POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics

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PURPOSE

- This Manual of Policies and Procedures (MAPP) describes actions taken in the Center for Drug Evaluation and Research (CDER) "to expedite the development and review of an application designated as a breakthrough therapy," and is consistent with requirements described in 506(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(a)(3)(A)). This MAPP outlines CDER actions from the time a breakthrough therapy designation has been granted until a marketing application has been submitted, as long as the breakthrough therapy designation has not been rescinded or withdrawn.

- This MAPP describes the policy and responsibilities of CDER review staff, regarding sponsor interactions and communications, and review timelines for the management of breakthrough therapy-designated drugs.[1] It is intended to facilitate and expedite development and review of investigational new drug application (IND) submissions for these drugs.

[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.

BACKGROUND

- Section 506(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) 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." The Guidance for Industry, *Expedited Programs for Serious Conditions — Drugs and Biologics*, contains further discussion on Agency interpretation and implementation of these standards.

- The Guidance for Industry: *Expedited Programs for Serious Conditions — Drugs and Biologics* outlines features of, and qualifying criteria for breakthrough therapy designation. This guidance also identifies the process for sponsors to submit a request for breakthrough therapy designation.

- Section 506(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(a)(3)(A)), provides that the Food and Drug Administration (FDA) shall assign a cross-disciplinary project lead (CDPL) to the review team during the review of the development programs for breakthrough therapy-designated drugs (i.e., during the IND phase). A CDPL facilitates an efficient review of the development program and serves as a scientific liaison between the review team and the sponsor for all breakthrough therapy designated drug development programs.

- A breakthrough therapy designation is not the same as a drug approval, and does not change the statutory standards for demonstrating the safety and effectiveness needed for a drug approval. A breakthrough therapy development program must generate substantial evidence of effectiveness and evidence of safety to meet the statutory standard for approval. A breakthrough therapy designation does not guarantee approval of a marketing application for the breakthrough therapy designated drug and indication.

- CDER gathered data from review staff working with breakthrough therapy-designated drugs to establish best practices. As CDER staff acquires additional experience working with breakthrough therapy-designated drugs, this MAPP may be updated.

POLICY

- When a drug is designated as a breakthrough therapy, CDER expedites its development and review of the designated drug program and marketing application through various interactions with the sponsor. Breakthrough therapy expedited actions include intensive CDER guidance on efficient drug development, assignment of a CDPL for the review team, and organizational commitment to involve senior management in collaborative, cross-disciplinary review.

- The review team, led by the CDPL, meets frequently with the sponsor to provide guidance on efficient drug development. CDER review staff and managers follow the processes and procedures outlined in the Guidance for Industry: *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* when scheduling and conducting meetings for breakthrough therapy-designated drugs.

- The review team, led by the CDPL, solicits input from senior managers and experienced reviewers of all affected disciplines to provide the sponsor with coordinated advice.

- CDER review staff and managers follow MAPP 6025.2 *Good Review Practice: Clinical Review of Investigational New Drug Applications*.

- CDER review staff and managers follow MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*. CDER response timeline exceptions are made for responses to the following submissions, with adjusted timelines below as resources allow:

    - Table 4, IND Submissions with Regulatory-Mandated or FDA-Established Timelines:

        - Initial pediatric study plan (PSP): 90 days

        - Amendment to agreed initial PSP: 90 days

        - Proprietary name review (submitted to the IND): 90 days

    - Table 6, IND Drug Development Submissions

        - Nonclinical information: 90 days, if possible

        - Carcinogenicity information: 90 days, if possible

- Table 7, Other Submission Types
  - Annual report/development safety update report: 90 days

RESPONSIBILITIES

Office of Regulatory Operations (ORO) Program Management Staff:

