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

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PURPOSE

- This 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 that is receiving an expedited review consistent with section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA).[1,2] This MAPP outlines CDER actions from the time such an application has been submitted until an action is taken on the application.[3]

- This MAPP does not address the specific content of scientific reviews. This MAPP does not cover the review of breakthrough therapy designation requests. This MAPP also does not cover CDER actions from the time a breakthrough therapy designation has been granted until a marketing application has been submitted. That information is covered in MAPP 6025.6 *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*.

[1] http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf.

[2] See POLICY for a detailed explanation of *expedited review*. Also see DEFINITIONS for definitions of terms used in this MAPP.

[3] This MAPP also addresses presubmission meetings, even though they are requested before a marketing application is submitted, because the marketing application is the subject of the presubmission meeting.

- This MAPP is one in a series of MAPPs designed to document good review practices (GRPs) for review staff in accordance with MAPP 6025.1 *Good Review Practices*. General policies, responsibilities, and procedures regarding all GRPs are contained in MAPP 6025.1 and apply to this MAPP.

BACKGROUND

- Section 902 of FDASIA 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 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*[4] 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.

- 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 is based on CDER staff experience to date with breakthrough therapy-designated drugs. As additional experience working with breakthrough therapy-designated drugs is acquired, as part of a quality systems approach to drug review, this MAPP may be updated.

POLICY

- CDER staff will designate the review of a marketing application for a breakthrough therapy-designated drug as a priority review if it meets the criteria for such a review designation. CDER staff and managers will follow MAPP 6020.3 Rev.2 *Review Designation Policy: Priority (P) and Standard (S)*.

[4] 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.

- If the application is designated as a priority review, CDER review staff and managers will consider whether the marketing application qualifies for an expedited review. CDER staff will consider an expedited review of a marketing application for a breakthrough therapy-designated drug whenever possible.

- Section 902 of FDASIA instructs 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 plans to act at least 1 month before the Prescription Drug User Fee Act (PDUFA) goal date,[5] provided that no unexpected review issues arise and/or the review team does not experience an unexpected shift in work priorities or team staffing.[6] For a breakthrough therapy-designated drug to be considered for an expedited review:

  – Preliminary review of results from clinical trials must indicate that the drug has demonstrated substantial improvement over existing therapies;

  – The marketing application must be designated as a priority review; and

  – The review team must have determined that a first cycle approval is likely.

- 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, taking all relevant factors into account, to determine if an expedited review is appropriate. Below are examples of factors that may influence the decision to conduct an expedited review even if other criteria for an expedited review are met (although they do not necessarily rule out an expedited review):

  – Resources to expedite the review are not available because of competing public health priorities (e.g., anthrax, Ebola, influenza)

  – An advisory committee (AC) meeting is needed for reasons such as clinical trial results or safety issues

  – An unanticipated safety issue is identified that requires a risk evaluation and mitigation strategy (REMS) with elements to ensure safe use

[5] For additional information on PDUFA goals, see PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017 at http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.

[6] See the CDER 21st Century Review Process: Desk Reference Guide, which further discusses an expedited review (http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM218757.pdf).

  - Manufacturing issues are identified

- Designation of an 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 NME NDAs and Original BLAs (the Program) will follow the Program review requirements.[7] In general, Program-related meetings will occur earlier in the review cycle for applications undergoing expedited reviews.

- FDA has determined that it is appropriate for a drug designated as a breakthrough therapy to be able to obtain rolling review;[8] however, granting rolling review is not a requirement for conducting an expedited review. If an expedited review is planned, CDER review staff and managers should encourage sponsors to submit portions of the marketing application under rolling review to facilitate meeting the expedited review timelines. CDER review staff will initiate a review of these portions shortly after receipt of the submissions, as resources allow.

PROCEDURES

General Considerations

- The Office of New Drugs regulatory project manager (OND RPM) should solicit information from sponsors about the timing of a planned marketing application submission for a breakthrough therapy-designated drug so that logistical and workload preplanning can occur.

