CDER 21st Century Review Process

Desk Reference Guide

New Drug Application and Biologics License Application Reviews
(NDA/BLA Review Process)

Version: September 2012

Recent Major Changes

September 2012:

- Streamlined document and updated to improve readability and add other minor clarifications.

- Updated document to incorporate PDUFA V requirements, including the following:
  - PDUFA V's "Program Review" requirements that apply to NME NDAs and original BLAs
  - The Pre-NDA/BLA Meeting section is expanded with the new PDUFA V pre-submission meeting requirements (Section 1.1)
  - The Filing Communication (74-day letter) PDUFA V requirement for communicating the planned date for the mid-cycle meeting and preliminary plans on holding an AC meeting (Section 3.2)
  - Requirement to communicate with the applicant two weeks after the mid-cycle meeting to provide an update on the review, including significant issues identified, IRs, thoughts on REMS, date for late-cycle meeting, AC meeting update (Section 4.4)
  - The addition to the review schedule of a late-cycle meeting with the applicant (Section 4.13)
  - Establishment evaluations for NDAs / establishment evaluations for BLAs are to be completed within 10 months from receipt date for standard and 6-months for priority applications (Section 4.8).

- PDUFA V changes are indicated by this logo: **PDUFA V Change**

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Objectives of this Guide

The CDER 21st Century Review Process Desk Reference Guide (DRG) describes the review activities required for NDA and BLA applications, including procedures designed to meet the principles and timelines described in FDA's "Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products (GRMP), dated April 2005," and process requirements described in the PDUFA V agreement entitled: "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017."

The DRG is intended for use in the review of New Drug Applications (NDAs), Biologics License Applications (BLAs), and efficacy supplements. Although it is focused on the review of original applications, the principles and procedures are applicable to resubmissions. In addition to explaining the steps in the review process, the DRG outlines expectations for reviewer conduct and provides timelines for completion of various review milestones. It describes the roles of review participants and signatory authorities and includes suggestions for working in a team environment to complete a timely, high-quality review.

The objectives of the DRG are to:

- Describe the steps and expected timelines for the review processes for the different types of applications.
- Provide a resource for CDER staff members.
- Describe the PDUFA V review model referred to as "The Program" that applies to New Molecular Entity New Drug Applications and original Biologics License Applications.

This Guide also discusses characteristics of a successful review process:

- A quality review with clarity of findings
- Identification of issues early in the review
- Collaboration across disciplines and respect for others' knowledge
- Clear communications and interactions
- Clear deadlines
- Consistency of practice across CDER offices and divisions
- Effective leadership
- Fair treatment
- Recognition of team participation and individual work products

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Process Overview

Conduct Review of New Drug Application (NDA) or Biologics License Application (BLA)

The review process takes place in six major steps. Each step will be described in detail later in this document; a graphic illustrating the steps can be found on page 6, a summary of the steps can be found on page 7.

General Roles & Responsibilities:

- Document Room Staff: Receive document, process, and distribute the application, archive all pertinent documents, and enter application data into the application database(s).
- Regulatory Project Manager: Manages the review process with the Cross-Discipline Team Leader, coordinates all application review communications (internal and external), maintains documentation of the review, conducts a regulatory review of the application and an initial PLR labeling format review for prescribing information, and serves as the primary contact for review-related regulations and policies.
- Primary Reviewer: Core review team member responsible for conducting a scientific review on an assigned section of the application using his/her particular scientific discipline, documents his/her review findings, and recommends the action to be taken on the application. Disciplines usually included on the core review team are:
  - Clinical (Medical)
  - Pharmacology/Toxicology (P/T)
  - Product Quality (formerly CMC)
  - Biometrics (Statistical)
  - Clinical Pharmacology and Biopharmaceutics
  - Clinical Microbiology (for anti-infective products)
  - Medication Error (for proprietary name)
  - Risk Management Analyst for Risk Evaluation and Mitigation Strategies (REMS) submissions*
  - Office of Scientific Investigations (OSI)
  - Office of Compliance's Office of Manufacturing Product Quality (OMPQ)

***Note:** A risk management analyst is assigned as a primary reviewer if at least one of the following is pertinent:

1. The product is an NME (regardless of whether a proposed REMS is included in the application)
2. The applicant submits a proposed REMS with the application
3. The product already has an approved REMS and the applicant is requesting approval of a new indication (i.e., the applicant has submitted an efficacy supplement)
4. The product will be part of a class of drugs that already has a REMS

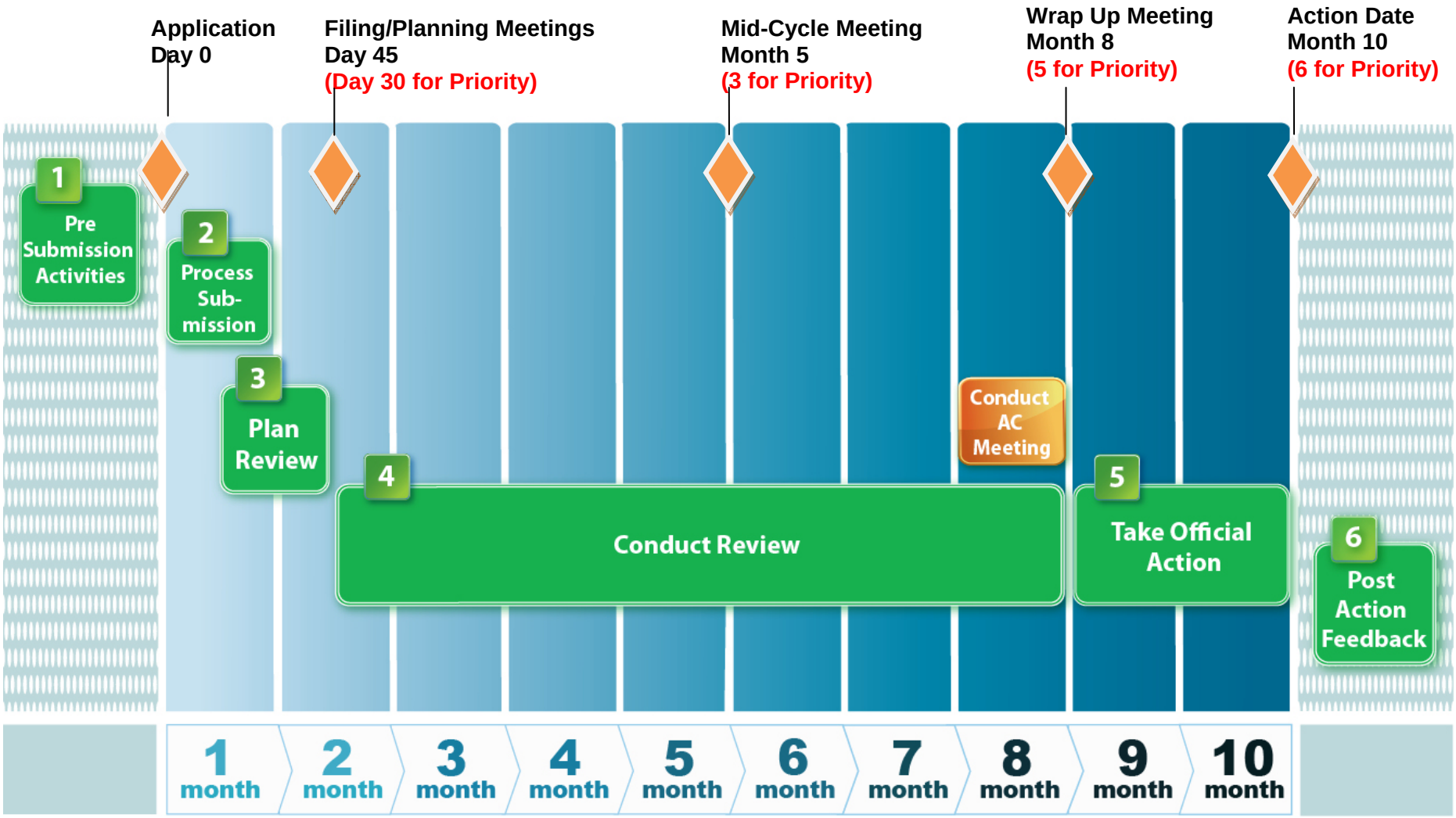
- Consultants/Subject Matter Experts: Review team members who work with the core review team to provide additional scientific expertise required for the review of certain portions or sections of the application. Such consultants may include: Study Endpoints and Labeling Development (SEALD), Office of Prescription Drug Promotion (OPDP), Pediatric and Maternal Health Staff (Pediatric Review Committee or PeRC), Bioresearch Monitoring (BIMO) Program, Controlled Substances Staff, Patient Labeling Team.
- Discipline Team Leader/Supervisor (DTL): Provides day-to-day management of the discipline-specific review, performs discipline-specific secondary review, and maintains consistency of regulatory decisions within their scientific discipline.
- Discipline Directors: Responsible for ensuring the quality and consistency of the discipline's review decision.
- Cross-Discipline Team Leader (CDTL): Generally the medical team leader for applications containing clinical data. 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. A CDTL review may not be needed for all efficacy supplement submissions.
- OND Division Director: Responsible for ensuring the quality of the review decision and associated administrative record. With the CDTL, handles conflicts that arise during the review. Attends milestone review team meetings. Writes a summary review that includes a decision or recommendation for regulatory action.
- Signatory Authority: Generally an Office of Drug Evaluation (ODE) Director or Division Director who writes a tertiary review and takes the action on the application. For applications signed off at the office level, tertiary review includes participation of the ODE Associate Director for Regulatory Affairs (ADRA), OND Associate Director for Pharmacology/Toxicology, ONDQA or OBP Division Director, OCP Division Director, and Biometrics Office Director.

Process Overview

21st Century Review

Summary of Review Team Responsibilities						
Primary Reviewer	**Discipline Team Leader (DTL)**	**Cross-Discipline Team Leader (CDTL)**	**Regulatory Project Manager (RPM)**	**Discipline Director**	**OND Division Director (includes Deputy)**	**OND ODE Director (includes Deputy)**
• Performs scientific review, labeling review, and recommends action. • Consults with TL, peers, and others while developing the review. • Works collaboratively within a team setting. • Raises issues and identifies to management potential solutions throughout the review. • Attends and participates in review team meetings as needed. • Organizes work to meet deadlines.	• Assigns and provides guidance and feedback to primary reviewer. • Provides clear direction to the primary reviewer; meeting regularly to provide feedback and discuss issues. • Resolves conflicts related to discipline area. • Attends review team meetings, as needed. • Attends and participates in key milestone team meetings. • Advises CDTL of potential schedule slippage and issues. • Signs off on primary review and writes a DTL secondary review, as needed. • Organizes work to meet deadlines.	• Provides day-to-day leadership to team and oversight of the review. • Works with the RPM and DTLs to address issues and resolve conflicts that arise within and across disciplines and to ensure efficient and timely reviews. • Attends all team meetings. • With RPM, monitors review progress and keeps OND management apprised of review status. • Writes a CDTL Review for each application bringing together highlights and perspectives of all disciplines. • Organizes work to meet deadlines.	• Serves as regulatory leader for review team. • Performs PLR format review of label and includes deficiencies in 74-day letter. • With the CDTL, manages day-to-day review activities. • Organizes and attends all review-related meetings -- usually facilitates meeting. • Tracks review progress, addresses potential review process issues, and resolves obstacles, keeping the CDTL informed. • Serves as the point of contact for communication with the applicant. • Maintains an accurate administrative record of the review. • Organizes work to meet deadlines.	• Is responsible for ensuring the quality and consistency of the discipline's review and recommendation for action. • Attends key milestone team meetings, as needed.	• Has signatory authority for non-NME applications. • Attends key milestone review team meetings. • Is responsible for ensuring the quality of the review decision, approved labeling, and associated administrative record. • Appoints and mentors the CDTL and works with the CDTL and RPM to ensure that review goals are being met. • With the CDTL handles conflicts that arise during the review. • Writes a tertiary "summary" review that includes a decision or recommendation for regulatory action. • Keeps Office Director apprised of review status and significant issues and organizes work to meet deadlines.	• Has signatory authority for NMEs, original BLAs, and other applications such as novel public health issues. • Attends key milestone review team meetings. • Writes a decisional memorandum for applications. • With the Division Director, ensures the quality of the review decision, approved labeling, and associated administrative record. • Organizes work to meet deadlines.

