POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics That Are Receiving an Expedited Review

Table of Contents

PURPOSE

- This Manual of Policies and Procedures (MAPP) describes actions taken in the Center for Drug Evaluation and Research (CDER) to provide review of a marketing application for a breakthrough therapy-designated drug receiving an expedited review consistent with section 506(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(a)(3)(A)).[1] This MAPP outlines CDER actions for pre-new drug application (NDA)/biologics licensing application (BLA) meetings and CDER actions from the time such an application has been received until an action is taken on the application.

BACKGROUND

- Section 506(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(a)(3)(A)). provides for designation of a drug as a breakthrough therapy "…if the drug is intended, alone or in combination with one 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 one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."

[1] For the purposes of this MAPP, all references to drugs or drug products include both human drugs and biological drug products regulated by CDER, unless otherwise specified.

- The Guidance for Industry: *Expedited Programs for Serious Conditions — Drugs and Biologics* provides information on:

  - The qualifying criteria for a breakthrough therapy designation.

  - The process for sponsors to submit a request for breakthrough therapy designation.

- A breakthrough therapy designation is not the same as a drug approval, and does not change the statutory standards for demonstrating safety and effectiveness.

- A breakthrough therapy development program must generate substantial evidence of effectiveness and sufficient evidence of safety to meet the statutory standard for approval.

- This MAPP also addresses pre-BLA/NDA meetings, even though they are requested before a marketing application is submitted. This is because the marketing application is the subject of the pre-BLA/NDA meeting.

- This MAPP is based on CDER staff experience with breakthrough therapy-designated drugs. As additional experience working with breakthrough therapy-designated drugs is acquired, this MAPP will be updated.

POLICY

- CDER staff will designate the review of a marketing application for each breakthrough therapy-designated drug as a priority review, if it meets the criteria for such a designation.

- 506(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(a)(3)(A)) instructs the Food and Drug Administration (FDA) to take such actions as are appropriate to expedite the development and review of a breakthrough therapy-designated drug. An "expedited review" of a marketing application is defined as one where the review team intends to act at least 1 month before the Prescription Drug User Fee Act (PDUFA) goal date, provided that no unexpected review issues arise and/or the review team does not experience an unexpected shift in work priorities or team staffing.

- For a breakthrough therapy-designated drug to be considered for an expedited review:

  - Results from clinical trials must indicate that the drug has demonstrated substantial improvement over existing therapies upon preliminary review of the marketing application.

  - The marketing application must be designated as a priority review; and
  - The review team must have determined that a first cycle approval is likely.

- If the application is designated as a priority review, the review team considers whether the marketing application qualifies for an expedited review.

- The review team considers expedited review of a marketing application for a breakthrough therapy-designated drug whenever possible. Not every marketing application for a breakthrough therapy-designated drug will receive an expedited review. Each marketing application will be evaluated on a case-by-case basis, to determine if an expedited review is appropriate. Factors that may influence the decision to conduct an expedited review include:
  - Resources to expedite the review are not available because of competing public health priorities (e.g., anthrax, Ebola, influenza, COVID).
  - An advisory committee (AC) meeting is needed to obtain advice on issues such as safety or the interpretation of clinical trial results.
  - An unanticipated safety issue is identified that requires a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU).
  - Manufacturing and product quality issues are identified.

- A designation of expedited review of a marketing application for a breakthrough therapy-designated drug will not change the PDUFA review performance goals.

- Applications for breakthrough therapy-designated drugs that qualify for the PDUFA V Program for Enhanced Review Transparency and Communication for New Molecular Entity (NME) NDAs and Original BLAs (the "Program") will follow the Program's review requirements. Program-related meetings typically occur earlier in the review cycle for applications undergoing expedited reviews.

- FDA has determined it is appropriate that a drug designated as a breakthrough therapy is eligible for rolling review. In particular, if an expedited review is planned, CDER review staff and managers encourage sponsors to request rolling review. If granted, portions of the marketing application are submitted under rolling review to meet the expedited review timelines. CDER review staff initiate a review of these portions shortly after receipt of the submissions, as resources allow.

RESPONSIBILITIES

Office of New Drugs (OND) Office of Regulatory Operations (ORO) Program Management Staff:

- Communicates notification of breakthrough therapy designation application, as appropriate, to colleagues from other CDER Offices and FDA Centers.
- Serves as the primary point of contact (POC) with sponsors. Ensures focused communications and discussions, rapid information exchange, and issue resolution.
- Schedules and ensures completion of all milestones, meetings, and meeting action items.
- Ensures each sponsor submits a complete list of clinical, clinical pharmacology, and manufacturing sites. Collaborates with the appropriate CDER Offices to schedule inspections and inspection-related activities.
- Notifies the CDER Breakthrough Therapy Program Manager if policy issues are identified.
- Sets up and manages review meetings, if required.
- In collaboration with the review team, ensures all substantive discussions and agreements with sponsors for NDA/BLA are documented in the appropriate CDER Electronic Records Keeping System (ERKS).

