

## SOPP 8212: Management of Breakthrough Therapy-Designated Products: Sponsor Interactions and Status Assessment Including Rescinding

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#### I. Purpose:

This Standard Operating Policy and Procedure (SOPP) provides guidance to the 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* from the time a breakthrough therapy designation has been granted until a marketing application has been submitted.

#### II. Scope:

- A. This SOPP includes the procedures for CBER-sponsor meetings and other communications, CBER periodic summary reviews of breakthrough therapy-designated biologic or drug product (product) development programs, and rescinding a breakthrough therapy designation under an Investigational New Drug (IND) submission.
- B. This SOPP does not cover the review of breakthrough therapy designation requests. Please see *JA 851.03: Management of Breakthrough Therapy:*

*Review of and Response to Requests for Breakthrough Therapy Designation, Reconsideration, and Withdrawal* for additional information.

- C. This SOPP does not address the specific content of scientific reviews.
- D. This SOPP does not cover the review of new 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 Agency 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 committee to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor;
  - 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. The regulatory project manager (RPM), review committee members, their immediate supervisors (laboratory or branch chiefs), and senior managers will follow the processes and procedures outlined in the *Guidance for Industry: Formal Meetings with Between the FDA and Sponsors or Applicants* 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.
- B. The review committee will establish a communication plan with the sponsor 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.
- C. 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.
- D. Review committee meetings and CBER-sponsor meetings will be facilitated by the RPM and led by the Scientific Liaison.
- E. The review committee, led by the Scientific Liaison, will solicit input from senior managers and experienced reviewers in all relevant disciplines when necessary.
- F. Review committee 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.
- G.** Review committee 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*.
  - H.** 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 be 60 days, unless a different timeline is indicated by statute or regulation (e.g., response to clinical hold) or by the Scientific Liaison with supervisory concurrence as appropriate.
  - I.** Whenever possible, CBER will target responding to sponsor inquiries (other than amendments) as soon as feasible, and for complex inquiries not more than 60 days from receipt. It is equally important to communicate to sponsors that they respond completely and promptly to CBER requests.
  - J.** The review committee will perform a periodic summary review on the status of the breakthrough therapy-designated product development program every six to twelve months, or at a greater frequency agreed upon at the first breakthrough therapy review committee meeting, to assess the continued adequacy of the proposed overall product development plan to facilitate an expedited development program and timeline.
  - K.** The frequency of the periodic summary review will depend on various factors, such as the stage of the product development program, the therapeutic area of the product, and the types of proposed and ongoing clinical trials. The frequency of the periodic summary review may be adjusted as the development program progresses.
  - L.** 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.
  - M.** 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.

- N.** If after review of additional information and meeting with the sponsor, if applicable, 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.

## **VI. Responsibilities**

### **A. Review Committee Members**

1. Participates in all review committee 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 committee, when necessary.
5. Meets regularly with their supervisor and the Scientific Liaison 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, Scientific Liaison, and the RPM as soon as possible.

### **B. RPM**

1. Collaborates with the Scientific Liaison on a regular basis to manage the day-to-day aspects of the IND for a breakthrough therapy-designated product.
2. Serves as the primary point of contact with the sponsor.
3. 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.

4. Ensures the review committee is kept up to date on all aspects, except scientific issues, of the product development program.
5. Schedules and facilitates all review committee and CBER-sponsor meetings (or designates a qualified staff member to facilitate, if unable to attend), working to ensure that review committee and CBER-sponsor meetings for breakthrough therapy-designated products are prioritized on the calendar.
6. 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 committee requires additional scientific expertise.

**C. Scientific Liaison:**

1. Serves as the lead reviewer of the review committee and ensures the review committee is kept up to date on scientific aspects of the product's breakthrough therapy development program.
2. Acts as the liaison between all members of the review committee for coordinated internal interactions.
3. Leads all review committee and CBER-sponsor meetings related to the development of breakthrough therapy-designated products.
4. Compiles the review committee's periodic review reports and determines whether a review committee meeting, including senior management when appropriate, is needed to discuss the continued adequacy of the proposed overall product development plan.
5. Prepares the Intent to Rescind Breakthrough Therapy Designation Memo when a product no longer meets the criteria for breakthrough therapy designation.
6. Prepares the Rescinding Breakthrough Therapy Designation Review Memo prior to issuance of a Rescind Breakthrough Therapy Designation letter.