Overview of the NDA/BLA Review Process and Major Steps for Completing the Review



Note: **See Appendix A for a timeline diagram for PDUFA V Program reviews.**

Summary of the Major Process Steps

CDER's NDA and BLA Review Process involves a total of six major steps, two of which occur outside the actual review time frame – namely, Pre-Submission Activities and Post-Action Feedback to the Applicant. Monitoring the progress of the review occurs continuously throughout the review process. The timelines to take action for applications that are not in the PDUFA V "Program" are 6-months from receipt for a priority review and 10-months for a standard review. The timelines for NMEs and BLAs that fall under PDUFA V's "Program" Review Model are 10-months for standard applications and 6-months for priority reviews **from the 60-day filing date** (or 12 months and 8 months respectively from the date of submission of the application).

PDUFA V Change

1 **Ensure Readiness for Application through Pre-Submission Activities** The first step in the process is composed of activities that applicants can take advantage of to improve the quality and content of their NDA/BLA application prior to submitting it to FDA.

2 **Process Submission** Applications are received and processed by document control room staff and then distributed to the appropriate review division. The RPM conducts an initial assessment of the NDA/BLA to assure that certain regulatory requirements are met and that a user fee has either been paid, the fee waived, or the application exempted. Reviewer assignments are made at this time.

3 **Plan Review of the Application** The review team conducts an initial assessment of the NDA/BLA and associated labeling. Each discipline makes a recommendation on *fileability* of the application at the filing meeting that is held by day 45 of the review (day 30 for priority reviews). If the application is found *fileable* a planning meeting is held to further discuss timelines and review activities.

4 **Conduct Scientific/Regulatory Review of the Application** During the review phase, the primary reviewers analyze their assigned portion of the application and write their reviews; team leaders interact with reviewers and provide guidance on a regular basis. For PDUFA V "Program" reviews, a late-cycle meeting is held between the review team and the applicant. An additional two months is available for PDUFA V "Program" applications to address complex review issues and attempt to remedy minor problems with the application.

PDUFA V Change

5 **Take Official Action on the Application** Based on the signatory authority's review of the Action Package and on discussions with the review team, the signatory authority determines the action to be taken on the application. The final action decision is conveyed to all team members.

6 **Provide Post-Action Feedback to the Applicant** The focus of this activity is on learning from the review experience. This optional meeting can take place as either an End of Review Conference, typically held following an action other than an approval, and/or a post-action feedback/lessons learned meeting. These two meetings can be combined into a single meeting if appropriate.

The following sections of this document detail the activities and timelines required for each of the steps of the review process outlined above.

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1 Ensure Readiness for Application through Pre-Submission Activities

PDUFA V Change

During this phase, applicants are strongly encouraged to request a meeting with the appropriate FDA review division prior to the submission of an NDA/BLA, particularly in the case of NMEs and BLAs covered under the PDUFA V "Program," to discuss the planned content of their application. Meetings include the traditional pre-NDA/BLA meeting and other meetings such as the electronic pre-submission meeting, if necessary. Ideally, good FDA-industry IND interactions and use of pre-NDA/BLA meetings will help to ensure that all submitted applications are complete and *fileable*.

1.1 Pre-NDA/BLA Meeting

Meeting Purpose: The purpose of a pre-NDA/BLA meeting is to discuss format and content of the anticipated application, including labeling and REMS (if applicable), presentation of data, dataset structure, acceptability of data for submission, as well as the projected submission date of the application. The meeting should be held sufficiently in advance of the planned submission of the application to allow for meaningful response to FDA feedback and should generally occur not less than two months prior to the planned submission.

Preparing for the Pre-Submission Meeting: In preparation for a pre-NDA/BLA meeting, the RPM evaluates the meeting request and meeting package, schedules the meeting with pertinent reviewers and provides them with the pre-meeting background package. The Office of Surveillance and Epidemiology (OSE) RPM is also given the meeting package and informs the OND RPM of the OSE reviewer assigned (as necessary) who should be invited to the meetings. The identified OSE staff members are invited to meetings if issues relating to a REMS, postmarketing safety study, or other safety concern(s) are identified.

The information to be provided by the applicant for the meeting includes:

- A timeline and list of prior FDA meetings and agreements, prior FDA advice, and any development changes. This would include meeting minutes and letters sent earlier, regulatory history, issues raised at the end-of-phase 2 meeting, etc.
- A summary of technical information to be submitted in the NDA/BLA, including the results of the pivotal trials, if they are available, and the proposed dataset structure.
- Highlights of any potential problems, including product quality issues, data integrity concerns, safety signals, etc.
- Proposed draft labeling.
- The proposed format for organizing the submission, including methods for presenting the data and a draft index if available.
- A discussion of the need for a REMS or post-marketing study/trial for any safety issue(s) that has emerged during development or during foreign marketing.
- Other information/issues that require discussion.

- List of questions for FDA.

Reviewers should review the meeting package and also be prepared to discuss internally the potential need for an Advisory Committee meeting, REMS, and PMRs. The reviewers draft responses to the pertinent questions submitted by the applicant. The project manager assembles reviewers' comments and sends them to the applicant at least 48 hours prior to the meeting.

Holding the Meeting: At the pre-NDA/BLA meeting, the FDA and the applicant will agree on the content of a complete application for the proposed indication(s), including preliminary discussions on the need for REMS or other risk management actions. Reviewers also describe how data should be presented in the NDA/BLA to facilitate its review. The agreement and discussions are summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

PDUFA V Change

For "Program" applications, during the pre-submission meeting the FDA and the applicant may reach agreement on submission of a limited number of application components not later than 30 calendar days after the submission of the original application. These components must be of a type that would not be expected to materially impact the ability of the review team to begin its review. Examples of application components that may be appropriate for delayed submission include updated stability data (e.g., 15-month data to update 12-month data submitted with the original submission) or the final audited report of a preclinical study (e.g., carcinogenicity) where the final draft report is submitted with the original application. Major components of the application (e.g., the complete study report of a Phase 3 clinical trial or the full study report of required long-term safety data) are to be submitted with the original application and are not subject to agreement for late submission. Any agreement that is reached on delayed submission of application components will be summarized at the conclusion of the meeting and reflected in the FDA meeting minutes.

FDA should request that the applicant submit information on all manufacturing facilities and/or preliminary data on pivotal clinical trials or bioequivalence study(ies) that would be useful in early determination of sites for inspection.

Meeting discussions may include what data will be submitted to support sought-after labeling or how labeling annotations should be linked to the primary supporting information in the eCTD. Container and carton labels can also be addressed during pre-submission meetings. Review teams should direct applicants to the website for the new requirements for prescribing information. (See New Requirements for Prescribing Information)

Applicants may request that an application be designated for fast-track review; applicants may also request to submit completed sections of the marketing application for review by FDA (rolling review). (See Fast Track, Accelerated Approval, and Priority Review)

Minutes from the Pre-NDA/BLA meeting are prepared and archived by the RPM.

1.2 Electronic Pre-Submission Meeting

If technical aspects of the submission have not been adequately addressed with the sponsor (e.g., at the pre-NDA/BLA meeting), an electronic pre-submission meeting may be held at the discretion of the review division 30-60 days prior to the submission of the application. The FDA may recommend this meeting for some applications. The focus of the NDA/BLA electronic pre-submission meeting is on navigation, formatting of electronic files, and layout of the application.

1 Pre-submission Activities

In preparation for an electronic submission meeting, the RPM evaluates the meeting request and works with the Division of Regulatory Review Support (email: esub@fda.hhs.gov) to load any provided (mock) data sets on the FDA computer system that support review of electronic applications. The review division prepares draft responses to any questions submitted by the applicant and sends them to the applicant prior to the meeting. Meeting minutes are prepared and archived by the RPM.

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2 Process Submission

All applications are expected to be complete at the time of original submission. The only potential exception would be for an application under the PDUFA V "Program," where an agreement for a late submissions exists. If the applicant does not have a pre-NDA/BLA meeting with FDA and no agreement exists between FDA and the applicant on the contents of a complete application or delayed submission of certain components of the application, the applicant's submission **must be complete at the time of original submission**.

PDUFA V Change

2.1 Receive Submission

The application review process begins upon receipt of the application. The PDUFA time clock begins on the FDA receipt date except for products submitted under "The Program" (i.e., NME NDAs and original BLAs). For these applications the PDUFA time clock begins 60 days after the application receipt date if the application is filed; however, the **review timeline** for all applications begins on the day of submission.

PDUFA V Change

The application is received either in hard copy by the Central Document Room or electronically in the Electronic Document Room and is processed (control number assigned, date stamped, and a DARRTS/ RMS-BLA record created or updated as appropriate). New applications are forwarded to the assigned review division's Chief Project Manager. Paper submissions are to be received by the division's CPMS/RPM by day 3 after receipt in the Central Document Room. Electronic NDA/BLA submissions on physical media are loaded in the Electronic Document Room by 3 business days from receipt at the Central Document Room. Electronic submissions may also be received via the Electronic Submission Gateway (ESG or "the Gateway").

Any Program application components that FDA agreed could be submitted after the original application must be received not later than 30 calendar days after receipt of the original application. Missing components may lead to a refusal-to-file decision.

PDUFA V Change

2.2 Ensure Conformance to Regulatory Requirements

The review process for new NDAs or BLAs begins with a determination by the RPM as to whether the user fees have been paid, waived, or exempted (PDUFA, Form FDA 3397). For both NDAs and BLAs, the RPM checks the daily PDUFA Payment & Arrears Report e-mail to determine user-fee status. For BLAs only, the RPM sends the user fee cover sheet to CBER RIMS (cberrims@fda.hhs.gov, or FAX 301-827-2875) to associate the User Fee check with the application number in RMS-BLA. If the user fee has not been paid within **5 days** of application receipt, or if the applicant is on the arrears list, the RPM drafts an "Unacceptable for Filing" letter (user fee "not paid") to the applicant and the review process is halted until the fees are received. Once the fees are received, the RPM sends an acknowledgment letter to the applicant with the new receipt date and this resets the PDUFA review clock. The RPM also notifies the review team of the change in the PDUFA date.

If all required fees have been paid, the review process continues with a determination by the RPM as to whether the application has been correctly coded in the document room. Any coding changes are routed to the document room for DARRTS database corrections for NDAs. The RPM is

responsible for correcting BLA information in the RMS-BLA database. The RPM also checks to make sure the application is administratively complete and compliant with content and format regulations and other regulatory requirements. The RPM ensures that any proposed proprietary name was submitted as a separate document and routed by the Document Room directly to OSE for review. (See Guidance for Industry and Concept Paper)

2.3 Establish Review Team and Distribute Submission

Submission Distribution: An NDA/BLA may be submitted either in paper or electronic format.

- For paper submissions, the RPM distributes review copies to the designated discipline team leaders for reviewer assignments. The RPM notifies the Document Room of the reviewer assignments and DARRTS or RMS-BLA is updated with this information. For subsequent NDA/BLA amendments, the RPM will ensure that assigned reviewers receive their copies of the submission.
- For a new NDA/BLA submitted in electronic format, the RPM forwards the location of the electronic application (i.e., server path) via e-mail to the appropriate discipline team leaders for reviewer assignments, and, if applicable, the OSE SRPM for OSE reviewer assignments.

Team Leader Assessment: Discipline team leaders (DTL) do a quick review of the contents of the application to determine whether a reviewer assignment is necessary for an original application or efficacy supplement submission and whether the package contains any obvious issues that may require special attention by the reviewers. They convey these issues to the assigned reviewer along with the pertinent application section. The DTL or OSE SRPM (for OSE reviewers) notifies the RPM via e-mail of the reviewer assignment or that no assignment is required. For OSE, the DRL notifies the OSE SRPM, who then notifies the RPM. Notification of the RPM must be done **by day 14**.

Reviewer Receipt: By day 14 discipline reviewers have been assigned to review the NDA/BLA and have received applicable review volumes or the link to the electronic submission.

2.4 Acknowledge Receipt of Submission

The RPM sends a letter acknowledging the receipt of the application to the applicant by day 14.

3 Plan for Review of the Application

There are two major tasks that must be accomplished during the first 60 days of the review period:

- **Determine Fileability --** discuss at the filing meeting
- **Plan the Review** -- discuss at the planning meeting

It is possible to combine these two meetings into one, but care must be taken to ensure that enough time is allocated for each of these functions.