- Provides regulatory leadership to the review team.
- Collaborates with the CDPL on a regular basis to manage the day-to-day aspects of the IND for a breakthrough therapy-designated drug.
- Acts as the primary point of contact (POC) with the sponsor.
- Keeps abreast of the breakthrough therapy drug development program progress. Informs the review team of this progress and periodically addresses issues or delays with the review team in a timely manner to meet expedited review timelines.
- Addresses potential review process issues, such as delays in targeted goals. Works with the review team and the sponsor to resolve these issues. Keeps the CDPL informed of the status of all relevant issues.
- Distributes discipline-specific information from sponsor communications, submissions, and internal and CDER-sponsor meetings to the review team. Ensures all review team members are informed of the drug development plan, status, and progress.
- Schedules and attends all internal and CDER-sponsor meetings.
- Informs the CDER Breakthrough Therapy Program Manager of regulatory actions and meeting milestones. Uses the Breakthrough Therapy Program Manager as a resource for questions and issues related to breakthrough therapy-designated drugs.
- Communicates with Project Managers in other CDER offices and FDA centers to exchange information, coordinate efforts, and conduct consultations for additional expertise.
- Notifies the review team if rescission of a breakthrough therapy designation is being considered.

Review Team:

- Collaborates with ORO staff, as appropriate. Reviews and responds to questions, as appropriate, within the appropriate timeline.
- Attends all scheduled meetings, reviews materials in advance of meetings, and provides expertise and feedback throughout the development and reviews each breakthrough therapy designated drug program.
- Works collaboratively as a member of a cross-disciplinary review team.
- Organizes work to meet expedited review timelines.
- Attends and participates in internal and formal sponsor meetings, as appropriate, or designates a qualified staff member to attend.

Discipline Primary Reviewer:

- Works as a member of the review team.
- Performs scientific review of incoming submissions to the IND. Documents review findings, as appropriate.
- Performs periodic high-level review of each breakthrough therapy drug development program to ensure that criteria for the designation continue to be met.
- Consults with subject-matter experts outside of the review team, when necessary.
- Meets regularly with the discipline team leader (DTL) to provide updates on the status and progress of the breakthrough therapy drug development program.
- Identifies issues with the development program, proposes potential solutions, and communicates issues to the review team, DTLs, the CDPL, and ORO staff, as soon as possible.

Discipline Team Leader (DTL):

- Works as a member of the review team.
- Establishes regular meetings with the primary reviewer to assess the status and progress of the breakthrough therapy drug development program and provides direction, guidance, and feedback.

- Identifies roadblocks or issues in the review of incoming IND submissions and works with the primary reviewer, CDPL, and ORO staff to determine mechanisms to resolve the issues.

- Facilitates resolution of discipline-specific conflicts and presents any differing scientific opinions to the CDPL.

- Notifies the CDPL of workload issues.

Cross-Disciplinary Project Lead (CDPL):

- Provides leadership to the review team and oversight of the expedited review of the breakthrough therapy drug development program.

- Works with ORO staff and DTLs to ensure a coordinated review, address issues, and resolve conflicts that arise within and across disciplines.

- Monitors review progress and keeps the division director apprised of the breakthrough therapy drug development program status and progress.

- Acts as the scientific liaison between members of the review team and the sponsor through communications with ORO staff.

OND Clinical Division Director (or designee):

- Ensures the quality and consistency of all discipline actions and reviews.

- Attends the initial comprehensive multidisciplinary breakthrough therapy meeting, critical IND milestone meetings, and subsequent Type B meetings, as appropriate.

- When a breakthrough therapy designation request is granted, assigns a CDPL.

- Meets with the CDPL to keep apprised of the breakthrough therapy drug development program status.

- Attends administrative rounds for status updates on the progress of breakthrough therapy drug development programs within the division.

- Informs the appropriate Office Director of breakthrough therapy drug development programs within the division.

- Resolves conflicts between disciplines, if needed.

OND Clinical Office Director (or designee):

- Stays apprised of status of breakthrough therapy drug development programs within their office through the division directors and attendance at administrative rounds.

- Attends the initial comprehensive multidisciplinary breakthrough therapy meeting, critical IND milestone meetings, and subsequent Type B meetings, as appropriate.

- Attends CDER regulatory briefings, Medical Policy and Program Review Council (MPPRC) meetings, and other related meetings to be apprised of the status of INDs for breakthrough therapy-designated drugs. Provide senior management updates on drug development program issues.