**D. Discipline Branch and Laboratory Chiefs:**

1. Meets regularly with the discipline review committee member and the Scientific Liaison 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 committee 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.

**E. 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.

**F. 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 committee 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.

## VII. Procedures

### A. First Breakthrough Therapy Review Committee Meeting

1. Schedule first breakthrough therapy review committee meeting after the *Grant Breakthrough Therapy Designation* letter has been issued to the sponsor. **[RPM]** Note: This meeting should take place no later than three weeks after breakthrough therapy designation has been granted.
2. Attend first breakthrough therapy review committee meeting. **[RPM, Review Committee Members, Discipline Branch/Laboratory Chiefs]** Discussion topics should include:
  - a. Product development phase and any product, clinical, or pre-clinical specific considerations anticipated.
  - b. The expedited review process for a breakthrough therapy designated product and expectations of the review committee regarding the review of breakthrough therapy related IND amendments.
  - c. CBER's proposed communication plan with the sponsor during the breakthrough therapy development period.
  - d. CBER's commitment to engage senior management in the development process.
  - e. The frequency of periodic summary reviews.
  - f. The proposed timing of future review committee meetings. **Note:** The timing and intervals for these meetings will depend on the stage of development of the breakthrough therapy product and the pace of IND amendments, as well as internal resource availability and constraints. The following are suggested time points for the review committee to meet:
    - i. After the review of certain IND amendments (i.e., amendments that contain clinical trial data), to discuss specific breakthrough therapy development program issues and plans to address these issues.
    - ii. After review committee members have completed their periodic summary review of a sponsor's breakthrough therapy product development program.
    - iii. When the product development program may no longer meet the criteria for breakthrough therapy designation to discuss the appropriateness of sending an *Intent to Rescind Breakthrough*

*Therapy Designation* letter to the sponsor (if not previously discussed during the periodic summary review meeting).

3. Document meeting; send for review to review committee members, finalize, enter into the appropriate system and upload through CBER Connect. **[RPM]**

## **B. Initial Comprehensive Multidisciplinary Meeting with Sponsor**

1. Receive and route sponsor request for initial comprehensive multidisciplinary meeting to all review committee 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.
    - i. Schedule pre-meeting and sponsor meeting using *R 851.01: Attendee Table for Breakthrough Therapy Meetings during the IND Phase* **[RPM]**
  - c. The initial comprehensive meeting may be an IND milestone meeting, e.g., End of Phase (EOP) 2, or pre-BLA/pre-NDA meeting.
  - d. 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.
2. 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.

3. Attend the pre-meeting for the initial comprehensive meeting with the sponsor [**RPM, Review Committee Members, Branch/Laboratory Chiefs, Division Directors**]
4. Attend initial comprehensive multidisciplinary meeting [**RPM, Review Committee Members, Branch/Laboratory Chiefs, Division Directors**]
  - 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:
    - i. General and/or regulatory plans.
    - ii. Planned clinical trials and endpoints.
    - iii. Plans for expediting the manufacturing development strategy.
    - iv. Studies that potentially could be completed after approval.
    - v. Refer to [Appendix A](#): *Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting* for a detailed list of possible discussion topics.
  - c. Establish 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. CBER will generally respond to information requests within 60 days or less if resources/circumstances (less complex inquiries, straightforward development questions, etc.) allow.
    - ii. 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.
    - iii. CBER will meet frequently with the sponsor outside of critical milestone meetings to provide intensive guidance on efficient product development. These meetings likely will be discipline-

focused to discuss specific development program data, milestones, and issues.

- 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*.

### C. Critical IND Milestone Meetings with Sponsors

1. Discuss with sponsor and agree upon the discipline-specific information to be covered at the milestone meeting. **[RPM, Scientific Liaison]**
2. Receive and route sponsor request for IND milestone meeting to all review committee members. **[RPM]**
3. Schedule pre-meeting and sponsor meeting. **[RPM]**
  - a. If necessary, separate discipline meetings, e.g., a meeting to discuss clinical/statistical issues, and a meeting to discuss chemistry, manufacturing and controls (CMC) and facility issues, may be held to ensure enough time to adequately cover the discussion topics
4. Attend pre-meeting and critical IND milestone meeting **[RPM, Review Committee Members, Branch/Lab Chiefs, Division Director(s)]**
  - a. Provide specific and targeted advice to sponsors about subsequent development and regulatory requirements, e.g., pediatric study plans must be submitted with 60 days after the EOP2 meeting.
  - b. Due to the accelerated pace of review of the breakthrough therapy-designated product, 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.
    - i. Proprietary name plans.
    - ii. Inspection and manufacturing facility(ies) considerations.
    - iii. Postmarketing study or clinical trial plans.