Each member of the review team prepares/completes their discipline-specific ***filing review template*** as well as develops his/her review plan (schedule) using the discipline's ***interim deliverable planning tool***. Overviews of the review timelines for all of the types of reviews are included in Appendix A and are also posted on the 21st Century Review website, as are the discipline filing review templates and planning tools. PDUFA V "Program" applications are not treated differently during this phase of the review cycle except for notifying the applicant of specific review milestones (see Appendix A).

3.1 Prepare for Review of the Application

3.1.1 Determine Signatory Authority

The determination of the signatory authority for the application is based on its chemical classification (i.e., the relationship between the active moiety(ies) and currently marketed products). New molecular entities (NMEs), new biologic products, new combination products, first in a drug class proposed for over-the-counter use, and other applications as determined appropriate by the Office of Drug Evaluation (ODE) Director are designated for ODE (office-level) action and sign-off. All other applications are generally designated for division-level action and sign-off.

3.1.2 Assign CDTL

The review division director appoints the cross-discipline team leader (CDTL) for the review prior to day 14, the CDTL is often selected based on the content of the application; often this is decided before the pre-submission meeting is held with the applicant. For most new NDAs/BLAs the clinical team leader is selected. For applications without clinical data, the appropriate discipline team leader is designated the CDTL. For efficacy supplements, a determination is made regarding the need for a CDTL and/or whether a CDTL review should be completed. Often secondary discipline reviews or concurrences will suffice for all disciplines negating the need for a CDTL review.

3.1.3 Determine Preliminary Priority/Standard Review Schedule

A tentative decision on priority designation should be made by day 14 to assist in scheduling the filing meeting (day 30 for a priority application or day 45 for a standard or Program-designated application). In addition, this tentative decision facilitates the planning of other goal dates (e.g., if an Advisory Committee meeting is necessary for a priority application). An informal meeting of at least the division director, CDTL, the clinical

reviewer, and RPM should be held by day 14 of the review cycle for original NDAs and BLAs that have the possibility of being designated for priority review. (See MAPP 6020.3) A final decision on priority designation is made at the filing meeting.

3.1.4 Schedule Initial Meetings

The RPM promptly schedules both the filing and planning meetings once the review team members have been identified.

3.1.5 Communicate Review Information

Once the pertinent parts of the application have been distributed to the review team, the RPM sends out an e-mail updating all team members of key application information. The e-mail should contain the following information:

- Team members' names and their disciplines (including consultants/subject matter experts)
- Electronic link to the NDA/BLA, if applicable
- Important dates (e.g., filing date, final action due date, and any known future meeting dates)
- Standard discipline filing review templates' web site link
- A standard reminder that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss
- Optional miscellaneous background information the RPM wishes to share with the team about the application

The team may hold an early (e.g., day 21) internal kick-off meeting. The optional kick-off meeting should not replace the filing or planning meetings.

3.1.6 Applicant Orientation Presentation

Within 45 days after arrival of the application, the review team may hold an optional meeting with the applicant for purposes of orienting the review team to the content and format of the application (an Applicant Orientation Presentation meeting).

3.2 Determine Application *Fileability*

PDUFA V Change

All NDA/BLA applications are expected to be complete at the time of submission. PDUFA V "Program" applications are subject to several additional *fileability* requirements, including the following:

- Applications are submitted as agreed between the FDA review team and the applicant at the pre-NDA/BLA meeting.

- If the applicant does not have a pre-NDA/BLA meeting with FDA, and no agreement exists between FDA and the applicant on the contents of a complete application or delayed submission of certain components of the application, the applicant's submission is expected to be complete at the time of original submission.
- Late submission of parts of the application, agreed to at the pre-submission meeting, are received within 30 calendar days after receipt of the original submission.
- Applications contain a comprehensive and readily located list of all clinical sites and manufacturing facilities included in or referenced in the application.

Applications that are subject to a Refusal-to-File action, and are subsequently filed over protest, will not be subject to the procedures of "The Program", but will instead be subject to the 6- and 10-month review performance goals for priority and standard applications, respectively.

3.2.1 Filing Review

The goal of the filing review is to determine whether the application, on its face, is sufficiently complete to permit a substantive review.

Initiate Filing Review: Upon receipt of the application, reviewers conduct a preliminary review of their sections of the application to assure it has the required components according to regulations (See 21 CFR 314.50 & 21 CFR 601.2(a)). For electronic submissions, reviewers also study the structure of data files and assess the overall navigation of the submission. For PDUFA V "Program" applications, reviewers check to make sure all application components agreed to at the pre-submission meeting are present.

Discipline Filing Review Templates: Each discipline uses its specific filing review template to evaluate the completeness of its technical section against application requirements. The filing review templates are designed to assist the reviewer in making a recommendation on *fileability* and document the basis of that decision. Completed filing review templates are sent through the discipline team leader or supervisor for review and concurrence, and copies are provided to the RPM prior to or at the filing meeting. The filing review templates are archived by the reviewer by the filing date.

Identify Filing Review Issues: During the filing review, reviewers identify any substantive deficiencies or concerns that appear to have been inadequately addressed in the application and merit particular attention during the review process. These issues may have significant impact on the Agency's ability to complete the review of the application or approve the application. Filing review issues are distinct from application deficiencies that serve as the basis for a Refusal-to-File action. If an application is filed, these filing review issues are communicated to the applicant in the filing communication. (See CDER MAPP 6010.5)

Address Potential *Fileability* Issues: If review team members identify any potential filing issues during the filing review, they inform the other members of the review team at or preferably before the filing meeting. For each filing issue, the team will determine whether to request a response from the applicant. Consultation with the division director (and ODE director, if necessary) may be needed on certain issues prior to discussion with the applicant.

Potential refusal-to-file issues should be conveyed to the applicant as soon as possible (preferably before the filing meeting) so the review team has adequate time to work with the applicant to try and resolve the deficiencies before the 60-day filing date. Filing issues may be conveyed by letter, teleconference, facsimile, secure e-mail, or other expedient means. Examples of potentially correctable deficiencies are:

- Electronic navigational problems
- Missing right of reference letter
- Incomplete or missing Form 356h
- Missing financial disclosure statement (Forms 3454 and/or 3455)
- Incorrectly worded Debarment Certification statement
- Missing pediatric waiver/deferral request or pediatric data
- Missing data
- Missing reports

Identify Potential Labeling Issues: The labeling review process begins with receipt of the application. The proposed labeling (i.e., prescribing information and patient labeling, if submitted) is reviewed at a high level to identify the applicant's efficacy and safety claims and identify any obvious deficiencies (e.g., missing sections, incorrectly submitted format). In addition, the labeling is reviewed by the RPM for adherence to PLR regulations and relevant CDER labeling guidance. The proposed labeling may be useful in conducting the filing review because it provides insight into what the applicant believes their data support. With this information, reviewers can evaluate the application in terms of whether it includes the appropriate information to support the proposed claims. Thus, the NDA/BLA application should contain all the information necessary to support the labeling. Detailed labeling discussions are held later in the review process.

Identify Potential REMS Issues: A REMS submitted with the application is reviewed at a high level by appropriate OSE staff to identify any deficiencies (e.g., missing REMS documents or materials, incorrectly submitted format). For Program-designated applications, the reviewer must check to make sure all REMS components and commitments agreed to at the pre-submission meeting have been addressed.

3.2.2 Refusal to File (RTF)

If application deficiencies cannot be rectified readily, an RTF should be considered. If an RTF decision is anticipated, the division director and the office director are notified and issues are discussed prior to the filing meeting. FDA has generally exercised its RTF authority in circumstances identified in Appendix B.

3.2.3 Filing Meeting

The filing meeting is held by day 45 for standard reviews and day 30 for priority reviews. (This meeting can be combined with the planning meeting; however, care should be taken to ensure enough time is available for the planning portion of the meeting.) The filing meeting has three main purposes:

3 Plan the Review

1. Decide *fileability* (reviewers should bring completed discipline filing review templates to the filing meeting)
2. Identify significant review issues, including labeling or REMS deficiencies, for the Filing Communication (Day-74 letter)
3. Determine final review classification (standard or priority designation) (See MAPP 6020.3)

Meeting Attendees: Attendees include primary reviewers, team leaders, CDTL, RPM; OND division director/deputy, OND Deputy Director for Safety (DDS), OND Safety RPM, ODE director (if the ODE director is the signatory authority); division director/deputy of discipline offices when determined appropriate; OSE review team members plus the OSE RPM assigned to the OND Division and, if it has been determined that a risk management analyst is needed, the DRISK primary reviewer and team leader; representatives from Office of Compliance (OSI and OMPQ issues); and OPDP are also generally invited; if they cannot attend they will often provide comments for the meeting discussion. Attendees may also include already identified consultants (e.g., Controlled Substances Staff). Office of Business Informatics (OBI) staff should be consulted for filing issues related to electronic submissions.

Meeting Agenda: An agenda for the filing meeting should be provided to the team members prior to the meeting. The CDTL chairs the meeting and the RPM serves as facilitator and is also responsible for documenting the meeting as part of the Regulatory Filing Review.

At the filing meeting, each reviewer is allotted time to discuss the *fileability* of the application. Team members come to the meeting prepared with completed filing reviews (which have TL concurrence), summaries of their respective discipline sections, and potential issues.

Filing Decision:

There are three potential decisions:

1. File the application – If there are no major omissions of data or other identified major deficiencies, the application is *fileable*. The applicant is expected to rectify any minor issues.
2. Potentially refuse to file the application – If the application has deficiencies that appear to be correctable, the review team can work with the applicant to rectify them. If the deficiencies are resolved, the application is filed.
3. Refuse to file the application -- If the application is incomplete on its face and the deficiencies cannot be rectified readily, an RTF should be considered. Missing information is judged against the regulations detailing the requirements of an application and the grounds on which an application can be refused for filing. (See circumstances outlined in Appendix B.)

The signatory authority has the responsibility for making the final filing decision.

A refusal-to-file decision ends the review process. The applicant's options are to resubmit the NDA/BLA with the deficiencies addressed (the resubmission is considered an original new application) or to request that the NDA/BLA be filed over protest. PDUFA V "Program" applications that are subsequently filed over protest are removed from "The Program" and become subject to the standard 6- or 10-month review clock, as applicable. The applicant must be notified of a refusal-to-file decision (via RTF letter) within 60 days after the original receipt date of the application.

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Review Classification Designation: The OND division director makes a final determination of the review designation for the application, i.e., standard (S) or priority (P).

Filing Communication: If the application is filed, the RPM issues a Filing Notification letter by day-60 for priority NDAs and all BLAs. The RPM also prepares a Filing Communication (the day-74 letter) describing deficiencies, filing review issues (See CDER MAPP 6010.5) and the final review designation. The RPM notifies the applicant of a priority review designation in writing by day-60, or of a standard review by day-74 (in the Filing Communication).

For a **Priority Review**, the RPM prepares one of the following three communication types:

1. If there are filing issues but they are not ready to send to applicant by day-60, send the "Priority Review Determination" letter by day-60 then send the "Filing Issues Identified" Letter by day-74.
2. If there are filing issues and they are ready to send to the applicant by day-60, send the "Filing Issues Identified" letter by day-60.
3. If there are no filing issues, send the "No Filing Issues Identified" letter to the applicant by day-60.

For a **Standard Review**, send either the "Filing Issues Identified" letter or the "No Filing Issues Identified" letter to the applicant by day-74. A single letter can be used to satisfy both the day-60 and day-74 requirements. The filing communication gives the applicant early notice of any review issues identified to this point. This communication also identifies review timelines (See *Planning Meeting* section below). The planned review timeline included in the day-74 letter for **applications in the PDUFA V "Program"** will include the planned date for the internal mid-cycle review meeting and preliminary plans on whether to hold an Advisory Committee (AC) meeting.

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3.3 Planning Meeting

If the application is filed, a planning meeting is held. (As noted above, these meetings can be combined; however, care should be taken to ensure enough time is available for the planning portion of the meeting.) The purpose of the planning meeting is to organize review tasks, minimize review overlap across review disciplines, and establish an agreed-upon internal review timeline, including a schedule of team meetings and deliverables.

3.3.1 Prepare for the Planning Meeting

Discipline Review Planning Tool: Each discipline uses its standard interim deliverable planning tool to record the required tasks and due dates to complete review of the application. The tools are not archived, but should be used to track progress throughout the review period.

Efficacy Supplements: Due to the various levels of complexity, efficacy supplements require a focused discussion at the planning meeting to determine if any part of the review process can be modified. Reviews that are deemed unnecessary for the supplement should not be included in the review team.