- Addresses specific or unresolved drug-development program issues through the discipline, the division, office management chain or MPPRC, as appropriate.

CDER Super Office Director (or designee):

- Stays abreast of status of breakthrough therapy drug development programs through the subordinate office directors.

- Attends CDER regulatory briefings, MPPRC meetings, as appropriate, and other related meetings to be apprised of the status of INDs for breakthrough therapy-designated drugs and to provide CDER senior management input.

- Addresses specific issues, roadblocks, or policy questions through the discipline, the division, or office management chain.

CDER Breakthrough Therapy Program Manager:

- Communications across CDER offices and other Centers all breakthrough therapy program updates to ensure the consistent implementation of the breakthrough therapy program.

- Coordinates with OND Policy on policy development for the review of breakthrough therapy-designated drugs.

- Provides guidance on the breakthrough therapy program to the review teams.

- Creates and maintains breakthrough therapy program letters, review templates, and checklists.

- Establishes archival and tracking requirements in the appropriate CDER Electronic Records Keeping System (ERKS) and provides data quality assurance.

- Disseminates information and provides training on the breakthrough therapy program to CDER staff, other centers and agencies, and stakeholders, as appropriate.

- Responds to internal and external inquiries from CDER staff, FDA leadership, Congress, the press, sponsors, and other interested parties on the breakthrough therapy program.

- Develops and maintains internal and external websites related to the breakthrough therapy program.

CDER Medical Policy and Program Review Council:

- Discusses breakthrough therapy policy-related topics and establishes related policy.

- Performs a portfolio review of breakthrough therapy-designated drug development programs including offering guidance on drug-specific drug development issues.

- Discusses decisions to rescind a breakthrough therapy designation with the OND Clinical review divisions to ensure consistency in policy implementation across the review divisions, as needed.

PROCEDURES

CDER-Sponsor Meetings and Other Communications

Initial comprehensive multidisciplinary breakthrough therapy (Type B) meeting

- The breakthrough designation granted letter requests the sponsor submit a request for a comprehensive multidisciplinary meeting to discuss the drug development program. This meeting is used to discuss overarching, high-level plans for drug development. Topics depend on the therapeutic area, development phase, and specific development program issues of the proposed drug and indication. This meeting is also used to establish a communication plan to ensure interactions between CDER and the sponsor are managed efficiently. Expectations are identified for the drug development timing, formats for interactions and for information exchange. (See Attachment 1.)

- The comprehensive multidisciplinary meeting is held between 2 and 6 months after granting breakthrough therapy designation. The meeting's timing is contingent on where the sponsor is in its drug development program. ORO staff

works with the sponsor to establish the earliest mutually acceptable date for the meeting, to facilitate an expedited development program.

- All CDER review disciplines are invited to attend and participate in this meeting. Only one person per discipline is required to attend.

- If a milestone meeting has recently been held or is scheduled for the near future this initial comprehensive multidisciplinary meeting may not be necessary.

Subsequent Type B meetings

- After the initial comprehensive multidisciplinary Type B meeting, the review team meets with the sponsor throughout the IND phase to address important issues at different development phases. The frequency of these meetings is determined by the communication plan typically agreed upon during the initial comprehensive multidisciplinary Type B meeting or other IND milestone meetings.

- Subsequent meetings with sponsors for breakthrough therapy-designated drugs are considered Type B meetings unless they meet the criteria for a Type A meeting. These meetings are typically discipline-focused and invited review team members will vary depending on the agenda.

Critical IND milestone meetings

- Critical IND milestone meetings typically take place in an accelerated time frame, as the development program for a breakthrough therapy-designated drug is expedited and topics are discussed earlier than outlined in MAPP 6030.9. For example, proprietary name plans, inspection and manufacturing facility considerations, human factors development program plans (as applicable), and postmarketing study or trial plans are discussed earlier than the pre- new drug application (NDA)/biologics licensing application (BLA) meeting. In advance of each milestone meeting, the review team and the sponsor discuss and agree on the discipline-specific information to be covered at each milestone meeting.

- All CDER review disciplines are invited to attend and participate in each milestone meeting. However, only one person from each affected discipline is required to attend.

Other communications with sponsors outside of CDER-sponsor meetings

- ORO staff, as primary POC with the sponsor, employ other communications tools, outside the formal meetings noted above, to ensure focused discussions, rapid information exchange, and issue resolution.

- When CDER receives an inquiry from the sponsor, ORO staff consults with the review team. ORO staff then shares the anticipated timeline for each response with the sponsor. Timelines for responses are based on the complexity of the inquiries. CDER strives to respond to inquiries within 30 days.

- ORO staff capture all substantive discussions and agreements with the sponsor in CDER's ERKS within 15 working days of responding to sponsor's inquiry.

CDER Internal Meetings and Communications

- CDER review staff hold internal meetings for high level program development discussions, to evaluate or adjust planned timelines, and to prioritize work. The timing and intervals of these meetings depends on the development stage, the pace of IND submissions, and internal resource availability and constraints. Suggested time points for review team meetings include:

    - Shortly after a drug has been designated as a breakthrough therapy, to discuss process, procedures, and expectations of the review team, including the time intervals for the periodic high-level reviews, and any drug-specific considerations anticipated.

    - After the review of IND amendments containing trial data, to discuss specific program development issues, and plans to address these issues.

    - Before MPPRC portfolio review meetings.

    - After CDER reviewers have completed their periodic high-level review of a sponsor's drug development program, to discuss assessments and workload management.

    - When a breakthrough therapy drug may no longer meet the designation criteria, to discuss the appropriateness of sending an Intent to Rescind Breakthrough Therapy Designation letter to the sponsor.

CDER Review of Breakthrough Therapy Drug Development Programs

- CDER review staff periodically perform high-level reviews of sponsors' breakthrough therapy-designated drug development programs. These high-level reviews assess the adequacy of the proposed overall drug development plan to facilitate an expedited development program and timeline.

    - The frequency of reviews depends on where the sponsor is in drug development, the therapeutic area of the drug product, and the types of proposed and ongoing clinical trials.

- After CDER reviewers have performed a high-level review of a sponsor's drug development program, an internal meeting is held to discuss findings and workload management for the application. Each discipline provides the CDPL with a high-level assessment of the overall breakthrough therapy drug development program, as it relates to their discipline. (See Attachment 2).

- CDER review staff request the sponsor share information on multiple aspects of the drug development program periodically, to ensure the drug development program is evaluated thoroughly.

- The MPPRC performs a portfolio review of drugs that have been granted breakthrough therapy designation. Portfolio review discussions focus on programs with novel or controversial study design, with unexpected clinical trial results, or that raise policy issues or broad or cross-cutting issues.

Rescinding a Breakthrough Therapy Designation

- When the criteria for breakthrough therapy designation are no longer met, CDER may rescind the breakthrough therapy designation. The review team considers rescinding when:

  - Emerging data no longer show substantial improvement over available therapy.

  - A drug receives traditional approval, or the clinical benefit is verified for a drug granted accelerated approval for the same indication as the designated drug, such that the designated drug no longer shows substantial improvement over existing available therapy.

  - The designated drug development program is no longer being pursued.

  - The draft guidance for industry, *Considerations for Rescinding Breakthrough Therapy Designation*, contains further discussion on Agency interpretation and implementation of these standards.

- The following outlines the procedures for rescinding a breakthrough therapy designation:

  - The review team identifies that a breakthrough therapy drug may no longer meet the designation criteria. A multidisciplinary internal meeting is held to discuss rescinding the designation. ORO staff ensure all members of the review team are included in the discussion. Division director concurrence is obtained on the intent-to-rescind decision.

  - The review division notifies the sponsor in writing of the intent to rescind the breakthrough therapy designation. The letter includes the reasons for the

determination and provides the sponsor with an opportunity to submit additional data to support continuing the breakthrough therapy designation, and to request a meeting with the division to discuss the breakthrough therapy designation for the drug.

- If no additional data are presented by the sponsor within 60 days, the review division will move forward with issuance of a rescission letter.

