POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

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

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PURPOSE

- This MAPP describes actions taken in the Center for Drug Evaluation and Research (CDER) "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). It outlines CDER actions from the time a breakthrough therapy designation has been granted until a marketing application has been submitted.

- This MAPP describes the policy, roles and responsibilities of CDER review staff, CDER-sponsor interactions and communications, and review timelines for the management of breakthrough therapy-designated drugs.[1] These descriptions are 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.

- This MAPP does not address the specific content of scientific reviews. This MAPP does not cover the review of breakthrough therapy designation requests or of new drug applications (NDAs) and biologics license applications (BLAs) submitted for breakthrough therapy-designated drugs.

- This MAPP is one in a series of MAPPs designed to document good review practices for CDER review staff in accordance with MAPP 6025.1 *Good Review Practices.*

BACKGROUND

- Section 506(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[2] provides for designation of a drug as a breakthrough therapy ". . . if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."

- The guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* provides information on the qualifying criteria for a breakthrough therapy designation and the process for sponsors to submit a request for breakthrough therapy designation, and outlines, at a high level, the features of a breakthrough therapy designation.[3]

- CDER has gathered the experiences of the review staff who have worked with breakthrough therapy-designated drugs and has established these best practices. As CDER staff acquires additional experience working with breakthrough therapy-designated drugs, as part of a quality systems approach to drug review, this MAPP may be updated.

- 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 sufficient evidence of safety to meet the statutory standard for approval.

[2] As amended by section 902 of FDASIA.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

POLICY

- When a drug is designated as breakthrough therapy, CDER will take actions to expedite the development and review of such drug. The features of a breakthrough therapy designation include intensive CDER guidance on an efficient drug development program, assignment of a cross-disciplinary project lead (CDPL) for the review team,[4] and an organizational commitment to involve senior management, as appropriate, in a collaborative, cross-disciplinary review.

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

- The review team, led by the CDPL, will solicit input from senior managers and experienced reviewers in all relevant disciplines and provide coordinated advice to the sponsor.

- CDER review staff and managers will follow MAPP 6025.2 *Good Review Practice: Clinical Review of Investigational New Drug Applications*, which describes the content of a review for an IND submission, when reviewing submissions for breakthrough therapy-designated drugs.

- CDER review staff and managers will follow MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*, which describes review management principles and practices, when reviewing submissions for breakthrough therapy-designated drugs. MAPP 6030.9 describes idealized time frames for review, to be implemented as resources permit. To provide timely advice for a breakthrough therapy-designated drug, the review timeline for all submissions noted in Tables 4, 5, 6, and 7 of Attachment 1 of MAPP 6030.9 will be 60 days unless a shorter timeline is indicated in the table, except for the following submissions:

  – 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

[4] Section 506(a)(3)(B)(iv) of the FD&C Act, as amended by section 902 of FDASIA, provides that the FDA shall assign a *cross-disciplinary project lead* to the review team during the review of the development programs for breakthrough therapy-designated drugs (i.e., during the IND phase).

- Table 6, IND Drug Development Submissions

  - Nonclinical information: 90 days
  - Carcinogenicity information: 90 days

- Table 7, Other Submission Types

  - Annual report/development safety update report: 90 days

ROLES AND RESPONSIBILITIES

The core review team responsibilities for IND development of a breakthrough therapy-designated drug are summarized below.