Review Team:

- Considers expedited review of a marketing application for a breakthrough therapy-designated drug, whenever possible, and determines when expedited review is or is not warranted, in collaboration with management.
- Communicates the expedited review decision to ORO staff.
- Consults with managers, when appropriate.
- Receives communications from ORO staff and collaborates on review timelines.
- Discusses all aspects of the breakthrough therapy application with OND management at review team meetings and other appropriate times.

CDER Breakthrough Therapy Program Manager:

- If required, coordinates with OND Policy (ONDP) to facilitate a discussion with the CDER Medical Policy and Program Review Council (MPPRC).

Affected CDER Office Project Managers:

- Collaborate with ORO staff on all marketing application review issues, as appropriate.

CDER Super Office Directors, or designees:

- Stays abreast of the status of expedited reviews for all breakthrough therapy-designated drugs.

PROCEDURES

General Considerations

- ORO staff and sponsors communicate frequently about the timing of a planned marketing application submission for a breakthrough therapy-designated drug and the appropriateness of an expedited review to ensure logistical and workload preplanning.

- A preliminary decision to conduct an expedited review is confirmed before the internal premeeting, which occurs prior to the pre-NDA/BLA meeting.

- ORO staff complete the scheduling for all milestone and other required CDER-sponsor and internal meetings within 14 working days of receipt of a marketing application for a breakthrough therapy-designated drug for which an expedited review is planned.

- ORO staff engage in frequent discussions with the project managers or representatives from other CDER Offices to notify them of the breakthrough therapy designation status and promote dissemination and exchange of application-specific information. Topics may include:

    - Identified issues and plans for resolution.

    - The status of internal goals and review timelines.

    - The sponsor's readiness to have the commercial drug product available for distribution by the targeted action date.

- ORO staff communicate information received from other CDER Offices to the review team in a timely manner.

- The CDER review team may initially determine an expedited review is appropriate, but during the review of the marketing application, decide the expedited review is not appropriate. This may occur if:
    - Issues arise that indicate a first cycle approval is unlikely, such as:
        - Unexpected application deficiencies are found.
        - The marketing application is of poor quality.
        - There is a need to hold an Advisory Committee (AC) meeting.
    - The sponsor fails to engage in collaborative communications, such as failure to respond to information requests (IRs) in a timely manner.
    - Unanticipated review issues arise.
    - The review team experiences an unexpected shift in work priorities or staffing.

    If the CDER review team determines an expedited review is no longer appropriate, the review timeline defaults to the priority review designation timeline. ORO staff communicates this decision and the rationale, to the applicant within five working days.

Pre-NDA/BLA Meeting

- Review teams should refer to MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review* for logistics of the pre-NDA/BLA meeting. Additional suggested topics for discussion include:
    - CDER statement of intent to conduct an expedited review of the application.
    - Discussion of preliminary trial results, other available data, and areas of potentially insufficient data.
    - Expectations for content and organization of the complete application, and readiness to submit.
    - Timing of planned late submissions or other amendments.
    - Clinical, clinical pharmacology, and manufacturing site readiness for inspection.
    - Plans for rolling review.

- Comparability of clinical lots to commercial lots and how much stability data have been collected, and other manufacturing and quality issues.
- Readiness to have the drug product available for marketing by the targeted action date, anticipated market demand, and ability to meet demand.
- Expanded access plans.
- Status of the proprietary name review.
- Status of the human factors development program, if applicable.
- Anticipated postmarketing requirements (PMRs) and postmarketing commitments (PMCs).
- AC meeting plans, if applicable.
- Any major safety issues and the potential need for REMS, if applicable.

CDER Communications and Interactions with Sponsors During the Review Cycle

- ORO staff work with the review team and sponsors to decide on mutually acceptable frequency for IRs and responses that will facilitate an expedited review, such as one at a time, bundled daily, or bundled biweekly. IRs are sent to sponsors with a summary statement giving context and rationale for the IR, and the response requested date.
- ORO staff use teleconferences, emails, and other communication tools for discussions, rapid information exchange, and issue resolution with the sponsor. ORO staff, in collaboration with the review team, capture all substantive discussions and agreements with the sponsor in an official document or memo to the BLA/NDA administrative file in the ERKS within ten working days after the substantive discussion was held or the agreement was made.

Internal CDER Communications and Meetings During the Review Cycle

- Filing/Planning Meeting. The Filing/Planning meeting is ideally held 2 to 3 weeks after the marketing application has been received. Discussion may include:
  - Confirmation that the review team still intends to perform an expedited review and agreement on targeted milestone dates (i.e., primary and secondary review timelines) and the internal meeting schedule.

- Completeness of application and timing of planned late submissions or other amendments, as agreed upon at the pre-BLA/NDA meeting.

- Plans for clinical, clinical pharmacology, and manufacturing inspections.

- Concurrence on if an AC meeting is needed. If an AC meeting is needed, plans to streamline the meeting preparations.

- Application Review Meetings and Status Updates. Throughout the review cycle, the review team discusses topics to ensure early communication of identified issues to all review team members. The discussion mechanisms may include dedicated application review meetings, one-on-one meetings, emails, or administrative rounds. Topics for discussion may include:

  - Discipline review status updates:

    - Application issues identified and plans for resolution, including findings from the reviews of portions of the application submitted under rolling review.