- If additional data are presented by the sponsor and, after discussion with the MPPRC, the review team still determines the criteria for breakthrough therapy designation are no longer being met, the review division sends a Rescind Breakthrough Therapy Designation letter to the sponsor, rescinding the breakthrough therapy designation. The letter provides a rationale for this decision.

- If additional data are submitted by the sponsor and, after review, the review division determines the criteria for breakthrough therapy designation continues to be met, plans for a path forward for the development of the drug are discussed, documented, and communicated to the sponsor via an advice letter.

- To note, a sponsor may withdraw a breakthrough designation at any time via a formal submission to the application.

REFERENCES

- 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).*

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

- 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 Records Keeping Systems*.

DEFINITIONS

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

Cross Disciplinary Project Lead (CDPL): This role is typically the clinical team lead during drug development. The CDPL performs the same types of functions as the cross disciplinary team lead (CDTL) during marketing application review. The CDTL provides day-to-day management of the review, performs a secondary review of the overall application, taking into account all discipline reviews and recommendations and maintains consistency of regulatory decisions and direction of the review.

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

IND Application: A request for authorization from the FDA to administer an investigational drug or biological product to humans. An IND must be authorized prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved NDA/BLA.

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
7/29/14	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.

ATTACHMENT 1: Possible Discussion Topics for the Initial Comprehensive Multidisciplinary Breakthrough Therapy Type B Meeting

The following are possible discussion topics for the initial comprehensive multidisciplinary breakthrough therapy Type B meeting depending on the therapeutic area, development phase, and specific development program issues.

General and/or Regulatory

- The planned target date for NDA/BLA submission, including plans for rolling review.
- The specific indication that studies are intended to support.
- Other indications in development.
- The plan for substantial evidence of effectiveness, including adequate and well-controlled studies and confirmatory studies.
- Expanded access plans, including the intent to communicate these plans publicly.
- Plans to seek accelerated approval.
- Regulatory status with non-U.S. regulatory agencies.
- Plans to defer or waive specific studies (e.g., pediatric studies), including those to be conducted as postmarketing requirements/postmarketing commitments.
- Critical aspects of proposed studies, including enrichment designs, noninferiority designs, and historical controls, and any planned novel approaches.
- Plans for submission of a proprietary name request.
- If a drug/device combination product, the device development information and plan with the Center for Devices and Radiological Health (CDRH).
- If a drug/device combination product, the human factors development program plan.
- If the use of the drug will require a diagnostic test, the in vitro diagnostic development plan with CDRH.
- The current development plan and proposed development timeline.

- The proposed communication plan for managing interactions between CDER and the sponsor, including the timing and format of these interactions.

Clinical and Statistical

- Existing and planned clinical sites and accrual data.
- Efficacy:
    - The status of all clinical trials and topline summary results.
    - The preliminary evidence of effectiveness.
    - The planned or completed clinical trials intended to support effectiveness including:
        - 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.
        - 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.
- Safety:
    - Potential safety issues identified in nonclinical studies and early clinical trials.
    - Liver, kidney, cardiac, immune suppression, carcinogenicity, genotoxicity, reproductive and developmental, and immunogenicity safety profiles.
    - The clinical trial safety monitoring plan for safety signals identified in nonclinical studies and early clinical trials, and for postmarketing drug safety and surveillance (i.e., pharmacovigilance).
        - The proposed size of the safety population
        - The plan or the need for long-term safety studies or trials
            - Preapproval
            - Postapproval

- The plans to mitigate or minimize risk, proposed risk evaluation and mitigation strategies, if needed.

- The proposed pediatric development plan with outlines and synopses of additional studies.

Clinical Pharmacology and Pharmacokinetics

- 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.

- Specific populations:

  - The dose, trial design, efficacy endpoints, size and composition of the population, and additional safety trials for populations such as:

    - Elderly patients

    - Pediatric patients

    - Hepatically and renally impaired patients

- The clinical pharmacology, pharmacodynamic, and pharmacokinetic trials: completed, ongoing, planned, and requests for deferral:

  - Immunogenicity assessments

  - Dosing information from pharmacodynamics studies:

    - Single ascending dose

    - Multiple ascending dose

    - Dose response study

  - Food-effect

  - Drug-drug interactions (DDI)

  - Thorough QT/QTc

  - Pharmacokinetic studies in patients with renal or hepatic dysfunction

  - Pharmacogenomics

- The plans for an in vivo bridging trial of the formulation studied in the clinical development program to the to-be-marketed formulation.

