Guidance for Review Staff and Industry

Good Review Management Principles and Practices for PDUFA Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2005
Procedural

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Contains Nonbinding Recommendations

Guidance for Review Staff and Industry[1] Good Review Management Principles and Practices for PDUFA Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document provides guidance to industry and the review staff in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) on good review management principles and practices (GRMPs) for the conduct of the first cycle review of a new drug application (NDA), a biologics license application (BLA), or an efficacy supplement under the Prescription Drug User Fee Act of 1992 (PDUFA). The GRMPs in this guidance are based on the collective experience of CDER and CBER with review of applications for PDUFA products and are intended to promote the practice of good review management based on sound fundamental values and principles. This guidance also clarifies the roles and responsibilities of review staff in managing the review process and identifies ways in which NDA and BLA applicants may further the effectiveness and efficiency of the review process.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On June 12, 2002, the President signed the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which includes the Prescription Drug User Fee Amendments of 2002 (PDUFA III). In conjunction with the reauthorization of PDUFA, the FDA agreed to meet specific performance goals (PDUFA goals). These PDUFA goals are described in *PDUFA*

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

Reauthorization Performance Goals and Procedures, an enclosure to a letter dated June 4, 2002, from the Secretary of Health and Human Services to Congress.[2] Under the PDUFA goals, CDER and CBER agreed to create this joint guidance for review staff and industry on good review management principles and practices as they apply to the first cycle review of NDAs, BLAs, and efficacy supplements. The emphasis of GRMPs is on first cycle reviews of NDAs and BLAs for PDUFA products in CDER and CBER. The principles of this guidance also pertain, in general, to all preapproval reviews of NDAs, BLAs, and efficacy supplements.

The fundamental values and principles described in this guidance are intended to support the FDA's primary public health mission for human drug and biologic products,[3] help the FDA continue to define processes that fulfill the Agency's PDUFA mandates, promote efficient use of the FDA's resources, and define ways in which both FDA review staff and applicants can further the effectiveness and efficiency of the review process. This guidance is expected to lead to greater consistency and efficiency of the review process within individual review divisions (also called divisions in this guidance), across review divisions, and between CDER and CBER.

The GRMPs include the Agency's current best practices, as well as goals for review management improvements. The best practices have evolved from more than a decade of review process innovations that began with the implementation of PDUFA in 1992, and many of the GRMPs are already in use. Under the PDUFA program, CDER and CBER have continuously improved review management for marketing applications to meet tightening review goals while maintaining the FDA's traditionally high standards for evaluation of safety, effectiveness, and product quality. Management and review capability enhancements have improved the planning and coordination of review team activities and engaged applicants in productive communications during product development (the investigational new drug application (IND) phase) and marketing application review.

The ability of review staff and managers to adhere to and consistently achieve these review management principles depends on the availability of adequate resources (e.g., staffing, information technology support). The FDA also needs the full cooperation and participation of applicants for effective implementation of the GRMPs. This guidance, therefore, describes best practices for both applicants and FDA review staff to facilitate efficient application review. The GRMPs outline the FDA's procedures and objectives for communicating with applicants during each phase of the review cycle. The GRMPs do not address the specific conduct or content of scientific reviews and do not alter existing Agency processes or standards for scientific and regulatory decision making. Applicants interacting with the Agency are strongly encouraged to be fully knowledgeable about the GRMPs.

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[2] The letter was sent to Congress with identical copies addressed to the Chairman and Ranking Minority Members of the Committee on Health, Education, Labor, and Pensions, United States Senate; and the Committee on Energy and Commerce, House of Representatives. The PDUFA goals can be found at http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html.

[3] The FDA mission statement can be found at http://www.fda.gov/opacom/morechoices/mission.html.

Additional Agency documents are available to supplement the information in this guidance, including staff instruction documents (i.e., CDER's Manual of Policies and Procedures (MAPP), and CBER's Manual of Standard Operating Procedures and Policies (SOPP)) and guidances for industry and review staff. The documents referenced in this guidance provide more detail on specific CDER and CBER processes, expectations for review staff performance, and recommendations for industry.

The GRMPs are an important foundation for implementing a quality systems approach for the new drugs and biologics review and approval process. This guidance serves as initial documentation of what has been, and continues to be, a work in progress.

III. FUNDAMENTALS OF GOOD REVIEW MANAGEMENT

The FDA's goal is to ensure that its review and approval process is managed in a consistent and efficient manner. The GRMPs described in this guidance, when applied consistently by review staff and applicants, are expected to improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to new drugs and biologics.

A. Fundamental Values

The fundamental values on which the GRMPs are based include quality, efficiency, clarity, transparency, and consistency.