- Early internal discussions about the appropriateness of an expedited review are critical because an expedited review demands substantial logistical planning from the review team and the sponsor. These internal discussions should occur after granting breakthrough therapy designation and no later than the internal premeeting before the presubmission meeting. A decision to conduct an expedited review should be made before the internal premeeting.

- The OND RPM should complete the scheduling for all milestone and other required CDER-sponsor and internal meetings within 14 working days of receipt

[7] See the following Web page for additional information on the Program: http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/proceduressopps/ucm350322.htm.

[8] Refer to Appendix 2 of the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

of a marketing application for a breakthrough therapy-designated drug for which an expedited review is planned.

- The OND RPM should engage in frequent discussions with the RPMs or representatives from other offices and centers to promote dissemination and exchange of application-specific information. Discussions could include such topics as identified issues and plans for resolution, the status of targeted internal goals, and the sponsor's readiness to have the commercial drug product available for distribution by the targeted action date. OND RPMs should communicate information received from other offices and centers to the core review team in a timely manner.

- There may be instances when the CDER review team has determined that an expedited review is appropriate, but during the review of the marketing application, the review team determines that an expedited review is no longer appropriate. This may occur, for example, if:

  – Unexpected application deficiencies are found

  – The marketing application is of poor quality

  – The sponsor fails to engage in collaborative communications (e.g., failure to respond to information requests (IRs))

  – There is a need to hold an AC meeting

  – Unanticipated review issues arise

  – The review team experiences an unexpected shift in work priorities or team staffing

  If the CDER review team determines that an expedited review is no longer appropriate, the review timeline will default to the priority review timeline. The OND RPM should communicate this decision and the rationale for the decision to the sponsor within 3 working days of making this decision.

- CDER review staff, through the RPM or directly, should bring regulatory, procedural, or process-related issues identified during the expedited review of marketing applications for breakthrough therapy-designated drugs to the attention of the CDER Breakthrough Therapy Program Manager[9] who will provide guidance, as needed, and will coordinate information dissemination and relevant activities through the RPM assigned to the marketing application.

[9] See MAPP 6025.6 *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*.

Presubmission Meeting

- CDER review staff should refer to MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review* and MAPP 4180.4 *NDAs/BLAs: Using the 21st Century Review Process Desk Reference Guide* for the purpose, invitee list, and suggested topics for discussion for the presubmission meeting.[10] 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 has been collected

  – 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

  – 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

[10] The development program for a breakthrough therapy-designated drug could be considerably shorter than for other drugs; therefore, the presubmission meeting should not be the first time that many of these topics are discussed.

CDER Communications and Interactions With Sponsors

- The OND RPM should work with the review staff and sponsors to decide on mutually acceptable patterns for IRs and responses, such as one at a time, bundled daily, or bundled biweekly. IRs to sponsors should include a response-requested date and a context and rationale for the IR.

- The OND RPM, as the liaison with the sponsor, should use other communications outside of IRs (i.e., teleconferences and emails) to serve as tools for focused discussions, rapid information exchange, and issue resolution. The OND RPM, in collaboration with the review team, as appropriate, should capture all substantive discussions and agreements with the sponsor in an official document or memo to the new drug application (NDA)/biologics license application (BLA) administrative file within 5 working days after the substantive discussion was held or the agreement was made.

Internal CDER Communications and Meetings

- Filing/Planning Meeting. This meeting should be held 2 to 3 weeks after the marketing application has been received. CDER review staff should reference MAPP 4180.4 *NDAs/BLAs: Using the 21st Century Review Process Desk Reference Guide* for the purpose, invitee list, and topics for discussion. Additional suggested topics for discussion include:

  – Confirmation that the 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 presubmission meeting

  – Plans for clinical, clinical pharmacology, and manufacturing inspections

  – Concurrence on whether an AC meeting is needed, and if so, plans to streamline preparation for the AC

  – Status of consultation with special government employees (SGEs), if needed

- Application Review Meetings/Status Updates. Throughout the review cycle, the review team should discuss the following topics regularly to facilitate early communication of identified issues to the entire core review team. These discussions may occur through dedicated application review meetings, one-on-one meetings, email exchanges, or administrative rounds, among others. Topics for discussion should 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 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

- CDER review staff, through the RPM or directly, should notify the CDER Breakthrough Therapy Program Manager[11] of policy issues 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 will facilitate a discussion with the CDER Medical Policy Council.