Regulatory Project Manager

- 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 regulatory liaison with the sponsor
- Keeps abreast of the breakthrough therapy drug development program progress and informs the entire review team of this progress periodically (i.e., at administrative rounds and internal meetings) and organizes work to meet expedited review timelines
- Addresses potential review process issues, such as delays in targeted internal goals, and works with the review team and the sponsor to resolve these issues while keeping the CDPL informed
- Distributes discipline-specific information from sponsor communications and submissions and internal and CDER-sponsor meetings to the entire review team so that all review team members are kept abreast of the drug development plan status and progress
- Schedules and attends all internal and CDER-sponsor meetings, working to ensure that internal team and CDER-sponsor meetings are prioritized on the calendar
- Informs the CDER Breakthrough Therapy Program Manager of regulatory actions and milestone meetings, and uses the Program Manager as a resource when questions and issues related to a breakthrough therapy-designated drug arise

- Communicates with regulatory project managers (RPMs) in other CDER offices and FDA centers to exchange information, coordinate efforts, and request consults when the review team requires additional scientific expertise

- Notifies all members of the review team if rescission of a breakthrough therapy-designated drug is being considered

- Uses project management tools, such as checklists, related to the breakthrough therapy program

Discipline Primary Reviewer

- Performs a scientific review of all incoming submissions to the IND and officially documents review findings, as appropriate

- Performs periodic high-level development program reviews, as discussed in the PROCEDURES section

- Consults with subject matter experts outside of the core 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 DTLs, the CDPL, and the RPM, as soon as possible

- Attends and participates in internal and CDER-sponsor meetings, as appropriate

- Organizes work to meet expedited review timelines

- Works collaboratively as a member of a cross-disciplinary review team

Discipline Team Leader

- 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 the RPM to determine mechanisms to resolve the issues

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

- Attends and participates in internal and CDER-sponsor meetings, as appropriate, or designates a qualified staff member to attend, if unable to attend

- Organizes work to meet expedited review timelines and notifies the CDPL of workload issues

Cross-Disciplinary Project Lead

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

- Works with the RPM 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 all members of the review team for coordinated internal interactions and communications with the sponsor through the RPM

- Attends and participates in internal and CDER-sponsor meetings, or designates a qualified staff member to attend, if unable to attend

- Organizes work to meet expedited review timelines

Division Director

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

- Attends the initial comprehensive multidisciplinary breakthrough therapy meeting,[5] critical IND milestone meetings,[6] and subsequent Type B meetings (these meetings are described in the PROCEDURES section), as appropriate

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

- Meets regularly 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

[5] See CDER-Sponsor Meetings and Other Communications in the PROCEDURES section.

[6] See Table 2 in MAPP 6030.9 for a list of critical IND milestone meetings.

- Informs the appropriate subordinate office directors of status of breakthrough therapy drug development programs within the division

- Organizes work to meet expedited review timelines

- Resolves conflicts between disciplines, as needed

Subordinate Office Director

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

- Attends the initial comprehensive multidisciplinary breakthrough therapy meeting,[7] critical IND milestone meetings,[8] and subsequent Type B meetings,[9] as appropriate

- Attends CDER regulatory briefings, Medical Policy Council (MPC) meetings, as appropriate, and other related meetings to be apprised of the status of INDs for breakthrough therapy-designated drugs and to provide senior management guidance on any development issues

- Addresses specific program development issues brought to his or her attention through the discipline, division, or office management chain, and periodically briefs the MPC on the status of breakthrough therapy-designated drugs in his or her office as part of the MPC portfolio review of the drugs with breakthrough therapy designation

Super Office Director

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

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

- Addresses specific issues, roadblocks, or policy questions brought to his or her attention through the discipline, division, or office management chain

[7] See the subsection, CDER-Sponsor Meetings and Other Communications, in the PROCEDURES section.

[8] See Table 2 in MAPP 6030.9 for a list of critical IND milestone meetings.

[9] See the subsection, Subsequent Type B meetings, in the PROCEDURES section.