- The plans for conducting population pharmacokinetics, exposure-response modeling, and simulation analyses.

- The plans to describe dose modifications in labeling based on drug-drug interactions, age, organ impairment, among others.

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

- 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. For planned studies, the timelines for initiation and submission of study reports. Examples of such studies include:

    - Subacute and chronic toxicology and associated toxicokinetics

    - Genetic toxicology

    - Reproductive and developmental toxicology

    - Carcinogenicity studies

    - Animal models of disease and pharmacokinetic parameters associated with efficacy

    - Evidence of mechanism of action

    - Absorption, distribution, metabolism, and excretion

    - Safety pharmacology, where appropriate

Pharmaceutical Quality/Chemistry, Manufacturing, and Controls

- Drug product:

    - The dosage form

    - The formulation description

    - Administration instructions, delivery systems (e.g., vials, prefilled syringes) proposed draft packaging, and disposal instructions

    - Critical quality attributes

- The control and stability strategies
- The proposed shelf life and required stability studies

- Drug substance:
  - Characterization
  - Critical quality attributes
  - The control and stability strategies
  - The proposed shelf life or retest period and required stability studies

- Proposed commercial processes:
  - The manufacturing process, in-process controls, scale-up plans.
  - A comparison of the proposed commercial manufacturing process to the clinical manufacturing process.
  - Comparability of lots used in clinical trials and commercial lots or a plan to establish analytical comparability.
  - The current manufacturing site(s) and proposed commercial site(s), if different, registration numbers, readiness, and manufacturing timelines.
  - The current release and stability testing site(s) and proposed commercial testing site(s), if different.
  - The anticipated market demand at launch.

- Proposed validation approaches:
  - The drug substance and drug product manufacturing process
  - Microbial control and sterility assurance
  - Viral clearance
  - The analytical methods

ATTACHMENT 2: Topics for CDER Periodic High-Level Review of Breakthrough Therapy Drug Development Program

General and/or Regulatory

- The anticipated date for NDA/BLA submission, including any plans for rolling review or accelerated approval.
- Previous major agreements and future meetings planned.
- Significant submissions, previous and anticipated (e.g., special protocol assessment, statistical analysis plan (SAP) and amendments, protocol amendments, trial reports, plans for prespecified interim, if any, and final analyses).
- The in vitro diagnostic or drug/device combination product development plan with CDRH, if appropriate.
- The timelines for human factors studies ongoing and planned. For planned studies, anticipated timeline for initiation, and submission of study reports.
- Regulatory status with non-U.S. regulatory agencies.

Clinical and Statistical

- *Clinical efficacy*. Clinical trials completed, ongoing, and planned. For planned trials, anticipated timelines for initiation and submission of trial reports. For completed trials, trial description, status, and results.
- *Clinical safety*. Potential safety issues identified, and risk management and safety monitoring plans.
- *Statistics*. SAPs, including prespecified interim analyses, if any.

Clinical Pharmacology

- The clinical pharmacology, pharmacodynamic, and pharmacokinetic trials, completed, ongoing, and planned. For planned trials, anticipated timelines for initiation and submission of trial reports. Plans for requests for deferral.
- Pharmacometric assessments including plans and timelines for conducting population pharmacokinetics, exposure-response analysis, and simulation approaches driving key regulatory decisions, including trial design and its use in dose selection.

- The justification for all dose selections, including number of doses and dose intervals, among others.

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

- The nonclinical studies completed, ongoing, and planned. For planned studies, anticipated timeline for initiation, and submission of study reports.

- The potential clinical safety issues identified, and actions planned to address these issues.

Pharmaceutical Quality/Chemistry, Manufacturing, and Controls

- The timelines for commercial manufacturing development plans, including processes and controls, identified issues, and actions planned to address these issues.

- The formulation changes and scale-up plans.

- The manufacturing facilities and timelines for readiness for inspection.