Quality: The FDA seeks the highest levels of quality in our reviews, our review processes, management, and outcomes. Consistent implementation of the GRMPs by review staff and applicants will enhance the quality of the review process and the resultant regulatory action. As the FDA continues to implement a quality systems approach to the new drugs and biologics review and approval process, internal assessment and public scrutiny will focus on defining additional ways to measure the quality of FDA review activity. We will work to establish better metrics of quality and identify more conclusive links among the numerous factors that influence the review process.

Efficiency: Efficiency is critical to the review process. Process efficiency, however, must not be achieved at the expense of quality. The FDA believes that the GRMPs will improve both the efficiency of the review process and the quality of the review product and outcomes.

Clarity: The clarity of the FDA's findings, expectations, and bases for decisions supports review efficiency and requires accurate review and effective communication. The GRMPs describe processes that support clarity throughout the review process, including critical review and decision activities that must be completed before the FDA can fully explain its views. Communications during the ongoing review, within CDER and CBER or with external groups such as the applicant or advisory committees (AC), are expected to consistently achieve the highest possible degree of clarity.

Transparency: Transparency ensures that review staff and applicants are kept informed of how the review is progressing. Both parties can then anticipate and plan the next steps and respond to potential problems as they are identified. The need for transparency, however, must not interfere with efficiency. The GRMPs describe an appropriate balance between transparency and the efficiency of the review process.

Consistency: Achieving consistent processes across review divisions and offices, and between CDER and CBER, is an important goal of good review management. Consistency can help prevent misunderstandings and confusion that can occur when review divisions adopt different procedures to accomplish the same fundamental review activity. Consistent practices for interaction with all applicants also preclude the need for FDA staff to develop new procedures with each applicant. Consistent application of the GRMPs by review staff, and applicant support of GRMPs, is critical to the overall success of good review management. The FDA recognizes that it may be appropriate to occasionally deviate from the processes and procedures described in the GRMPs to meet other goals. FDA staff are expected to deviate from the GRMP process only when the thorough assessment of an individual situation justifies doing so. Changes that become generally accepted as new best practices under GRMPs should be documented and shared across divisions and, if possible, across centers for broader implementation.

B. Operational Principles

The following principles form the Agency's current perspective on the essential elements of good review management. This section provides definitions for each element. The subsequent sections, detailing model review management practices, describe how these principles are implemented.

The principles of good review management are expected to remain stable despite changes in other factors (e.g., regulatory, economic, scientific), but the processes that stem from them may change to adapt and respond to individual application review circumstances and to further develop new best practices.

- *The foundation for good review management is created during product development.*

Effective interaction between the FDA and applicants during product development, prior to NDA/BLA submission, is critical to maximize first cycle approvals for marketing applications. We recognize that the product development phase is under the primary management of the applicant, but there are important reasons for applicants to discuss development plans with the Agency. First, the review staff can provide valuable scientific and regulatory advice to the applicant during the product development phase, resulting in more efficient and robust development programs. Second, FDA staff can interpret the general requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Public Health Services Act, and other applicable statutes to help applicants define adequate evidence of effectiveness (e.g., endpoints, study design, patient populations), safety (e.g., sample size, dose response, assessment of drug-drug interactions, demographic differences), and quality (e.g., manufacturing procedures, facility compliance with good manufacturing practices). It is critical for applicants to ascertain the

Agency's views on the applicable statutory requirements well in advance of submission of a marketing application.

It is preferred that open communication of advice, guidance, and notification of deficiencies occur at pivotal points during product development. This communication can lead to identification of potential filing and review issues that the applicant can, and should, address before the marketing application is submitted for review. We recommend that the milestones of development be marked with meetings to exchange ideas on program status and planning. These meetings include, but are not limited to, pre-IND, end-of-phase 1, end-of-phase 2, and pre-NDA/BLA meetings. The FDA guidance for industry *Formal Meetings with Sponsors and Applicants for PDUFA Products*[4] provides information on meeting procedures.

Another FDA guidance for industry, *Special Protocol Assessment (SPA)*, explains that the SPA process can be used for clinical trials that will form the basis of an efficacy claim in an NDA or BLA. Applicants are particularly encouraged to use the SPA process for trials in which the proposed study design or endpoints are unusual, or for studies that involve an indication or disease for which the FDA has not previously approved a drug or biologic product.

New initiatives affecting product development are being pursued under the PDUFA goals, including enhanced preapproval attention to risk management by the FDA and the applicant. In addition, two pilot programs exploring the continuous marketing application (CMA) concept for fast track designated products are underway and are the subject of separate FDA guidances, *Continuous Marketing Applications: Pilot 1 — Reviewable Units for Fast Track Products Under PDUFA,* and *Continuous Marketing Applications: Pilot 2 — Scientific Feedback and Interactions During Development of Fast Track Products Under PDUFA*.

An applicant's effective management of the period before NDA/BLA submission is essential to create an application that is likely to satisfy the regulatory requirements and that can be readily reviewed. We encourage applicants to inform the review division of circumstances that arise during development that may affect product approval (e.g., inability to carry out agreed-upon protocols, new preclinical or clinical safety concerns, important manufacturing problems). This information can also help prevent deficiencies that could cause the FDA to refuse to file the application or that could result in unnecessary multiple review cycles. In addition, identifying the anticipated application submission date helps the review division manage its overall workload, including allocation of review staff and consultant time.