    - Status of labeling reviews.

    - Discussion of anticipated PMRs and PMCs.

  - Targeted milestone internal goals:

    - Ability to meet targeted internal goals.

    - Workload and coverage needs.

    - Adjustment of timeline, if required.

Senior Management Involvement

- The review team notifies the CDER Breakthrough Therapy Program Manager of policy concerns identified during the review of marketing applications for breakthrough therapy-designated drugs that are receiving an expedited review. If required, the CDER Breakthrough Therapy Program Manager coordinates with OND Policy to facilitate a discussion with the CDER MPPRC.

- Affected CDER Super Office Directors, and designees, stay abreast of expedited reviews for breakthrough therapy-designated drugs through internal meetings with their review teams. Provide guidance and direction, as appropriate.

Advisory Committee (AC) Meetings

- AC meetings are not typically convened for the following reasons:
    - The safety profile is typically acceptable for the indication;
    - The clinical trial design and endpoints are determined to be acceptable;
    - The application does not raise significant safety or efficacy issues that were unexpected for a drug of the class or in the intended population;
    - The application does not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease; or
    - Outside expertise is not necessary; there were no controversial issues that would benefit from AC discussion.

Clinical, Clinical Pharmacology, and Manufacturing Inspections

- ORO staff ensure each sponsor submits a complete list of clinical, clinical pharmacology, and manufacturing sites before the pre-BLA/NDA meeting.
- ORO staff ensure inspection-related activities are scheduled as early as possible in the application review process. Activities are scheduled within three weeks of the receipt of each complete marketing application receiving expedited review, as resources allow. This ensures inspection results are available for the review team and allows time for the sponsor to address significant inspection findings. The following offices may be involved in inspection-related activities:
    - Office of Compliance (OC), Office of Scientific Investigations (OSI), for clinical investigator sites, and sponsors or clinical research organizations who monitor sites evaluating good clinical practice compliance.
    - Office of Translational Sciences (OTS), Office of Study Integrity and Surveillance (OSIS), for clinical and analytical sites conducting bioequivalence/bioavailability studies, and good laboratory practice labs conducting pharmacology/toxicology studies.
    - Office of Pharmaceutical Quality (OPQ) for manufacturing sites.

REFERENCES

- The Prescription Drug User Fee Act (PDUFA) 1992. Fifth authorization, 2017.

- Section 506(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(a)(3)(A)).

- Guidance for Industry*: Expedited Programs for Serious Conditions – Drugs and Biologics.* (May 2014).

- Guidance for Industry: *Considerations for Rescinding Breakthrough Therapy Designation* (June 2022).

- Guidance for Industry: *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023).

- CDER MAPP 4301.1 (Rev 3), *Center for Drug Evaluation and Research Medical Policy Council*.

- CDER MAPP 5015.13*, Quality Assessment for Expedited Programs*

- CDER MAPP 6010.5, *NDAs and BLAs: Filing Review Issues*.

- CDER MAPP 6010.8, Rev. 1 *NDAs and BLAs: Communication to Applicants of Planned Review Timelines*.

- CDER MAPP 6020.3, Rev. 2 *Review Designation Policy: Priority (P) and Standard (S)*.

- CDER MAPP 6025.2, *Good Review Practice: Clinical Review of Investigational New Drug Applications*.

- CDER MAPP 6025.6, *Good Review Practice: Management of Breakthrough Therapy – Designated Drugs and Biologics*.

- CDER MAPP 6030.9, *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*.

- CDER MAPP 7600.11, *CDER Electronic Record Keeping Systems*.

DEFINITIONS

Application Review Team: Often called "review team," typically includes ORO staff, OPQ Regulatory Business Project Manager (RBPM), primary and secondary reviewers (e.g., clinical, clinical microbiology, biostatistics, clinical pharmacology, pharmacology/toxicology, and product quality), cross-discipline team lead (CDTL), OND Clinical review division director and/or deputy division director, and OSE and OPQ representatives. Additional disciplines may be included as needed, such as the Office of

Prescription Drug Promotion (OPDP) team, and the Patient Labeling Team (PLT), both within the Office of Medical Policy (OMP).

Drugs and drug products: In this MAPP, drug and drug products include both human drugs and biological drug products regulated by CDER.

Expedited review of a marketing application: A marketing application review where the review team plans to act at least 1 month before the PDUFA goal date, provided that no unexpected review issues arise and the review team does not experience an unexpected shift in work priorities or team staffing.

Marketing Application: In this MAPP, marketing application refers to original NDAs, BLAs and efficacy supplements.

Medical Policy and Program Review Council (MPPRC): For information related to the MPPRC, refer to MAPP 4301.1, *Center for Drug Evaluation and Research Medical Policy Council*.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
3/9/15	Initial	N/A
2/28/24	1	Updated to align with: • Current OND organizational structure. • User fee agreement commitments. • CDER workflow procedures and best practices.