CDER Breakthrough Therapy Program Manager

- Coordinates across the CDER offices and other Center breakthrough therapy liaisons to ensure the successful implementation of the breakthrough therapy program
- Leads the policy development for the review of breakthrough therapy-designated drugs
- Provides regulatory and policy 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 information technology systems and provides data quality assurance
- Disseminates information and provides training on the breakthrough therapy program to CDER staff, and other centers and agencies, as needed
- Responds to internal and external inquiries from CDER staff, FDA leadership, Congress, the press, sponsors, and other stakeholders on the breakthrough therapy program
- Develops and maintains internal and external Web sites related to the breakthrough therapy program

Medical Policy 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 review divisions to ensure consistency in policy implementation across the review divisions

PROCEDURES

CDER-Sponsor Meetings and Other Communications

Initial comprehensive multidisciplinary breakthrough therapy meeting

- The breakthrough designation granted letter should include a request that the sponsor submit a request for a comprehensive multidisciplinary meeting to discuss the drug development program. This meeting is a Type B meeting, used to discuss the overarching, high-level plan for drug development. Discussion topics will depend on the therapeutic area, development phase, and specific development program issues of the proposed drug and indication. The discussion can include topics such as planned clinical trials and endpoints, plans for expediting the manufacturing development strategy, and studies that potentially could be completed after approval. This meeting also should be used to establish a communication plan with the sponsor so interactions between CDER and the sponsor related to the breakthrough therapy drug development program can be managed efficiently. The communication plan should include expectations on the timing and format of interactions and information exchange. See Attachment 1 for a complete list of possible discussion topics for this meeting.

- This meeting should be held between 60 days to 6 months after granting breakthrough therapy designation. The timing of this meeting depends on where the sponsor is in its drug development program. The RPM should work with the sponsor to establish the earliest mutually acceptable time frame for holding this meeting to facilitate an expedited development program.

- All disciplines should be invited to attend and participate in this meeting; however, only one person from each relevant discipline is required to attend to represent the discipline.

Subsequent Type B meetings

- After the initial comprehensive multidisciplinary Type B meeting is held, the review team should continue to meet with the sponsor throughout the IND phase, outside of the critical IND milestone meetings, to address important issues at different development phases. The frequency of these meetings should be determined by the communication plan established at the initial comprehensive multidisciplinary meeting.

- Subsequent meetings with sponsors for breakthrough therapy-designated drugs should be considered Type B meetings, unless they meet the criteria for a Type A meeting. These meetings likely will be discipline-focused and the review team members invited will depend upon the topics to be discussed.

Critical IND milestone meetings

- Critical IND milestone meetings likely will take place in an accelerated time frame. Because the development program for a breakthrough therapy-designated drug is expected to be expedited as compared to that of a nonbreakthrough therapy-designated drug, topics should be discussed earlier than outlined in MAPP 6030.9. For example, proprietary name plans, inspection and manufacturing facility considerations, and postmarketing study or trial plans should be discussed earlier than the pre-NDA/BLA meeting. In advance of each milestone meeting, CDER review staff should discuss with the sponsor and agree upon the discipline-specific information to be covered at each milestone meeting.

- All disciplines should be invited to attend and participate in the milestone meeting; however, only one person from each relevant discipline is required to attend to represent the discipline.

Other communications with sponsors outside of CDER-sponsor meetings

- The RPM, as the liaison with the sponsor, should use other communications outside the formal meetings noted above (i.e., teleconferences, information requests, and emails) to serve as tools for focused discussions, rapid information exchange, and issue resolution. These communications may involve procedural, regulatory, or scientific topics.

- When CDER receives an inquiry from the sponsor, the RPM, after consulting with the review team, should communicate the anticipated timeline for each response to inquiries. The timelines for response should be based on the complexity of the inquiry. For example, some questions may be able to be addressed within a few working days, whereas a more complex question or issue may require several weeks. Whenever possible, CDER should respond within 30 days to all inquiries. RPMs, in collaboration with review staff, as appropriate, should capture all substantive discussions and agreements with the sponsor in an official document or memo to the IND administrative file within 15 working days after responding to the inquiry.