### D. Documenting CBER-Sponsor Meetings

1. Capture all substantive discussions and agreements with the sponsor, including the communication plan from the initial comprehensive meeting,

in a meeting summary following established procedures and timelines using regulatory template *T 820.06: Meeting Summary*. **[RPM]**

2. Circulate draft meeting summary to all CBER attendees. **[RPM]**
3. Review content of the draft meeting summary. **[CBER Attendees]**
4. Finalize meeting summary, issue to sponsor, and enter communication into the appropriate system and upload through CBER Connect. **[RPM]**

#### **E. CBER Periodic Summary Review of Breakthrough Therapy-Designated Product Development Programs**

1. Schedule a periodic summary review committee meeting to review the status of the breakthrough therapy product development program using *R 851.01: Attendee Table for Breakthrough Therapy Meetings during the IND Phase*. **[RPM]**
2. Perform a periodic summary review using regulatory template *T 815.01: Breakthrough Therapy Periodic Review Report* to assess the continued adequacy of the breakthrough therapy-designated product to facilitate an expedited development program and timeline. **[Review Committee 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.
  - vii. Whether the product development program continues to meet the criteria for breakthrough therapy designation. **[Clinical Reviewer]**
3. Provide the Periodic Review Report to the RPM and Scientific Liaison no later than four business days prior to the meeting **[Review Committee Members]**
  4. Review Periodic Review Reports and make decision to hold or cancel meeting **[Scientific Liaison, RPM]**
    - a. If the decision is made to cancel the meeting:
      - i. Notify the RPM that the periodic summary review meeting should be cancelled if the determination was made that there were no significant changes to the breakthrough therapy product development program since the previous periodic summary review and the product development program continues to meet the criteria for breakthrough therapy designation. **[Scientific Liaison]**  
**Note:** This decision will be made in consultation with his/her immediate supervisor and Division Director, as appropriate
      - ii. Send cancellation notice to all attendees. **[RPM]**
      - iii. Prepare a memo using *T 815.02: Breakthrough Therapy Product Development Program Meeting Summary/Review Update*, that briefly summarizes the status of the product development program and send to the RPM. **[Scientific Liaison]**
      - iv. Distribute summary memo to the review committee and supervisors, enter into the appropriate system and upload through CBER Connect. **[RPM]**
    - c. If the decision is made to hold the meeting:
      - i. Prepare an agenda for the periodic summary review meeting with times allocated for discipline topics based upon issues identified in the Periodic Review Report. **[RPM, Scientific Liaison]**
      - ii. Distribute Periodic Review Reports and meeting agenda to all meeting participants no later than two business days before the periodic summary review meeting. The Periodic Review Reports

may be collated into one document or attached as separate documents. **[RPM]**

- iii. Review all Periodic Review Reports prior to attending the meeting. **[Meeting Participants]**
- iv. Participate in periodic summary review meeting. **[RPM, Review Committee Members, Branch/Laboratory Chiefs, (Division Directors and/or Deputies)]** **Note:** The Division Director for each relevant discipline is required to attend if the discipline is considering rescinding the breakthrough therapy designation.
- v. Provide a high-level assessment of the status of the breakthrough therapy product development program, focusing on significant issues or changes in the development program identified during the periodic summary review for their respective discipline. **[Review Committee Members]**
- vi. Agree with *Intent to Rescind Breakthrough Therapy Designation* letter if appropriate. **[Division Director]**
- vii. Draft meeting summary documenting action items and decisions using *T815.02: Breakthrough Therapy Product Development Program Meeting Summary/Review Update*. **[RPM]**
- viii. Distribute the summary to all meeting attendees; enter the communication into the appropriate system, and upload into through CBER Connect. **[RPM]**

#### **F. 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 Committee, Scientific Liaison]**
2. Write a brief memo using *T 815.03: Intent to Rescind Breakthrough Therapy Memo* and distribute to the RPM and review committee members. **[Scientific Liaison]**
3. Route memo through immediate supervisor to Division Director for concurrence. **[Scientific Liaison]**
4. Return signed memo to Scientific Liaison, with a cc to the RPM. **[Division Director]**
5. Notify senior management, the ADRM and the Deputy Center Director when the product development program no longer meets the criteria for breakthrough therapy designation and *Intent to Rescind Breakthrough*