Determine Review Activities and Schedule: The team should establish an agreed-upon review schedule that provides for the completion of all primary reviews, establishment inspections, BIMO site audits, PeRC assessment, 505(b)(2) assessment, exclusivity assessment, and consult reviews, by the timeline specified in Appendix A of this Desk Reference Guide. The following activities are typical of those to be planned for and managed by the designated CDTL, the RPM, and discipline team leaders:

- Plan review timeline (e.g., frequency of team meetings, review target goals) using the appropriate review planning tool
- Identify interim deliverables for each discipline (See 21st Century Review website under Reviewer Tools and Templates)
- Identify additional resources needed for review

3.3.2 Determine Need for Consultant Reviewers

The planning meeting provides another opportunity for the team to determine the need for additional review team members. The RPM, with input from appropriate team leaders and/or reviewers, prepares and sends consult and/or inspection requests with appropriate materials. Consult requests should identify any specific questions to be addressed and anticipated timelines for response. For example, the following consults may be appropriate:

- **OSE Review:** The OSE SRPM is the key contact point for the OND RPM for purposes of identifying OSE core reviewers and consultants, and determining OSE meeting attendees. OSE should be involved from the beginning of the review, particularly if the application contains postmarketing safety activities (e.g., PMR, PMC, REMS). In addition, OSE should be consulted whenever an important safety concern has been identified that requires postmarketing activities or additional OSE expertise. OSE members of the review team (core reviewers and consultants) should be included in any meeting relevant to their discipline involvement.

  OSE (DRISK and DEPI) should attend team meetings where REMS or PMRs that require OSE expertise (such as observational epidemiologic studies) will be discussed. OSE members of the review team (core reviewers and consultants) are expected to attend meetings relevant to their section(s) of the review. In addition, an OSE Epidemiologist and OSE Safety Evaluator will attend the mid-cycle meeting. The wrap-up meeting will include an Epidemiologist, Safety Evaluator and other OSE staff; an agenda topic called Postmarket Safety Surveillance Plan will be included.

- **Office of Compliance:** The Office of Compliance's Office of Scientific Investigations (OSI) provides overall guidance for, oversight of, and recommendations on BIMO specific issues. OSI/REMS Compliance Team should be included in meetings for applications that include REMS. Office of Manufacturing and Product Quality (OMPQ) provides overall and facility specific recommendations, discusses inspectional findings, and provides overall guidance and oversight for manufacturing and product quality-related compliance issues. OMPQ is involved in the review of all original applications.

- **Patient Labeling Team Review**: The Office of Medical Policy's Patient Labeling Team should be consulted to review draft patient labeling (Patient Package Insert, Medication Guides, and Instructions for Use) for all new NDAs/BLAs, new indications, dosage forms, route of administration, any new risk supplements, PLR conversions, and any other label changes that may affect patient labeling.

The Patient Labeling Team will complete their review within 14 days from the time they receive substantially complete package insert (SCPI). The Patient Labeling Team should be involved from the beginning of the review and be invited to mid-cycle, labeling, and wrap-up meetings.

- **Office of Prescription Drug Promotion (OPDP) Review:** OPDP should be consulted to review all draft labeling that affects promotion. Consults should be sent to OPDP, utilizing the *DDMAC Labeling Consult Form*, immediately following the filing and planning meetings. These consults should request the review of both the professional labeling (PI and carton/container) and consumer directed labeling (PPI, Medication Guide, and Patient Instructions for Use) for all new NDAs/BLAs, new indications, dosage forms, route of administration, any new risk supplements, PLR conversions, and any other label changes that may affect promotion. Consults should be sent to the CDER-OPDP-RPM mailbox with a *cc* to appropriate OPDP reviewers (if known.) Since OPDP needs to review substantially complete (marked-up by the CDER review team) labeling, there is no need to include the initial applicant proposed draft labeling in the consult. The OPDP review team (professional and consumer reviewer and RPM) should be invited to mid-cycle, labeling, and wrap-up meetings.
- **Additional Reviewers/Consults:** Depending on the issues raised in the review, additional reviewers may be added to the review team. Reviewers from organizations such as the Controlled Substances Staff (CSS) (See MAPP 4200.3). SEALD Endpoints, Pediatric & Maternal Health Staff (PMHS), QT-Interdisciplinary Review Team (QT-IRT) or other FDA Centers should be added as relevant to regulatory, clinical or scientific issues that are identified in the review. Consultant reviewers get a copy of all information relevant to the review they are asked to complete.

3.3.3 Establish Plan for Labeling Review

At the planning meeting, the CDTL and the RPM should make clear:

- Who is accountable for the different sections of the labeling.
- The process for making revisions to the labeling (plan for archiving and making accessible the working version, working within the discipline).
- The expected dates for completion of the subsections *and* substantially complete prescribing information (timeline [see section 4.7] must include all pertinent parties: SEALD, DRISK, DMEPA, Patient Labeling Team, OPDP, and Maternal Health Team when needed).

3.3.4 Finalize Need for Advisory Committee (AC)

Under FDAAA, an Advisory Committee meeting must be held for all NMEs and original BLAs, unless an adequate justification is documented explaining the decision to not hold a meeting (for NMEs and Original BLAs, this reason is to be included in the approval letter). For other applications the review division, in consultation with the office director, may decide to convene an Advisory Committee meeting. A review division may need AC input, for example, when: 1) the clinical trial design used novel clinical or surrogate endpoints; 2) the application raises significant issues on the safety and/or effectiveness of the drug or biologic; or 3) the application raises significant public health questions on the role of the drug or biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

The decision to go to AC should be made as soon as possible, perhaps even before receipt of the application, especially for priority reviews. It should be made no later than the filing meeting for standard reviews; however, if issues arise during the review, a decision to hold an AC meeting may be made later. If an Advisory Committee is deemed necessary, the appropriate Designated Federal Official (DFO) in the Division of Advisory Committee and Consultant Management (DACCM) is immediately notified so that they can begin the scheduling process.

3.3.5 Finalize Sites for Bioresearch Monitoring (BIMO) Inspections

FDA calls its program of on-site inspections for Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) its "Bioresearch Monitoring Program" or "BIMO". This includes inspections of Clinical Investigators, Sponsors/Applicants, Monitors, Contract Research Organizations, Institutional Review Boards, Bioequivalence labs and facilities and GLP facilities (non-clinical studies). The goal of the program is to verify the quality and integrity of bioresearch data and to protect the rights and welfare of human research subjects. These inspections can be performed during any phase of product development; however, they are most likely to occur after NDA/BLA submission.

GLP Inspections: In general, the need for an audit of non-clinical study sites will have been identified as a result of the review of the preclinical data during the IND phase of the drug or drug product. However, reviewers may not have audited some of the available preclinical data in the NDA/BLA application from the IND phase. The pharmacology/toxicology (non-clinical) team will be responsible for determining whether preclinical study site audits should be requested and will present their recommendation at the planning meeting.

GCP Inspections: As part of the preparation for the planning meeting, clinical reviewers, in concert with the statistical reviewers and representative(s) from the Office of Scientific Investigations (OSI), determine which clinical trial sites should be audited to confirm data validity. Consideration for routine clinical inspections for NDAs/BLAs is based upon the chemical and therapeutic classifications, the therapeutic importance of a new indication, and the specific population for which the compound is intended. These issues need to be considered prior to the planning meeting. OSI has developed a risk-based tool that assists the review team in selecting clinical sites for inspection. The OND Medical Officer, the Biometrics Reviewer and the RPM will meet with a representative from OSI about one week prior to the filing/planning meeting. This meeting should be scheduled for all NDAs, BLAs and efficacy supplements for which a clinical site audit is needed, even if the applicant has not made the voluntary submission of the dataset for the risk-based tool (i.e., clinical sites still need to be selected early in the review process, regardless of whether the site selection tool can be utilized). The OND RPM will schedule this meeting, but is not expected to attend. Review divisions may elect to include team leaders and others, as appropriate, in these meetings.

3.3.6 Evaluate Manufacturing Establishments for Inspection(s)

Any proposed manufacturing site for the drug substance or drug product that has not been previously inspected by FDA should be inspected. Manufacturing may be performed at external establishments which are also considered manufacturers (including but not limited to: testing facilities, sterilizers, packaging, labeling (refer to 21 CFR 207.3(a)(8)). Additionally, other factors determine the need to inspect proposed manufacturing facilities, including the implementation of a substantially different manufacturing process or dosage form than previously covered at the establishment, drug substance derivation is high risk, or the intended use of the drug substance has significantly changed. Office of

Manufacturing and Product Quality, in concert with input from the Product Quality Reviewer and Office of Regulatory Affairs, will determine which manufacturing facilities will need to be inspected prior to taking a regulatory action on the application.

3.3.7 Determine Schedule for Review

Schedule Review Meetings: The RPM schedules the required meetings. All staff are expected to keep their Outlook calendars updated so that meetings can be reliably scheduled based on invitee availability, as indicated by Outlook.

Review Timeline: As mentioned in the section on the filing meeting, the filing communication (day-74 letter) includes filing review issues that have been identified during the filing review and also informs the applicant of the planned timeline for review activities. The milestones to be communicated to the applicant in this letter must include, at a minimum, the target dates for transmitting initial labeling and PMR/PMC comments. The planned review timeline included in the day-74 letter for PDUFA V "Program" applications must include the planned date for the internal mid-cycle review meeting and also include preliminary plans on whether to hold an Advisory Committee meeting to discuss the application. A caveat is included noting that timelines are flexible and subject to change based on workload and other issues that may arise (e.g., AC meeting determined to be necessary). Subsequent significant changes to the planned timeline are conveyed to the applicant should they arise. (See MAPP 6010.8)

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3.3.8 Action Package

The formal **Action Package**, a compilation of all division and office documentation generated during an application's review and other pertinent applicant submitted documentation, is generally started by the RPM at the end of the filing period. The RPM adds documents to the action package as they are produced throughout the review. (See MAPP 6020.8)

4 Conduct Review

After filing the application and planning the review, the review team begins its in-depth reviews. In conducting their independent reviews, primary reviewers consult with each other and with their team leader on a regular basis. OND division directors, ODE directors (if the signatory authority), and discipline managers stay abreast of review issues and provide feedback throughout the review, in part by participating in the major meetings (e.g., filing/planning, mid-cycle, and wrap-up). The review team communicates information requests to the applicant. Drafts of reviews may have to be completed earlier than usual if an Advisory Committee meeting schedule makes it necessary.

Reviewers should identify approvability issues by mid-cycle in order to facilitate the planning of internal labeling and REMS work. Important items such as boxed warnings and contraindications should be discussed at or before the mid-cycle meeting. At the mid-cycle meeting, in accordance with established interim deliverables, team members and consultants present key findings, issues that could impact approval, and begin high-level discussion of labeling and postmarketing activities. Reviewers take the discussion at this meeting into account when finalizing their reviews. The major milestones during the review phase for each of the types of review cycles are shown in Appendix A.

4.1 Review Management

During this phase of the review process, in addition to completing the relevant regulatory reviews (e.g., labeling, pediatric page, 505(b)(2) assessment), the RPM continues to coordinate the review team activities, monitors the overall status of the review, and makes any needed schedule adjustments. These activities may include:

- Sending information requests and discipline review letters (See Guidance for Industry)
- Setting up meetings/teleconferences with applicant
- Setting up *ad hoc* team meetings (e.g., practice meetings for the Advisory Committee)
- Handling PeRC-related activities
- Keeping management informed as to the progress of the review

4.2 Communicate with Applicant

Several types of communication take place with the applicant during the review process. They include, but are not limited to, the following:

- Information requests: The review team communicates information requests (conveyed by letter, secure e-mail or facsimile) to the applicant in a timely manner throughout the review process, rather than waiting until the mid-cycle meeting. Additionally, this may include preliminary feedback and deficiencies regarding proposed postmarketing studies or REMS.

- Meeting or teleconference: In addition to the post mid-cycle communication and the late-cycle meeting required for PDUFA V "Program" applications, applicants or the review team can request a meeting during the review process. The review team considers the timing and appropriateness of an applicant's meeting request. Minutes generated during these conferences are prepared jointly by the RPM and the review team and are archived.
- Status updates: Requests for status updates are generally handled by the RPM over the telephone or by e-mail rather than in a meeting format.