- Relevant subordinate office and super office directors should stay abreast of the status of expedited reviews for all breakthrough therapy-designated drugs through administrative rounds and internal meetings with their leadership teams, and should provide guidance and direction, as necessary.

Advisory Committee Meetings

- It is anticipated that during the expedited review of marketing applications for breakthrough therapy-designated drugs, an AC meeting likely will not be convened. This is likely because the following are generally expected in the case of a breakthrough therapy-designated drug:
  - The safety profile is acceptable for the indication;
  - The clinical trial design and endpoints are acceptable;

[11] For CDER Breakthrough Therapy Program Manger contact information, see http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm329491.htm.

- The application did not raise significant safety or efficacy issues that were unexpected for a drug of the class or in the intended population;

- The application did not raise significant public health questions on the role of the drug and the diagnosis, cure, mitigation, treatment, or prevention of a disease; and/or

- Outside expertise was not necessary; there were no controversial issues that would benefit from AC discussion.

- In lieu of a full AC meeting, the CDER review team may consult SGE(s) during the review. This decision should be made early in the expedited review cycle. The SGE(s) should be identified and cleared through the Division of Advisory Committee and Consult Management staff as soon as a need for SGE(s) is determined.

Clinical, Clinical Pharmacology, and Manufacturing Inspections

- OND RPMs should work with sponsors to ensure that a complete list of clinical, clinical pharmacology, and manufacturing sites is submitted as early as possible, generally no later than the presubmission meeting.

- OND RPMs should work with the appropriate offices noted below to ensure that inspection-related activities are scheduled as early in the application review process as possible, but no later than 3 weeks after the receipt of a complete marketing application that is receiving an expedited review, to ensure that inspection results are available for review team evaluation and to allow time for the sponsor to address significant inspection findings, if possible:

  - Office of Compliance, Office of Scientific Investigations, for clinical investigator sites, and sponsor/clinical research organization/monitor sites evaluating good clinical practice compliance

  - Office of Translational Sciences, Office of Study Integrity and Surveillance, for clinical and analytical sites conducting bioequivalence/bioavailability studies, and good laboratory practice labs conducting nonclinical studies

  - Office of Pharmaceutical Quality (OPQ) for manufacturing sites

REFERENCES[12]

Section 902 of FDASIA:
http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf

PDUFA V:
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327030.htm

21st Century Review Desk Reference Guide, Managers Toolkit, and the Four Timeline Diagrams:
http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/21stCenturyReview/ucm2004690.html

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

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

MAPP 6010.5 *NDAs and BLAs: Filing Review Issues*

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

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

MAPP 6025.1 *Good Review Practices*

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

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

[12] Guidance 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.

DEFINITIONS

CDER NDA/BLA Core Review Team — OND RPM, Quality RPM, primary and secondary reviewers (clinical, clinical microbiology, biostatistics, clinical pharmacology, nonclinical, and quality), cross-discipline team lead, OND deputy division director, OND division director, Office of Surveillance and Epidemiology representatives, Office of Medical Policy Patient Labeling representatives, OPQ representatives.

Drugs or Drug Products — For the purposes of this MAPP, include both drugs and biological drug products regulated by CDER.

Expedited Review — A review of a marketing application when the review team plans to act at least 1 month before the PDUFA goal date.[13]

Marketing Application — For the purposes of this MAPP, applies to original NDAs and BLAs and efficacy supplements.

Note to reader: The following definitions are out of alphabetical order to improve clarity.

Office — An office that reports to the CDER Director that is neither a super office nor a subordinate office.

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.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

[13] http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf