requests and other submissions to the IND related to the breakthrough therapy product development program.
 - i. Teleconferences and secure emails, as appropriate, may serve as tools for focused discussions, rapid information exchange, and issue resolution on procedural, regulatory, or scientific matters regarding the nonclinical and clinical development of the breakthrough therapy-designated product.
 - ii. CBER will communicate frequently with the sponsor outside of critical milestone meetings to provide intensive guidance on efficient product development. These communications likely will be discipline-focused to discuss specific development program data, milestones, and issues.
 - iii. IND amendments related to critical issues in the development of breakthrough therapy -designated products will generally be reviewed within 60 days, unless a different timeline is indicated by statute, regulation (e.g., response to clinical hold), or user fee agreements.
 - iv. CBER will follow the principles set forth in the *Guidance for Industry and Review Staff: Best Practices for Communication between IND Sponsors and FDA during Drug Development*.
6. Document meeting per established procedures. See *SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products*. **[RPM, Review Team Members]**

D. CBER Periodic Summary Review of Breakthrough Therapy-Designated Product Development Programs

1. Perform a periodic summary review to assess the continued adequacy of the breakthrough therapy-designated product to facilitate an expedited development program and timeline. Regulatory template *T 815.01: Breakthrough Therapy Periodic Review Report* may be used for documentation. **[Review Team Members]**

- a. The Periodic Review Report should be a continuous document updated during the life cycle of the breakthrough therapy product development program.
- b. The normal review of IND amendments received since the previous periodic review may form the basis of the Periodic Review Report. The Periodic Review Report should succinctly summarize:
 - i. Status of product development for each discipline;
 - ii. Upcoming milestone meetings, if applicable;
 - iii. The status of the clinical plan agreed upon during the initial comprehensive meeting, e.g., has any agreed upon clinical trial(s) started;
 - iv. Outstanding Information Requests (IRs);
 - v. Key findings and substantive issues and/or major deficiencies identified;
 - vi. Potential impact the substantive issues and/or major deficiencies might have on the product development program, and plans for addressing them, e.g., product scale up and/or facility issues; and
 - vii. Whether the product development program continues to meet the criteria for breakthrough therapy designation **[Clinical Reviewer]**

E. Intent to Rescind a Breakthrough Therapy Designation

1. Determine that the breakthrough therapy product development program no longer meets the criteria for breakthrough therapy designation. **[Review Team]**
2. Document rationale/findings using *T 815.03: Intent to Rescind Fast Track, Breakthrough Therapy, or RMAT Designation Memo* and distribute to the RPM and review team members. **[Appropriate Discipline Reviewer]**
3. Route memo through immediate supervisor to Division Director for concurrence. **[Appropriate Discipline Reviewer]**
4. Return signed memo to the RPM. **[Division Director]**
5. Notify senior management (the ADRM and the Deputy Center Director) that the product development program no longer meets the criteria for breakthrough therapy designation and an *Intent to Rescind Breakthrough Therapy Designation* letter will be issued to the sponsor. **[Review Team, Division Director]**