In general, any communication with the applicant is managed/documented by the RPM in coordination with the CDTL. Reviewers can communicate directly with applicants for discipline-specific information requests such as for missing forms or tables, minor clarifications, etc. All substantive applicant calls are documented and archived by the RPM. The RPM, appropriate discipline team leader(s), and CDTL need to be copied on any information requests (e.g., copy of e-mailed request or teleconference summary) from reviewers.

4.3 Perform Scientific and Regulatory Reviews

4.3.1 Perform Primary Review

When conducting their reviews, primary reviewers consult with each other and with their team leader on a regular basis. The discipline team leader works with the reviewer to ensure a complete discipline review. Reviewers should use standard discipline templates to complete their reviews. Reviewers may provide drafts of their review for team leaders to provide comments.

Team Leader Meetings with Individual Reviewers to Discuss Progress: The primary and secondary reviewers continue to discuss data, analyses, and review findings as they evolve so that there is mutual understanding of any differences of opinion. Discipline team leaders and other supervisors/managers should meet with reviewers to provide feedback throughout the course of the review. Issues that may have an impact on the review or need broader discussion are brought to the attention of the entire review team.

Labeling: Certain sections of the labeling can oftentimes be reviewed prior to the mid-cycle meeting (e.g., "DESCRIPTION" and "HOW SUPPLIED/STORAGE AND HANDLING"). When possible, DMEPA, ONDQA and OBP should work together to review the carton/container labeling in advance of the mid-cycle meeting. The Pediatric and Maternal Health Staff and OPDP generally cannot provide labeling comments until draft reviews are available from the primary reviewers.

4.3.2 Conduct Team Meetings

Regularly scheduled team meetings are held during the review phase. The purpose of team meetings is to provide a forum to discuss issues arising during the review of the application and share information and items needing cross-disciplinary input. The status of review issues and highlights of findings may be discussed. Primary reviewers should comment on whether they expect to complete their reviews on time and whether there are any outstanding issues. Other topics include determining if there is a need for information requests, additional internal meetings, identifying labeling issues and concerns, identifying the need for postmarketing activities, etc. Team meetings may result in mid-cycle meeting agenda topics,

issues for an Advisory Committee, and identification of regulatory issues and applicant/application issues. Before the mid-cycle meeting, the team discusses safety findings with OSE (DRISK, DEPI) to better inform REMS and/or PMR discussions at the mid-cycle meeting (this can occur at a regularly scheduled review team meeting).

Frequency of Team Meetings: The frequency of team meetings is determined at the planning meeting or at the discretion of the CDTL or division director It is strongly recommended that teams hold at least one meeting between the filing/planning and mid-cycle meetings (e.g. to discuss issues such as safety signals that would potentially warrant postmarketing studies or a REMS) and one between the mid-cycle and wrap-up meeting (or late-cycle meeting for Program applications).

Team Meeting Participants: An agenda is prepared to identify necessary participants. All discipline reviewers, respective team leaders, deputy division director(s) and division director(s), and consultants **deemed necessary**, should be invited to the team meetings. Division and/or deputy directors may opt out of attendance, depending on the subject matter of the meeting.

Agendas: The RPM prepares and distributes the agenda prior to the meeting.

Summary of Action Items: The RPM documents agreed-upon decisions and action items from the team meetings. **The summary should not document preliminary review findings.** The summary does not need to be archived, but should be distributed to the review team members.

4.4 Conduct Mid-Cycle Meeting

The mid-cycle meeting is held by month 5 for Program and standard reviews (month 3 for priority reviews). The mid-cycle meeting provides an opportunity for management to review the work of the review team thus far in the review cycle.

Objectives of the meeting are to:

- Present status and key findings of all reviews, consults, and inspections.
- Confirm the decision that was made regarding the need for an Advisory Committee meeting.
- Identify any issues that could preclude an approval action.
- Begin high-level discussion of labeling (e.g., are major claims supported) and need for PMRs and/or PMCs.
- Determine if a REMS is needed (if not already determined) and, if so, the goals and the elements of the REMS.
- Revise the review plan and interim timelines, if needed.
- Solicit feedback from the signatory authority and other discipline directors.

4 Conduct the Review

The RPM e-mails all meeting participants with the meeting date and draft agenda for the meeting. As the meeting approaches, the RPM takes special care to ensure that all presentations will fit within the time allocated for the meeting. Discipline team leaders provide guidance to the primary reviewers as they prepare for the mid-cycle meeting.

Attendees: Meeting participants include all discipline reviewers and respective team leaders, review division director and deputy division director, deputy director for safety, Safety RPM, and the ODE director, if he/she is the signatory authority. When the OND office director is attending, discipline division directors should be invited as needed. The DDMAC OPDP reviewers, OSE RPM, an OSE Epidemiologist and an OSE Safety Evaluator will also attend the meeting. If a risk management analyst has been included as a primary reviewer, the DRISK reviewer and team leader will also attend. If a REMS is included in the submission and/or is considered necessary for approval, the DRISK reviewer and team leader will also attend.

Agenda: The agenda for the meeting should include:

- Specified time slots for each of the reviewers to present important summary findings and issues (e.g., Product Quality, Pharmacology/Toxicology, Clinical, Statistical, Clinical Pharmacology, Safety reviewers)
- Consultant review updates
- Bioresearch monitoring (BIMO) audits, facility inspections, and EER updates
- Confirmation of the decision that was made regarding need for an Advisory Committee meeting
- REMS, PMRs/PMCs, as relevant to the application

Additional topics for the agenda might include:

- Discussion of issues and strategies for resolution
- Determination of what to convey to applicant with regard to identified key deficiencies and the need for additional information
- Labeling issues

The presentations should include the reviewer's key analyses using handouts and/or slides/presentations that include tables and figures. Problems and issues, especially any safety concerns, should be discussed. The division director and/or ODE director should provide direction to the review team regarding areas that may require a more focused review, principles for developing labeling and post-marketing activities, and any other insights or considerations.

The discussion that follows the presentations should be led by the CDTL and facilitated by the RPM. The meeting should identify showstoppers, roadblocks, key issues, and, if needed, a possible path forward. Perceived deficiencies to date should be broken down into three categories:

- Deficiencies that can be handled through mechanisms such as labeling or PMRs/PMCs

- Deficiencies for which the division can request information and expect the applicant's response during the current review cycle
- Deficiencies that require significant additional work by the applicant and will be conveyed to the applicant in an appropriate action letter

During the meeting the team should determine how to handle labeling in the current cycle if approval is not likely. The signatory authority should decide if labeling will not be addressed or whether draft labeling will be appended to the Complete Response (CR) letter in the anticipation of an early resubmission. The goal should be to work on the labeling when scientific issues are fresh in mind, especially parts that will not change regardless of the final action taken.

Additional information needed from the applicant and any feedback that can be relayed to the applicant are identified (i.e., safety issues identified, difficulty reproducing key analyses, and additional information requests). The discussion should include who will relay this information to the applicant and by what mechanism the information will be conveyed (phone, fax, email, etc.). Acceptable timeframes for response should also be determined.

All team members have an opportunity to ask questions and raise concerns about the NDA/BLA. The team is reminded of any upcoming meetings and interim goals, such as labeling meetings, and is encouraged to send labeling comments to the RPM as soon as possible.

The RPM notes decisions and follow-up actions from the mid-cycle meeting. **A *meeting summary does not need to be archived, but, if it is, it should not document preliminary review findings and should not have presentations or draft reviews attached.***

4.5 Mid-Cycle Communication for PDUFA V "Program" Applications

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For "Program" applications, the RPM and other appropriate members of the review team (e.g., CDTL) will call the applicant, generally within 2 weeks following the mid-cycle meeting to provide an update on the status of the review. The RPM will coordinate the specific date and time of the telephone call with the applicant. The update should include:

- Any significant issues identified by the review team to date
- Any new information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management
- Proposed date(s) for the late-cycle meeting
- Updates regarding plans for the AC meeting (if an AC meeting is anticipated)
- Other projected milestones dates for the remainder of the review cycle

For non-Program applications, the review team should consider sending a communication to the applicant within a month following the meeting to request additional information and analyses, as needed. Wording should be similar to the Filing Communication.

If a REMS is considered necessary for approval, and a proposed REMS was not included in the submission **or** the proposed REMS is considered insufficient to address the risk(s), a REMS notification letter is sent to the applicant within 4 weeks (priority review) or 6 weeks (standard review) following the mid-cycle meeting. If REMS with elements to assure safe use (ETASU) are being considered, concurrence from senior management is required prior to issuing a REMS notification letter.

4.6 Manage Amendments to Application

Applicants provide additional information during a review by submitting an amendment to the original application. Unsolicited amendments sent by the applicant during the review cycle are usually minor in nature and are often reviewed during the review cycle. Since Program applications are expected to be complete at the time of submission, unsolicited amendments are expected to be rare and not to contain major new information or analyses.

If the applicant sends an unsolicited amendment, FDA decides whether to review the new information during the current review cycle. Solicited amendments are usually reviewed during the current cycle provided they are received early enough. The RPM processes the amendment and distributes it to the review team.

Extending the Review Clock: A major amendment (e.g., a significant amount of new information, new analyses, new study or trial report) can extend the review clock (PDUFA goal date) three months. The review team decides whether to extend the review clock and review the information or defer review to a subsequent review cycle. This decision should be based, in part, on whether the amendment has the potential of bringing the application into condition for approval. If there are deficiencies that cannot be addressed by the amendment, the division should generally defer review of the amendment until a subsequent review cycle without extending the review clock. If the review clock is extended, the RPM sends an Extension Letter to the applicant to notify them of the new goal date. If the planned date for discussion of labeling and PMRs/PMCs is changed, the RPM will notify the applicant. (See MAPP 6010.8)

For PDUFA V "Program" applications, the new planned review timeline will include a new planned date for the internal mid-cycle review meeting, if appropriate, depending on when during the course of review the major amendment(s) is accepted for review. All other milestones are adjusted to the new goal date.

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4.7 Obtain Expert Advice

The review team can seek expert advice at any time during the review. Advice can come from other FDA divisions or centers, through an Advisory Committee meeting or an internal Regulatory Briefing, or from a Special Government Employee (SGE) consultant. (See Guidance for Industry)

4.7.1 Advisory Committee (AC) Meetings

An Advisory Committee meeting may be held for one or more of the following reasons. Note that this is not an exhaustive list.

1. The application is an NME.
2. The clinical trial design used novel clinical or surrogate endpoints.
3. There are significant issues regarding safety and/or effectiveness of the drug or biologic.
4. The application raises significant public health questions regarding the role of the drug or biologic in the treatment or prevention of a disease.

REMS with elements to assure safe use (ETASU) must be discussed with senior management through the REMS Oversight Committee (ROC) before any planned Advisory Committee meetings at which the REMS might be discussed. The purpose of this is to ensure consistency within CDER with regard to incorporation of ETASU in REMS (i.e., consistency of use of "restricted distribution" programs).

PDUFA V Change

For PDUFA V "Program" reviews, AC meetings generally take place no later than 3 months for standard reviews or no later than 2 months for priority reviews prior to the PDUFA goal date (or 9 months from submission for standard and 6 months from submission for priority). Milestones for major Advisory Committee Meeting tasks are shown in Appendix A. Many of the milestones apply to all types of applications. The table also contains milestones for the late-cycle meeting to be held for PDUFA V "Program" applications, which are tied directly to the AC meeting if held. The Division of Advisory Committee and Consultant Management (DACCM) may change target dates as needed.

Notify the Designated Federal Official (DFO): The RPM notifies the DFO in DACCM and provides the DFO with information needed to draft a Federal Register Notice. It is essential that review division's request screening of potential advisory committee members as early as possible, even before an application is received, if possible.

Plan for the AC meeting: The RPM schedules a meeting of relevant internal participants to initiate planning and preparation for the AC meeting. OSE staff should be invited to all planning meetings as relevant to REMS, PMRs, or other safety issues (See Draft Guidance for Industry, Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drugs and Convened by the Center for Drug Evaluation and Research Beginning on January 1, 2000).

Prepare AC Meeting Background Package: Questions for the advisory committee and an agenda are prepared and the Advisory Committee Meeting Background Package is assembled in accordance with DACCM timelines.

Best Practices for Review Division AC Planning Activities: A list of best practices to help review teams manage advisory committee follows.

1. Plan far in advance.
2. Anticipate issues.

3. Consider the need for an AC before submission and after the submission of the application.
4. Determine the applicant's dates for submission of the application.
5. Find experts early.
6. Adjust the review schedule to work constructively with the AC schedule.
7. Notify applicant of any changes to review timeline.
8. Use addenda to reviews to incorporate feedback from the AC discussion.