*Therapy Designation* letter will be issued to the sponsor. [**Scientific Liaison**]

6. Draft *Intent to Rescind Breakthrough Therapy Designation* letter. [**RPM**]
7. Route draft letter to the review committee members, Scientific Liaison, branch/laboratory chiefs, and senior management. [**RPM**]
8. Review letter and provide clearance to RPM. [**Review Committee Members, Scientific Liaison, 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. [**Product Office Director**]
11. Issue letter to sponsor and enter communication into the appropriate system and upload through CBER Connect. [**RPM**]

**G. Sponsor's Response to *Intent to Rescind Breakthrough Therapy Designation* letter**

1. Receive sponsor's response and route to review committee. [**RPM**]
2. Review additional information, data and/or rationale provided in the sponsor's response. [**Scientific Liaison, Review Committee Members**]
3. Schedule multidisciplinary internal meeting and sponsor meeting using R 851.01: Attendee Table for Breakthrough Therapy Meetings during the IND Phase if the sponsor's response includes a request for a meeting. [**RPM**]
  - a. Attend pre-meeting and sponsor meeting [**Review Committee Members, Branch/Laboratory Chiefs (Discipline Division Director(s))**] Discussion topics should include:
    - i. The additional information, data and/or rationale for maintaining breakthrough therapy designation provided in the sponsor's response.
    - ii. Explanation of why the breakthrough therapy designation should be maintained or rescinded.
    - iii. If the recommendation is to maintain breakthrough therapy designation, plans for a path forward for the development of the product.

4. Make decision to maintain or rescind breakthrough therapy designation. **[Review Committee, Scientific Liaison, Division Directors (Office Director, ADRM)]**

#### H. 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. **[Scientific Liaison]**
2. Distribute review update memo to the review committee and supervisors, enter into the appropriate system and upload through CBER Connect. **[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. **[Scientific Liaison, Review Committee Member(s), RPM]**
  - a. Review committee members should participate based upon the discipline specific topics to be discussed.
5. Document teleconference in the appropriate system and upload into through CBER Connect. **[RPM]**

#### I. Rescinding Breakthrough Therapy Designation

1. Complete *T 815.04: Rescinding Breakthrough Therapy Designation Review Memo*. Route through Immediate Supervisor to Product Office Division Director for sign off. **[Scientific Liaison]**
2. Return signed memo to Scientific Liaison, with a cc to the RPM. **[Product Office Division Director]**
3. Notify the entire review committee, immediate supervisors, senior management, the ADRM and Deputy Center Director that a *Rescind Breakthrough Therapy Designation* letter will be issued to the sponsor. **[Scientific Liaison]**
4. Draft Rescind Breakthrough Therapy Designation letter. **[RPM]**
5. Route draft letter to the review committee members, Scientific Liaison, branch/laboratory chiefs, and senior management. **[RPM]**

6. Review letter and provide clearance to RPM. **[Review Committee Members, Scientific Liaison, 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 through CBER Connect. **[RPM]**

#### VIII. [Appendix](#)

- A. Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting with the Sponsor

#### IX. References

- A. References listed below are CBER internal:
  1. CBER Letter Template Share Point Online site
  2. JA 851.03: Management of Breakthrough Therapy: Review of and Response to Requests for Breakthrough Therapy Designation, Reconsideration, and Withdrawal
  3. R 851.01: Attendee Table for Breakthrough Therapy Meetings during the IND Phase
  4. T 815.01: Breakthrough Therapy Periodic Review Report
  5. T 815.02: Breakthrough Therapy Product Development Program Meeting Summary/Review Update
  6. T 815.03: Intent to Rescind Breakthrough Therapy Designation Memo
  7. T 815.04: Rescinding Breakthrough Therapy Designation Review Memo
- B. References below can be found on the internet

1. [Federal Food, Drug and Cosmetic Act](#)
2. [Food and Drug Administration Safety and Innovation Act \(FDASIA\)](#)
3. [Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants](#)
4. [Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics](#)
5. [Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development](#)
6. [SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products](#)

## X. History

Written/Revised	Approved By	Approval Date	Version No	Comments
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

## **SOPP 8212 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 committee 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
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  - 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