6. Draft Intent to Rescind Breakthrough Therapy Designation letter. **[RPM]**
 7. Route draft letter to the review team members, branch/laboratory chiefs, and senior management. **[RPM]**
 8. Review letter and provide clearance to RPM. **[Review Team Members, Branch/Laboratory Chiefs, Senior Management]**
 9. Finalize letter and circulate for final concurrence and sign-off. **[RPM]**
 10. Sign Intent to Rescind Breakthrough Therapy Designation letter. **[Division Director]**
 11. Issue letter to sponsor and enter communication into the appropriate system and upload to the CER. **[RPM]**
- F. Sponsor's Response to Intent to Rescind Breakthrough Therapy Designation letter**
1. Receive sponsor's response and route to review team. **[RPM]**
 2. Review additional information, data and/or rationale provided in the sponsor's response. **[Review Team Members]**
 3. If the sponsor's response includes a request for a meeting, schedule multidisciplinary internal meeting and sponsor meeting. **[RPM]**
 4. Attend pre-meeting and sponsor meeting. **[Review Team Members, Branch/Laboratory Chiefs (Discipline Division Director(s))]** Discussion topics should include:
 - a. The additional information, data and/or rationale for maintaining breakthrough therapy designation provided in the sponsor's response.
 - b. Explanation of why the breakthrough therapy designation should be maintained or rescinded.
 - c. If recommendation is to maintain breakthrough therapy designation, plans for a path forward for the development of the product.
 5. Make decision to maintain or rescind breakthrough therapy designation. **[Review Team, Division Directors (Office Director, ADRM)]**
- G. Maintaining Breakthrough Therapy Designation**
1. Create review update memo to document decision to maintain breakthrough therapy designation using *T 815.02: Breakthrough Therapy Product Development Program Meeting/Review Update* and send to the RPM. **[Appropriate Discipline Reviewer]**

2. Distribute review update memo to the review team and supervisors, enter into the appropriate system and upload to the CER. **[RPM]**
3. Schedule a teleconference with sponsor to inform the sponsor of CBER's decision to maintain the breakthrough therapy designation and discuss plans for a path forward for development of the product. **[RPM]**
4. Participate in the teleconference. **[Review Team Member(s), RPM]**
 - a. Review team members should participate based upon the discipline specific topics to be discussed
5. Document teleconference in the appropriate system and upload to the CER. **[RPM]**

H. Rescinding Breakthrough Therapy Designation

1. If the sponsor does not submit additional justification or supportive data or request a meeting within 60 days of receipt of the Intent to Rescind Breakthrough Therapy Designation letter, complete *T 815.04: Rescinding Fast Track, Breakthrough Therapy, or RMAT Designation Review Memo*. Route through Immediate Supervisor to Product Office Division Director for sign off. **[Appropriate Discipline Reviewer]**
2. Return signed memo to the RPM. **[Product Office Division Director]**
3. Notify the entire review team, immediate supervisors, senior management, the ADRM and Deputy Center Director that a *Rescind Breakthrough Therapy Designation* letter will be issued to the sponsor. **[RPM]**
4. Draft Rescind Breakthrough Therapy Designation letter. **[RPM]**
5. Route draft letter to the review team members, branch/laboratory chiefs, and senior management. **[RPM]**
6. Review letter and provide clearance to RPM. **[Review Team Members, Branch/Laboratory Chiefs, Senior Management]**
7. Finalize letter and circulate for final concurrence and sign-off. **[RPM]**
8. Sign Rescind Breakthrough Therapy Designation letter. **[Product Office Director]**
9. Issue letter to sponsor and enter communication into the appropriate system and upload to the CER. **[RPM]**

I. Request for Withdrawal

1. Receive request for withdrawal of breakthrough therapy-designation or breakthrough therapy-designation request and forward to the RPM and RIB. **[DCC]**
2. Characterize the request in the appropriate system. **[RIB]**
3. Notify upper management including Center Director, Center Deputy Director, ADRM and Product Office RPM by e-mail that request for withdrawal has been received. **[RIB]**
4. Verify that the request has been characterized accurately, and update/correct as needed in the appropriate regulatory system. **[RPM]**
5. Route the request to the IND review team members. **[RPM]**
6. Alert IND review team members and office leadership that a request for withdrawal has been received. **[RPM]**
7. Acknowledge request for withdrawal by issuing Withdrawal – Breakthrough Therapy Request letter no later than 14 calendar days after CBER receipt. **[RPM]**
8. Enter communication into appropriate regulatory system and upload letter into the CER. **[RPM]**

VIII. Appendix

- A. [Appendix A](#): Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting with the Sponsor

IX. References

- A. References below are CBER internal:

1. CBER Letter Template SharePoint Online Site
2. JA 851:01: Preliminary Breakthrough Therapy Designation Request Advice
3. JA 851.03: Management of Breakthrough Therapy: Review of and Response to Requests for Breakthrough Therapy Designation, Reconsideration, and Withdrawal
4. T 843.03 CBER Breakthrough Therapy Designation Determination Review
5. T 815.01: Breakthrough Therapy Periodic Review Report

6. T 815.02: Breakthrough Therapy Product Development Program Meeting Summary/Review Update
 7. T 815.03: Intent to Rescind Fast Track, Breakthrough Therapy, or RMAT Designation Memo
 8. T 815.04: Rescinding Fast Track, Breakthrough Therapy, or RMAT Designation Review Memo
 9. T 815.05: Preliminary Breakthrough Therapy Designation Request Advice Template
 10. T 815.06: Memorandum of Teleconference: Preliminary Breakthrough Therapy Designation Request Advice
 11. SOPP 8001.5: Inter-Center Consult Review Process
- B. References below can be found on the Internet:**
1. [Food and Drug Administration Safety and Innovation Act \(FDASIA\)](#)
 2. [Frequently Asked Questions: Breakthrough Therapy](#)
 3. [Fact Sheet: Breakthrough Therapies](#)
 4. [Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products](#)
 5. [Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics](#)
 6. [Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development](#)
 7. [Guidance for Industry and Food and Drug Administration Staff: Breakthrough Devices Program](#)
 8. [Draft Guidance for Industry: Considerations for Rescinding Breakthrough Therapy Designation](#)
 9. [SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products](#)
 10. [SOPP 8217: Administrative Processing and Review Management Procedures for Investigational New Drug Applications](#)

X. History

Written/Revised	Approved By	Approval Date	Version Number	Comments
Monser	N/A – Technical Update	August 1, 2023	6	Corrected typos in preliminary advice section
Monser	Katie Rivers Acting Chief, RABOB/DROP/ ORO	February 23, 2023	5	Update to signatory authority for intent to rescind letter and for 2023 CBER reorganization.
Monser	Darlene Martin, MS, PMP ORO/DROP Director (Acting)	October 17, 2022	4	Revised to current procedures and to include preliminary advice requests, designation requests and withdrawals
Monser	N/A	February 3, 2022	3	Technical update to re-associate Appendix A and update to current format/font.
Monser	N/A	December 11, 2020	2	Technical Update for retirement of EDR and replacement of “database” with “system”
KSchneider	Christopher Joneckis, Ph.D.	June 7, 2016	1	First version of this SOPP

Appendix A: Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting with the Sponsor

Note: The specific topics for discussion will depend on the product, therapeutic area, proposed indication, development phase, and specific development program issues.

The communication plan between the sponsor and the review team must be discussed and documented in the meeting summary using *T820.06: Meeting Summary Template*.

General and/or Regulatory

1. The planned target date for BLA/NDA submission, including plans for rolling review
2. The specific indication that studies are intended to support
3. Other indications in development
4. Expanded access plans, including the intent to communicate these plans publicly
5. Plans to seek accelerated approval
6. Regulatory status with non-U.S. regulatory agencies
7. Plans to defer or waive specific studies (e.g., pediatric studies), including those that may be conducted as postmarketing requirements/postmarketing commitments
8. Critical aspects of proposed studies, including enrichment designs, non-inferiority designs, historical controls, and any planned novel approaches
9. Plans for submission of a proprietary name request
10. If a biologic/device combination product, the device development information, and plan
11. If the use of the product will require a diagnostic test, the in vitro diagnostic development plan with the Center for Devices and Radiological Health (CDRH) or Center for Drug Evaluation and Research (CDER) as appropriate
12. The proposed communication plan for managing interactions between CBER and the sponsor, including the timing and format of these interactions