AC Meeting Preparation: The RPM schedules at least two practice sessions for internal participants (OSE staff should be invited to all planning meetings relevant to REMS, PMRs/PMCs, or other safety issues). Presenters are selected based on expertise, familiarity with the data, and presentation abilities. The division director should attend the practice sessions. The office director should attend the final practice session. Attendees include presenters, representatives from each consulting group, team leaders and the RPM.

About 6-8 weeks before AC meeting the following activities take place:

- DFO handles logistics for scheduling meeting, publishing Federal Register notice of the meeting, sending the meeting briefing package to the applicant, and obtaining security clearances for Special Government Employee (SGE) committee members and consultants, and guest speakers.
- Review team identifies need for additional expertise on committee (SGEs members or consultants). Reviewers, team leaders and division directors work to find appropriate consultants for the committee. Names are provided to DFO.
- Review team puts together background package and rehearses presentations for the meeting.

The review division director (DD) should call the chair of the AC prior to the meeting. In this phone call the DD should discuss the draft questions, format of the meeting, and expectations. Others may participate in the call as appropriate.

DFO sends FDA's background package for the AC meeting to the applicant not less than 20 calendar days before the AC meeting.

The DACCM Staff will provide final questions for the AC to the applicant and the AC members 2 calendar days in advance of the AC meeting.

Hold Advisory Committee Meeting: Applicant and FDA make presentations relevant to the issues under discussion. The advisory committee addresses FDA's questions and deliberates and develops its recommendations.

Prepare and Distribute Meeting Minutes: After the meeting is held, a 48-Hour Alert Memorandum is prepared by the DFO, and DACCM staff prepare the meeting minutes. Both documents are distributed, and the minutes and transcripts are posted on the FDA Advisory Committee Internet web page.

Conduct Post-AC Meeting: An internal AC debrief meeting of the review team is held within 2 weeks after the AC meeting to discuss AC input and, if needed, request or conduct additional analyses. In some cases, a subsequent discussion may be held with the applicant to share FDA's perspective of the advice provided by the advisory committee at the meeting.

Post-Action AC Feedback: Following the final regulatory action on the application, the review division sends notification to the AC members of decisions made relating to the issues discussed at the AC meeting and how the FDA used the committee's input. This notification should be sent as a letter through the DFO within 30 days of the action.

4.7.2 Conduct Regulatory Briefing

Sometimes a CDER Regulatory Briefing is held when there are scientific and/or regulatory issues that would benefit from further discussion with upper management and with review peers*; the briefing does not serve as a regulatory decisional meeting*. Members of the committee include the Center Director and Deputy Director, Director and Deputy Director of the Office of New Drugs, the Director of the Office of Regulatory Policy, selected other Office Directors and other CDER officials.

The division director in consultation with the review team decides if a regulatory briefing should be requested; the project manager notifies the pertinent person on CDER's Division of Executive Operations to secure a place on the committee's agenda.

Meeting minutes and briefing recommendations are prepared by the RPM and reviewed by the CDTL and division director, finalized, distributed to all pertinent parties, and sent to the designated Executive Operations contact for intranet posting, and archiving.

4.8 Develop Labeling, PMRs/PMCs, and REMS Comments

Activities required for PMRs/PMCs and REMS have a series of interim deliverables and milestone dates. These activities are intertwined and interdependent with labeling activities. The table in Appendix A shows the activities and dates.

4.8.1 Labeling

Within one week after the mid-cycle meeting, a separate short labeling team meeting is held if planning for labeling did not take place at the planning meeting or at the mid-cycle meeting. The goal of the meeting is that each reviewer understands the sections they are responsible for revising, including which sections overlap with other reviewers. Separate division and/or discipline-specific working meetings may be needed (e.g., ONDQA/OBP, DMEPA, Patient Labeling, pharmacology/toxicology, Pediatric and Maternal Health Staff (PMHS), clinical pharmacology, and clinical/statistical). The planning meeting can also include determining the schedule of upcoming labeling meetings and key attendees.

Prior to each labeling meeting, a focused agenda and an attendee list should be prepared by the RPM. The respective disciplines should develop a discipline view of labeling comments to be discussed at the labeling meeting. It may be helpful to invite only the key stakeholders to each meeting. Managing the meetings might include the following activities:

- The RPM sends an agenda for each meeting so all review team members (including OPDP reviewers) are informed of the sections of the labeling to be discussed. Staff can then choose which meetings they need to attend; attendance at the meetings can be optional for other review team members.
- Each discipline is responsible for their section(s) of the labeling. Primary reviewers and their team leaders should discuss their sections of the labeling before meetings, not at meetings. Meeting participants should come to the meeting with proposed changes that have TL (discipline) concurrence.
- The most updated version of labeling with changes tracked should be made available to meeting attendees at least one day in advance of the labeling meeting.
- A decision maker is needed at the meetings, so either the review division director or deputy should attend. These small focused meetings provide an opportunity for each discipline to present their labeling issues/conclusions to the decision maker.
- The meetings should be used to discuss areas of concern and/or controversial issues and important issues; minor formatting or wording changes can be discussed outside of meetings (e.g., via email, eRoom, one-on-one).
- The RPM maintains overall administrative responsibility for managing the labeling. Minutes are generally not prepared for these working meetings; the RPM makes an updated version of the labeling available to all interested parties after each meeting (e.g., on a shared drive/eRoom/email taking into account whether all disciplines/consultants have access to the file).
- After the disciplines have completed their sections of the labeling, a full review-team labeling meeting is held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP, and the Patient Labeling Team. Once the substantially complete labeling is received, Patient Labeling and OPDP complete their reviews within 14 calendar days.
- Draft labeling, including FDA's rationale for major changes requiring explanation, is sent to the sponsor very soon after the wrap-up meeting with a one-week applicant response required. (For Program applications, labeling is sent after the pre-meeting for the Late-Cycle meeting.)

Development of final labeling is an iterative process between the applicant and FDA; the RPM makes applicant-submitted changes available for review by the review team. The RPM should inform review team members when they need to finish looking at this new version or when it will be discussed by the team. Labeling is finalized with the sign-off of the signatory authority when taking the final action on the application.

The review team should strive to transmit initial labeling comments according to the dates specified in the filing communication letter. If it is necessary to delay this transmission due to the advisory committee meeting schedule, this should be discussed with the applicant. When significant deficiencies preclude discussion of labeling, those deficiencies are generally communicated in a Discipline Review letter by the target date identified in the planned timeline. (See MAPP 6010.8) (See Section 4.9, below)

4.8.2 PMRs/PMCs and REMS

PMRs/PMCs and REMS are also discussed at team meetings and, as with labeling, are finalized via an interactive process that includes applicant input (See MaPP 6010.9 and MAPP 6700.6); FDA participants from OND and OSE include the applicable discipline reviewers and respective team leaders, review division directors and deputy division directors, the deputy director for safety (DDS), OND Safety RPM, OSE SRPM, and the ODE director, if he/she is the signatory authority. If a REMS is being discussed, a representative(s) from the Office of Compliance and Patient Labeling and OPDP reviewers (if patient labeling is discussed) may also be required.

ETASU REMS must be discussed with senior management through the REMS Oversight Committee (ROC) before the applicant is told that a REMS is required. The purpose of this is to ensure consistency within CDER with regard to incorporation of ETASU in REMS (i.e., consistency of use of "restricted distribution" programs).

Discussion of the REMS with the applicant should begin within two weeks of issuing the REMS notification letter (if not already started). These discussions should continue (amongst the division, the applicant and OSE/DRISK) as needed throughout the review cycle. If a REMS was not included in the initial submission, and an important safety concern is identified that potentially requires a REMS, OSE/DRISK should be consulted as soon as possible. If a REMS was included in the initial submission, and a revised REMS proposal is submitted in response to a REMS notification letter, a consult request does not have to be sent to OSE/DRISK, as DRISK will already have been included as a primary discipline reviewer. Instead, the OND RPM should simply notify the OSE SRPM that the REMS has been submitted as an amendment to the application.

The review team should strive to transmit initial PMR/PMC and REMS comments according to the dates specified in the filing communication letter. As described above, if it is necessary to delay this transmission due to the AC meeting schedule, this should be discussed with the applicant. Also, when significant deficiencies preclude discussion of PMRs/PMCs, those deficiencies are generally to be communicated in a Discipline Review letter by the target date identified in the planned timeline.

The PMR/PMC Development Template should be completed and signed off by the DDS four weeks before the end of the review cycle. The PMRs/PMCs and REMS are finalized with the signoff of the signatory authority when taking the final action on the application.

4.9 Complete Primary and Secondary Reviews

A summary of due dates for reviews can be found in Appendix A. Graphics of the timelines can be found on the 21st Century review web site.

Primary Reviews: As mentioned earlier, reviewers and team leaders interact frequently during the review period, with reviewers providing drafts of sections of their reviews for team leaders to read and comment on.

A primary review is considered final after it has been signed-off in DARRTS by the discipline team leader. The TL should type “I concur” when signing off in DARRTS if there is concurrence between TL and reviewer and no additional TL review will be needed. The sign-off indicates the team leader has found the review to be complete, and of acceptable scientific quality.

Consultant Reviews: Consultant reviews, including inspections, should be completed by the agreed-upon timeframe in the request. Potential delays in completion should be communicated to the RPM as soon as possible.

Secondary Reviews: Each discipline team leader assesses the primary review and writes a brief summary memorandum if he/she does not agree with the primary review or the recommended regulatory action. This memorandum should address any discrepancies between the discipline team leader's and primary reviewer's recommendations and the rationale for the differences.

When the CDTL is also a discipline team leader, the CDTL review will serve as the secondary review memo for that discipline.

Inspections and Compliance Reviews for PDUFA V "Program" Applications: FDA's goal is to complete all GCP, GLP, and GMP inspections and Compliance review within 10 months of receipt for standard applications and within 6 months for priority applications. This will provide 2 months at the end of the cycle for the applicant to address identified deficiencies.

PDUFA V Change

4.10 Issue Discipline Review Letters

Each discipline's review comments (reflecting TL concurrence) should generally be conveyed by the RPM to the applicant in a Discipline Review letter (see Guidance for Industry). This letter gives the applicant a preliminary notice of issues and deficiencies identified by that discipline. These preliminary comments and deficiencies may or may not be included by the signatory authority in the subsequent action letter on the application. The discipline review letter is also used to inform the applicant if the deficiencies preclude discussion of labeling and PMRs/PMCs (see MAPP 6010.8). FDA intends to issue DR letters in advance of the late-cycle meeting, so they can be included in the Agency briefing package for that meeting.

4.11 Pharmacology/Toxicology Coordination Review

Pharmacology/ Toxicology carcinogenicity studies are reviewed by the primary reviewer and team leader and then presented to a coordinating committee for tertiary review – the ECAC (Pharmacology Toxicology Coordinating Committee's Executive Carcinogenicity Assessment Committee). (See CAC MAPP)

4.12 Hold Pre-Meeting for Late-Cycle Meeting

PDUFA V Change

An internal review team meeting for PDUFA V "Program" applications is held after reviews are complete at month 8 in order to prepare for the late-cycle meeting with the applicant. Prior to the meeting the CDTL and RPM will canvas discipline reviewers for review issues to include in the late-cycle meeting agenda and briefing memorandum (the agency briefing package is described in the next section).

The purpose of the pre-meeting is to brief the ODE Director and Division Director on review issues proposed for discussion at the late-cycle meeting and to plan the meeting. Discussion should cover review outcomes and determination of what issues can be fixed or are amenable to

correction in the current review cycle and what issues could affect the outcome of the review. The meeting planning discussion should include the goals of the late-cycle meeting, who should attend and who will chair the meeting, the agenda for the meeting, and plans for the advisory committee meeting.

4.13 Hold Late-Cycle Meeting with Applicant for PDUFA V "Program" Applications

PDUFA V Change

For all applications included in the PDUFA V review "Program," a meeting is held late in the review cycle between members of the FDA review team and the applicant to discuss the status of the review. The meeting can take place as a teleconference if the applicant agrees. No meeting request is required for the late-cycle meeting.

For applications that will be discussed at an Advisory Committee meeting, the late-cycle meeting will occur not less than 12 calendar days before the date of the AC meeting. For applications that will not be discussed at an AC meeting, the late-cycle meeting will generally occur not later than 3 months (standard review) or 2 months (priority review) prior to the PDUFA V goal date.