CDER Internal Meetings and Communications

- CDER review staff should hold internal meetings, as necessary, to discuss the development program at a high level, evaluate and adjust planned timelines, and prioritize work. The timing and intervals for internal meetings depends on the development stage and the pace of IND submissions, as well as internal resource availability and constraints. The following are suggested time points for the review team to meet:

  – 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 (refer to the subsection CDER Review of Breakthrough Therapy Drug Development Programs), and any drug-specific considerations anticipated

- After the review of certain IND amendments (i.e., amendments that contain trial data), to discuss specific development program issues and plans to address these issues

- Before MPC 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 the criteria of breakthrough therapy designation is no longer met, to discuss the appropriateness of sending an Intent to Rescind letter to the sponsor

CDER Review of Breakthrough Therapy Drug Development Programs

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

  - The frequency of these reviews depends on various factors, such as where the sponsor is in drug development, the therapeutic area of the drug product, and the types of proposed and ongoing clinical trials. In general, these reviews should be performed approximately every 3 to 6 months, as agreed upon by the review team, and adjusted accordingly as the development program progresses.

  - After CDER reviewers have performed their periodic high-level review of a sponsor's drug development program, an internal meeting should be held to discuss their assessments and workload management. Each discipline should provide the CDPL with a high-level assessment of the status of the overall breakthrough therapy drug development program, as it relates to their discipline. Suggested topics for discussion at this meeting can be found in Attachment 2.

  - To evaluate the drug development program thoroughly, CDER review staff need current and complete information from the sponsor regarding its drug development program. CDER review staff should request information on various aspects of the drug development programs from sponsors, as needed, if information from the sponsor is missing or inadequate.

- The MPC should perform a portfolio review of drugs that have been granted breakthrough therapy designation. Discussions should focus on programs with novel

or controversial study design, with interesting 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 choose to rescind the breakthrough therapy designation. The review team may consider rescinding in instances, such as:

  – Emerging data no longer show substantial improvement over available therapy

  – A drug gains traditional approval or the clinical benefit is verified for a drug granted accelerated approval for the same indication as the designated drug, and the designated drug no longer shows substantial improvement over the new available therapy

  – The designated drug development program is no longer being pursued

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

  – The review team should identify that a breakthrough therapy drug may no longer meet the designation criteria. A multidisciplinary internal meeting should be held to discuss rescinding the designation. The RPM should ensure that all members of the review team are notified and included in the discussion. Division director concurrence should be obtained on the intent-to-rescind decision.

  – The review division should notify the sponsor in writing of its intent to rescind the breakthrough therapy designation. The letter should include a description of the reasons 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 the division to discuss the breakthrough therapy designation for the drug.

  – If additional information is presented or submitted and, after discussion with the MPC, the division's determination that the criteria for breakthrough therapy designation are no longer being met is unchanged, the review division should send an official letter to the sponsor rescinding the designation and provide a rationale for this decision in the letter.

  – If additional information is presented or submitted and, after review, the review division determines that the criteria for breakthrough therapy designation continue to be met, plans for a path forward for the development of the drug should be discussed, documented, and communicated to the sponsor via a letter or teleconference.

REFERENCES[10]

Section 506 of the FD&C Act, as amended by Section 902 of FDASIA: http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf

Guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*

Guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants*

MAPP 6025.1 *Good Review Practices*

MAPP 6025.2 *Good Review Practice: Clinical Review of Investigational New Drug Applications*

MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*

DEFINITIONS

Note to reader: The following three definitions are out of alphabetical order for clarity sake.

Super Office — An office that reports to the CDER Director and to which subordinate offices report.

Subordinate Office — An office that reports to a super office.

Division — An office that reports to a subordinate office.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

[10] Guidances for industry can be found on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. MAPPs can be found on the Manual of Policies and Procedures Web page at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

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
- 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
- If the use of the drug will require a diagnostic test, the in vitro diagnostic development plan with the Center for Devices and Radiological Health (CDRH)
- The Gantt chart of the 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 (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 DDI, 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

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 Programs

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
- 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 and plans for 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.

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