Clinical and Statistical

1. Existing and planned clinical sites and accrual data
2. Efficacy:
 - a. The status of all clinical trials and topline summary results
 - b. The preliminary evidence of effectiveness
 - c. The planned or completed clinical trials intended to support effectiveness including:
 - i. The overall trial design, the population to be studied, trial size, proposed indications, endpoints, power, plans for interim analyses, plans for resizing of trials or any other adaptation, type I error control, and expected initiation and completion dates.
 - ii. The validity of the outcomes and endpoints. If using patient-reported outcomes or surrogate endpoints, support for those endpoints or plans to support or validate them, as necessary.
3. Safety:
 - a. Potential safety issues identified in nonclinical studies and early clinical trials
 - b. Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, reproductive and developmental, and immunogenicity safety profiles
 - c. The clinical trial safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for postmarketing drug safety and surveillance (pharmacovigilance)
 - d. The proposed size of the safety population
 - e. The plan or the need for long-term safety studies or trials
 - i. Preapproval
 - ii. Post-approval
 - f. The plans to mitigate or minimize risk, proposed risk evaluation and mitigation strategies, if needed
4. The proposed pediatric development plan with outlines and synopses of additional studies

Clinical Pharmacology and Pharmacokinetics

1. The justification for all dose selections, including number of doses and dose intervals and a discussion of all clinical trials that will provide dose-response information
2. Specific populations:
 - a. The dose, trial design, efficacy endpoints, size and composition of the population, and additional safety trials for populations such as:
 - i. Elderly patients
 - ii. Pediatric patients
 - iii. Hepatically and renally impaired patients
3. The clinical pharmacology, pharmacodynamic, and pharmacokinetic trials: completed, ongoing, planned, and requests for deferral
 - a. Immunogenicity assessments
 - b. Dosing information from pharmacodynamics studies
 - i. Single ascending dose
 - ii. Multiple ascending dose
 - iii. Dose response study
 - c. Food-effect
 - d. Drug-drug interactions (DDI)
 - e. Thorough QT/QTc
 - f. Pharmacokinetic studies in patients with renal or hepatic dysfunction
 - g. Pharmacogenomics
4. The plans for an *in vivo* bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation
5. The plans for conducting population pharmacokinetics, exposure-response modeling, and simulation analyses

6. The plans to describe dose modifications in labeling based on DDI, age, organ impairment, among others

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

1. The nonclinical studies completed, ongoing, and planned, including the number and sex of animals per dose, doses, route of administration, toxicities, duration of study, and study results.
2. For planned studies, the timelines for initiation and submission of study reports. Examples of such studies include:
 - a. Subacute and chronic toxicology and associated toxicokinetics
 - b. Genetic toxicology
 - c. Reproductive and developmental toxicology
 - d. Carcinogenicity studies
 - e. Animal models of disease and pharmacokinetic parameters associated with efficacy
 - f. Evidence of mechanism of action
 - g. Absorption, distribution, metabolism, and excretion
 - h. Safety pharmacology, where appropriate

Chemistry, Manufacturing, and Controls

1. Drug product:
 - a. The dosage form
 - b. The formulation description
 - c. Administration instructions, delivery systems (e.g., vials, prefilled syringes) proposed draft packaging, and disposal instructions
 - d. Critical quality attributes
 - e. The control and stability strategies
 - f. The proposed shelf life and required stability studies

2. Drug substance:
 - a. Characterization
 - b. Critical quality attributes
 - c. The control and stability strategies
 - d. The proposed shelf life or retest period and required stability studies
3. Proposed commercial processes:
 - a. The manufacturing process, in-process controls, scale-up plans
 - b. A comparison of the proposed commercial manufacturing process to the clinical manufacturing process
 - c. Comparability of lots used in clinical trials and commercial lots or a plan to establish analytical comparability
 - d. The current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines
 - e. The current release and stability testing site(s) and proposed commercial testing site(s), if different
 - f. The anticipated market demand at launch
4. Proposed validation approaches:
 - a. The drug substance and drug product manufacturing process
 - b. Microbial control and sterility assurance
 - c. Viral clearance
 - d. The analytical methods