Agency Briefing Package: The briefing package for the late-cycle meeting should be sent to the applicant not less than 8 days before the meeting if an AC is to be held and 12 days before the meeting if no AC meeting is planned. The package should consist of:

- Meeting agenda
- List of attendees
- A current assessment of the need for REMS or other risk management actions (if not already determined)
- A brief memorandum from the review team outlining:
  - Dates of any discipline review letters issued to date. The memorandum should not duplicate the information from the DR letters.
  - Substantive application issues not included in a DR letter, including potential questions and/or points for discussion for the AC meeting. If there are no substantive issues for a discipline, a statement to that effect should be included.
  - Date the Agency's background package for the AC meeting was sent by DFO, if an AC meeting is to be held.

The briefing package should be signed off in DARRTS by either the RPM or the CDTL. The applicant should not submit "preliminary comments" on the background package to the Agency.

Meeting Chair: The roles and responsibilities for the LCM are currently under development and will be updated at a later date.

Meeting Attendees: FDA representatives at the late-cycle meeting include the following:

- The signatory authority for the application
- Review team members from appropriate disciplines
- Appropriate team leaders and/or supervisors from disciplines for which substantive issues have been identified in the review to date.

Topics for Discussion at the Late-Cycle Meeting: The late-cycle meeting is intended to share information, identify deficiencies, plan for the AC in order to avoid redundancy, and plan the rest of the review. The meeting is not to focus on the final regulatory decision for the application. No new data should be discussed in detail at the late cycle meeting. However, if new information is introduced, FDA may be able to determine whether it is adequate for review. The FDA review team and the applicant should discuss whether such data will be reviewed by the Agency in the current review cycle and, if so, whether the submission will be considered a major amendment and trigger an extension of the PDUFA goal date.

Potential topics for discussion at the late-cycle meeting include the following:

- Major deficiencies identified to date
- Issues to be discussed at the AC meeting (if planned)
- Current assessment of the need for REMS or other risk management actions
- Information requests from the review team to the applicant
- Additional data or analyses the applicant may wish to submit
- Major labeling issues, if appropriate (do not discuss line-by-line labeling)
- Also any available information on the status of inspections

The RPM will archive minutes of the late-cycle meeting.

4.14 Develop Final Labeling, REMS and PMRs/PMCs

When significant deficiencies preclude discussion of labeling, REMS, or PMRs/PMCs, those deficiencies are generally communicated in a Discipline Review letter(s) by the target date identified in the planned timeline (See MAPP 6010.8; see also section 4.9 of this Guide). If the application will receive a Complete Response letter, the action letter may include the division's proposed labeling. The "complete response" letter will also include the REMS requirement, if it is determined that a REMS is necessary.

If the application is likely to be approved, labeling (and REMS, if applicable) discussions, taking into account review wrap-up determinations, proceed between the review team and the applicant and continue until agreement is reached on the wording and final labeling (and REMS) is produced. Because essential labeling and REMS discussions occur by necessity toward the end of the review cycle when available time is limited, it is important that communication between the FDA and applicants be clear and efficient. Labeling discussions beginning too close to the end of the review cycle frequently result in inadequate time available to discuss labeling that both the applicant and the Agency can agree upon.

As with the labeling and REMS, the review team and applicant work to develop PMRs/PMCs, as appropriate, with input from OSE and the review division director, deputy director for safety, and the ODE director, if the signatory authority (See MAPP 6010.9).

4.15 Hold Wrap-Up Meeting

The outcomes of all review activities are integrated during the wrap-up meeting, an internal meeting to facilitate the development of a comprehensive understanding of the safety, efficacy and quality of the proposed product and a preliminary decision on the regulatory action. At the meeting, a plan for resolution of issues is discussed. Depending on the issue, they will be resolved either internally or with the applicant.

Attendees: Primary reviewers, team leaders, discipline division directors, OSE RPM, OSE epidemiologist, OSE safety evaluator, OSE management, OSE consultants, the review division's deputy director for safety, Safety RPM, and the review division director and/or signatory authority, OPDP review team (professional and consumer reviewers and RPM), plus appropriate consultants (e.g., OSI, CSS).

Agenda: Reviewers discuss the approvability of the application and address any outstanding critical issues that have not been resolved. Consideration should be given to critical elements such as major labeling issues, PMRs/PMCs, the need for REMS if not already required, and the need for Office or Center-level input. Typical agenda topics include:

- Primary reviewers and consultants presentations of outstanding issues
- Discussion of proposed action to be taken
- Discussion of outstanding labeling issues
- Discussion of outstanding PMR/PMC issues
- Discussion of outstanding REMS
- Discussion of Postmarket Safety Surveillance (If an approval action, OSE RPM will specify amount of time needed.)
- Other safety issues that will need ongoing monitoring
- FDA outreach if approval action is to be taken (e.g., Press Release)

If FDA communication is planned for the approval action, the RPM informs the FDA Press Office and coordinates with them on the development and division clearance of a draft Press Release. The RPM also informs the CDER Executive Operations office who will prepare an Information Alert.

4.16 Conduct CDTL Review

The CDTL, as part of the wrap-up activities, can either hold team meetings or meet with reviewers and team leaders to identify any remaining discipline specific review issues and recommendations. The outcome of reviews and input from all review disciplines, consultants, inspection results, and the advisory committee are integrated by the CDTL to provide to the signatory authority for consideration an overall recommendation for action and the summary basis for that recommendation. See Appendix A for due dates.

4 Conduct the Review

A CDTL review memorandum may not be required for all efficacy supplement applications. The factors to be considered in whether a review is needed include complexity/number of disciplines involved in the review, whether an advisory committee meeting was held, whether a REMS is needed, or to discuss disagreements between review disciplines on the recommended action.

5 Take Official Action

During this phase of the review, the team works to resolve remaining issues such as labeling, PMRs/PMCs, and REMS. The action package and letter are finalized based on the regulatory action to be taken (see MAPP 6020.8). Refer to the table in Appendix A for detailed timeline.

5.1 Conduct Division Director/Office Director Review(s)

The CDTL (and division director for ODE director sign-off) briefs the signatory authority on any issues in the action package.

The review conducted by the signatory authority includes a final decision whether to approve an application. Prior to initiating the review, the action package is provided to the division director and/or ODE director. See Appendix A for due dates. (See MAPP 6020.8)

The signatory authority writes a review documenting the issues, how they were resolved, and summarizes the basis for the final action on the application. For ODE level sign-off, the division director also writes a summary memorandum that is included in the action package.

5.2 Finalize Action, Letter and Action Package

It is important that any communication with the applicant before the official regulatory action (i.e., signed letter) makes it clear that a decision has not yet been made, and there should be no speculation on the nature of the final action.

If a REMS is determined to be necessary for the product, action on the proposed REMS is finalized at this time. DRISK's final REMS check and final sign-off in DARRTS also occurs.

For BLAs, to ensure that new facility information learned by FDA after the initial TB-EER is completed and incorporated into the recommendation, OC completes a final Therapeutic Biologic Establishment Inspection Evaluation request (TB-EER) during the review period. It is expected that the TB-EER be dated within 30 days of the action. The final TB-EER is initiated by OC.

If the signatory authority's decision is to not approve the application, the RPM drafts a Complete Response (CR) letter, which includes the deficiencies found by the review team and recommendations for corrective action. The need for a REMS, or any REMS deficiencies are included in the CR letter. If the application deficiencies are not significant enough to preclude discussion of labeling, REMS, and PMRs/PMCs (See section 4.7), labeling and REMS (if applicable) comments and preliminary descriptions of potential PMRs/PMCs should be included in the CR letter. The draft letter is circulated for editing by the review team (including the signatory authority). (See 21 CFR 314.110 and 21 CFR 601.3)

If the signatory authority's decision is to approve the application, the RPM drafts an Approval Letter and circulates it for editing by the review team (including the signatory authority).

All reviews must be finalized and signed (in DARRTS) before the action letter is signed and issued.

The RPM also prepares the Officer/Employee list that includes all who participated in the decision to approve the application and who consent to have their name included on this list (this does not have an impact on their name being on signed reviews).

After the action letter is signed, the RPM sends a copy by FAX or secure e-mail to the applicant and **promptly** contacts the applicant to confirm that the applicant has received the official written regulatory action. This approach provides a clear record of the timing of communication of the official action to the applicant and provides the applicant with the full text of the official regulatory action. In the case of an approval action, once the applicant confirms receipt, the RPM **immediately** notifies the FDA Press Officer if an FDA communication was prepared. The RPM also sends an e-mail within one business day to the "CDER-Approvals" system distribution list to notify the necessary personnel of the action; the letter (with any attachments) and division director's "summary" review is attached. The official letter is also sent to the applicant via U.S. Postal mail. The review clock stops when the action letter is signed.

The RPM finalizes the action package, and in the case of an approval, notifies the document room by email [cder-drtl-all] that the package is forthcoming, and delivers it to the document room within 2 business days of approving an application or efficacy supplement. For each review cycle, all documents generated during that cycle are added to the action package prior to review by the signatory authority. In the case of a collaborative review that involves more than one new drug review division or two centers, a single action package is compiled for the application. The package is returned to the RPM after the document room copies/scans it. The completed Action Package Checklist is archived in DARRTS.

5.3 Provide Post-Decision Feedback to Review Team

The signatory authority's review and the action letter are shared with the review team prior to taking the action. In instances where there are outstanding questions or a need for additional clarity, he/she can meet with the review team to provide feedback to them on the rationale for the action.

6 Post-Action Meetings

During the post-action phase, an optional feedback or lessons learned meeting may be held with the applicant to discuss the successful aspects of the review process and to identify other aspects that could benefit from future improvement. The feedback/lessons learned meeting is not to be confused with the End of Review Conference, which an applicant may request after receiving a CR letter. A single meeting may address the two distinct meeting objectives.

6.1 Post-Action Feedback Meeting

Post-action feedback meetings are offered for all NMEs and Original BLAs. This meeting is intended to discuss the process, including quality of the application and the communication process between the applicant and the Agency during the review. It is not intended to address scientific issues or approvability requirements. The meeting should focus on those items that provide lessons learned for future applications.

This meeting is not considered a PDUFA meeting and minutes are not required.

6.2 End of Review Conference

For Complete Response (CR) actions, it is optimal for applicants and FDA to ensure a common understanding (not necessarily agreement) of deficiencies and the expected responses. This mutual understanding may be accomplished through an End of Review Conference (via teleconference or meeting) [21 CFR 314.102(d)] requested by the applicant and scheduled by FDA to discuss deficiencies and further steps that need to be taken by the applicant before the application can be approved. Priority for granting this meeting will be given to applications for NMEs, major new supplemental indications, and for the first duplicates of such drugs. If the meeting is requested within three months of the CR action, this meeting will be considered a Type A meeting. The RPM should prepare and archive minutes of this meeting.

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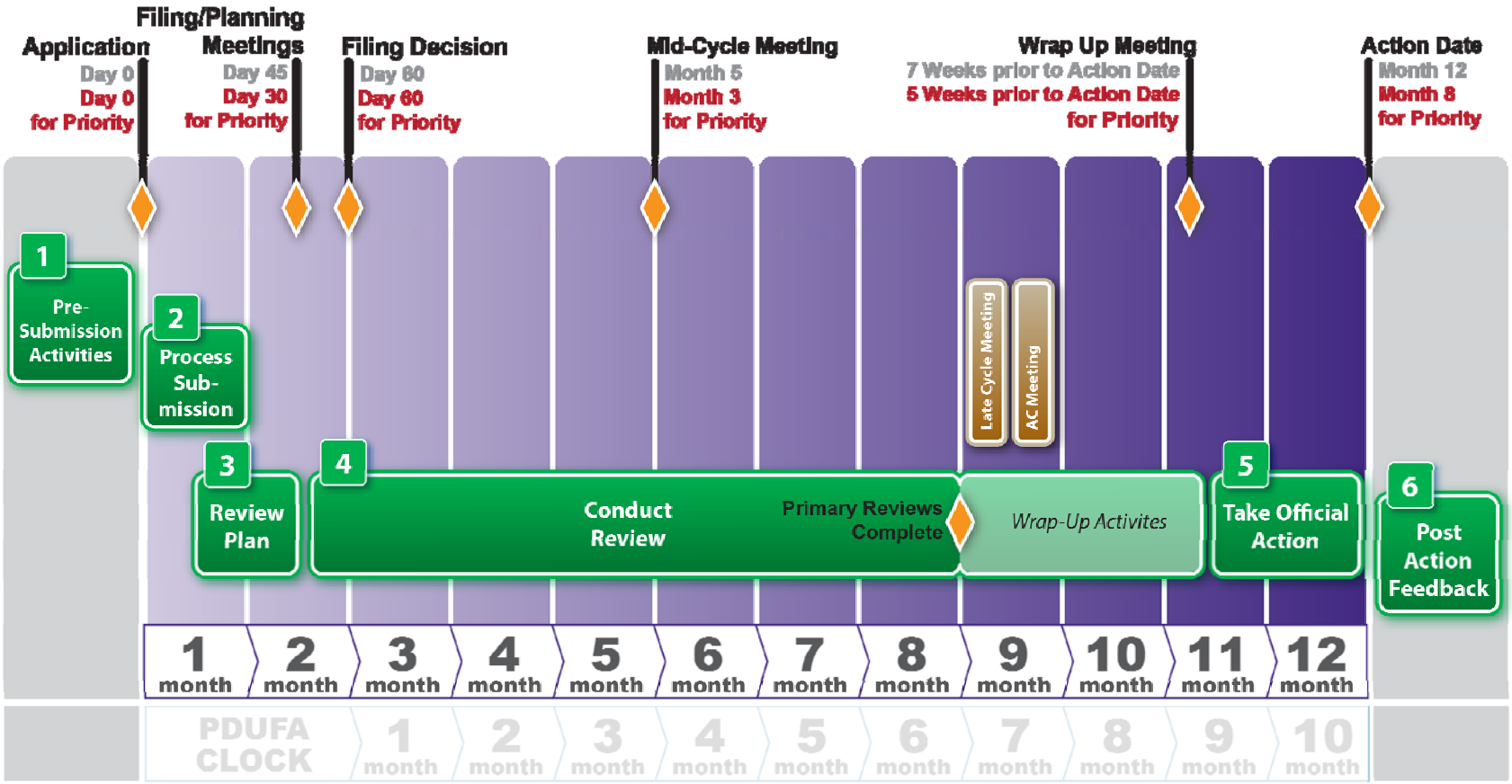
Timelines and Milestones

The application review process begins upon receipt of the application. For products under "The Program" described in PDUFA V (i.e., NME NDAs and all BLAs), the PDUFA time clock begins 60 days after the application receipt date if the application is filed. For all other applications, the PDUFA time clock begins on the FDA receipt date. Regardless, the timelines described in the DRG are based upon the receipt date of the application. In the interest of clarity and consistency, all timeline due dates in the DRG up until the Take Official Action phase are calculated from the application receipt date; all due dates after the Take Official Action phase are calculated from the PDUFA goal date.

This diagram presents a high-level illustration of the new timeline for NMEs and original BLAs under PDUFA V:



Summary of Milestones for the Full Review Cycle

The following table summarizes the milestones throughout the review cycle and cites the DRG section where the milestone is described.

	Standard Review			Priority Review		
	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**
Milestones for Steps 2 and 3: Filing Determination and Review Planning						
1. Application Receipt (2.1)	Day 0					
2. Assign RPM (2.1) Begin Regulatory Filing Review	Days 0-14					
3. Acknowledge application receipt in writing (2.4)	By Day 14					
4. Assign Review Team Schedule filing and planning meetings	By Day 14					
5. Determine Signatory Authority (3.1.1), CDTL (3.1.2), and preliminary Priority/ Standard review designation (3.1.3)	By Day 14					
6. Hold BIMO site selection meeting	By day 38 (day 23 for priority)					
7. Hold Applicant Orientation Presentation (optional) (3.1.6)	By Day 45 (by day 30 for priority)					
8. Conduct filing review, request standard Consults, identify Inspection actions, convey potential RTF issues to Applicant (3.2.1)	By Day 45 (by day 30 for priority)					
9. Hold filing meeting to make filing decision (3.2.3)	By Day 45	By Day 45	By Day 45	By Day 30	By Day 30	By Day 30
10. Hold planning meeting to plan the review (3.3)	By Day 45	By Day 45	By Day 45	By Day 30	By Day 30	By Day 30

A Appendix A: Timelines & Milestones

	Standard Review			Priority Review		
	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**
11. Inform Applicant of a Priority Designation in Writing Communicate Filing Determination to Applicant (for BLAs and priority NDAs) Notify Applicant of a Refuse-to-File determination (3.2.3)	By Day 60					
12. Communicate Filing Review Issues (3.2.2)	By Day 74					
13. Communicate "Program" Review Timeline to Applicant (3.3) (if applicable)			By Day 74			By Day 74
Milestones for Step Four: Conduct Review						
14. Conduct Review (4)	Month 1.5-8.0	Month 1.5-8.75	Month 1.5-8.0	Month 1.0-5.0	Month 1.0-5.25	Month 1.0-5.0
15. If applicable, discuss safety findings with OSE (re: REMS, PMRs) and OC-OSI (re: REMS)	Before the Mid-Cycle Meeting at a regularly scheduled Review Team Meeting					
16. Hold Mid-Cycle Meeting (4.4)	Month 5.0	Month 5.0	Month 5.0	Month 3.0	Month 3.0	Month 3.0
17. Post-Mid-Cycle Meeting Communication with Applicant (4.5)			Month 5.5			Month 3.5
18. Complete Primary Reviews, including Secondary Review Sign-Off (4.9)	Month 8.0	Month 8.75	Month 8.0	Month 5.0	Month 5.25	Month 5.0
19. Complete Secondary Review (when needed) (4.9)	Month 8.25	Month 9.0	Month 8.25	Month 5.1	Month 5.25	Month 5.1
20. Issue Discipline Review Letters (4.10)			1 week after primary review			3 days after primary review
21. Hold Wrap-Up Meeting, including Safety Discussion (4.16)	8 wks prior to PDUFA goal date	5 wks prior to PDUFA goal date	7 wks prior to PDUFA goal date	4 wks prior to PDUFA goal date	2 wks prior to PDUFA goal date	5 wks prior to PDUFA goal date

	Standard Review			Priority Review		
	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**
22. Complete CDTL Memo (4.17)	6 wks prior to PDUFA goal date	3 wks prior to PDUFA goal date	6 wks prior to PDUFA goal date	3 wks prior to PDUFA goal date	2 wks prior to PDUFA goal date	4 wks prior to PDUFA goal date
Milestones for Labeling, PMRs/PMCs, REMS						
23. If indicated, send REMS Notification Letter to Applicant (REMS memo must be completed) (4.5)	Within 6 weeks after Mid-Cycle Meeting					
24. Begin REMS Discussions with Applicant (if not already started) (4.8.2)	By Month 6 (or within 2 weeks after REMS notification letter is issued)					
25. Review Team Drafts Labeling, PMC, PMR (4.8.1)	Month 5.5–7.0	Month 5.5–7.0	Month 5.5–7.0	Month 3.5–4.5	Month 3.5–4.5	Month 3.5 – 4.5
26. Send Labeling/PMR/PMC to Applicant (4.8.1)	Month 8.25	Month 9.0	Month 8.25	Month 5.0	Month 5.25	Month 5.0
27. Labeling/PMR/PMC Discussions with Applicant Begin (4.8.1)	Month 8.5	Month 9.25	Month 8.5	Month 5.25	Month 5.5	Month 5.25
Milestones for Late-Cycle Meeting						
28. Hold Pre-Meeting for Late-Cycle Meeting (4.12)			Month 8.0			Month 5.25
29. Send Agency Late-Cycle Meeting Briefing Package to Applicant (4.13)			By 20 days before AC Meeting or 12 days before Late Cycle Mtg if no AC Mtg			By 20 days before AC Meeting or 12 days before Late-Cycle Mtg if no AC Mtg

	Standard Review			Priority Review		
	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**
30. Hold Late-Cycle Meeting with Applicant (4.13)			12 days before AC Meeting or by Month 9.0 if no AC Mtg			12 days before AC Meeting or by Month 6.0 if no AC Mtg
Milestones for AC Meeting						
31. Plan AC Meeting (4.7.1)	Begin when need for AC meeting is identified					
32. Send draft questions for AC to DFO (4.7.1)	12 weeks prior to meeting					
33. Disseminate and disclose applicant and background materials (4.7.1)	4 weeks prior to meeting					
34. Hold internal practice meetings to prepare for AC meeting (4.7.1)	2-6 weeks prior to meeting	2-6 weeks prior to meeting	2 weeks prior to meeting	2-6 weeks prior to meeting		2 weeks prior to meeting
35. Submit final questions for AC to applicant (4.7.1)			2 days before AC Meeting			2 days before AC Meeting
36. Conduct AC Meeting (4.7.1)	Month 7.0-8.0		By Month 9.0	Month 4.0-5.0		By Month 6.0
37. Hold internal post-AC meeting (4.7.1)	Within 2 weeks after AC meeting					
38. Confidential memo to AC to announce action and interpretation of AC input (4.7.1)	Within 30 days of taking action					
Milestones for Step 5: Take Action						
39. Hold PeRC meeting	4-6 weeks prior to action					

	Standard Review			Priority Review		
	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**	ODE Signatory	DD Signatory	ODE Signatory **PDUFA V Program**
40. Compile and Circulate Action Letter and Action Package (5.2)	6 weeks prior to action	3 weeks prior to action	6 weeks prior to action	3 weeks prior to action	2 weeks prior to action	3 weeks prior to action
41. Division Director Review of Action Package and Decision (5.1)	3-6 weeks prior to action	0-3 weeks prior to action	6 weeks prior to action	1.5-3 weeks prior to action	0-2 weeks prior to action	1.5-3 weeks prior to action
42. REMS finalized; DRISK review of REMS finalized (5.2)	1-2 weeks prior to action					
43. ODE Review of Action Package and Decision (5.1)	0-3 weeks prior to action		0-3 weeks prior to action	0-1.5 weeks prior to action		0-1.5 weeks prior to action
44. OC clearance of confirmatory TB-EER (BLAs only)	At least 30 days before Approval Action					
45. Issue Action Letter (5.2)	Month 10.0	Month 10.0	Month 12.0	Month 6.0	Month 6.0	Month 8.0

Refusal to File Considerations

1. Omission of a required section of the NDA/BLA or presentation of a section in so haphazard a manner as to render it incomplete on its face. The required sections include:
    a) A comprehensive table of contents;
    b) A summary of the application that includes, among other things, summaries of the technical sections, an annotated package insert, and the marketing history of the drug outside the United States;
    c) Required case report forms and tabulations;
    d) Complete information on manufacturing and testing facilities and specific activities at each.
2. Inadequate content, presentation, or organization within the required technical sections and integrated summaries that would render a section incomplete on its face such as illegibility; data tabulations (line listings) or graphical displays that are not interpretable, inadequately labeled, or that do not indicate the origins of the data in them; inadequate notation in summaries of where individual studies or clinical trials can be found or inadequate guidance in reports to the location of individual data and records, and absence of protocols for clinical trials; and omission of critical statistical analyses, such as an "all patients" analysis where one is obviously necessary or the statistical analysis described in the protocol.
3. Clear failure to include evidence of effectiveness compatible with statute and regulations, for example:
    a) Lack of any adequate and well-controlled clinical trials, including use of obviously inappropriate or clinically irrelevant study endpoints;
    b) Presentation of what appears to be only a single adequate and well controlled clinical trial without adequate explanation of why the trial should be regarded as fulfilling the legal requirement for adequate and well-controlled investigations;
    c) Use of a trial design clearly inappropriate (as reflected in regulations or well-established agency interpretation) for the particular claim, e.g., active control non-inferiority trials to support effectiveness of an antidepressant; and
    d) For a combination drug product, failure to present studies/trials that assess the contribution of each component.
4. Omission of critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate direction for use, for example:
    a) Omission, without explanation, of animal carcinogenicity studies for a chronically administered drug;
    b) Omission, without explanation, of animal reproduction studies for drug that will be administered to people of reproductive age;
    c) Total patient exposure (numbers or duration) at relevant doses that is clearly inadequate to evaluate safety;

d) Clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets;

e) Absence of a comprehensive analysis of safety data, e.g., as recommended in the Clinical/Statistical Guideline;

f) Absence of an analysis of data supporting the proposed dose and dose interval; or

g) Absence of bioavailability/bioequivalence data comparing the product(s) proposed for marketing with the product(s) studied in clinical trials (if the to be marketed product is different).