- *The applicant is responsible for submission of a complete marketing application to maximize the efficiency of the review process and reduce the need for multiple cycle reviews.*

Central to PDUFA is the agreement that industry will submit a complete application that will receive a comprehensive and complete review within a specified time. A complete application contains all required and expected information to support approval of the proposed claims, labeling, and dosage forms. A complete application is also in a readable, well-organized,

[4] All guidances referenced in this guidance are available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

preferably electronic, format. Numerous FDA guidances are available to provide information on the format and content of high-quality submissions, including those in electronic formats. It is important for the applicant to provide a complete application *at the time of initial submission* to limit the need for unsolicited or unexpected amendments during the review process. Significant omissions lead to requests for amendments or more data (i.e., not a first cycle approval). An application is not considered complete if it meets the regulatory criteria for filing, but lacks important information needed for approval. The focus on initial submission of a complete application does not preclude agreements between an applicant and a division on a postsubmission planned amendment, but it is expected that such agreements will be needed only in exceptional situations.

- *Effective and efficient management of the review process is primarily an FDA responsibility.*

During the product development phase, the applicant retains the primary management role, and the Agency's regulatory role is to ensure public safety and to provide guidance on the development program. However, the submission of a marketing application shifts the primary management responsibility to the FDA. The FDA's obligation is to manage the review process and determine whether a submitted application meets the legal and scientific requirements for approval of the product.

- *Active applicant involvement is important during the review process.*

Although the responsibility for review management lies primarily with the FDA, applicant involvement during the review is essential. The role of the applicant, a role that changes during the various stages of the review process, is summarized in later sections of this guidance.

- *FDA staff adherence to internal review timelines is critical for optimal review performance.*

FDA staff should establish and observe internal review timelines to help ensure efficiency and consistency in the review process. As described in Section II, Background, FDA practices review management mindful of both the Agency's primary public health responsibility and review efficiency standards set by PDUFA. The timelines for many of the elements of first cycle review are in part established by PDUFA. A well-managed review process helps FDA staff to allocate the time and resources necessary to complete reviews soon enough to accommodate and adequately consider unanticipated events or findings that may develop during the course of the review. Adherence to these timelines with key internal milestones helps avoid the potential errors associated with crisis-style management dealing with unresolved issues at the end of the review cycle.

Review divisions are expected to inform applicants about major elements of the internal review timeline for each application, anticipating some flexibility for resolution of unanticipated review findings that require adaptation of the review plan. Changes to the review plan can stem from additional team interactions, interactions with senior management, need for consult input, problems identified during facilities inspections, and requests for additional data or analyses from the applicant. Staff should communicate any significant changes in the review timeline to the applicant.

- *Good review management requires targeted input from the entire review team.*

An effective review team maintains a strong interdependence and communication among its members and engages in frequent interactions with supervisory reviewers. In addition, the core review team, comprised of individuals representing the primary review disciplines and project management, should seek and consider appropriate consultative input. Given the multilevel nature of the review and decision-making process, it is important that the review team, supervisory staff, and consultants adhere to the agreed-upon timelines.

- *Good review management increases first cycle approvals.*

A complete and well-formatted marketing application that meets the standards for approval will be approved on the first cycle. Good review management allows sufficient time for careful regulatory decision making and, if needed, time to work with the applicant to resolve minor and readily correctable deficiencies in the application. For applications that otherwise meet the standards for approval, good review management allows for finalization of labeling and other regulatory issues (e.g., negotiation of postmarketing commitments) and issuance of an approval letter on or before the PDUFA goal date. While this document focuses primarily on the first review cycle, good review management principles and practices also pertain to subsequent review cycles.

- *Effective and timely communication between the FDA and applicants enhances the review process.*

Communication within the Agency and with applicants promotes understanding of multiple perspectives, and is invaluable when appropriately tailored to each phase of the review process. Communication between applicant representatives and the review division regulatory project manager (RPM) is generally the most effective and timely mechanism for interaction. Applicants are encouraged to work with RPMs, particularly at the time of application submission, to create a clear communication strategy. RPMs should promptly bring issues that arise during communication with the applicant to the attention of other review staff. In some cases, direct communication between the applicant and the reviewers may be appropriate and may contribute to review efficiency. Emerging review issues should be communicated to all review team members, and substantive issues (e.g., when agreements or understandings are reached, deficiencies are conveyed, or additional information is requested) should be documented in the file by RPMs or reviewers.

For applications found to have significant deficiencies that may affect approval, the review team should obtain appropriate input from the signatory authority and communicate the deficiencies promptly to the applicant. Timely notification of correctable deficiencies allows the applicant to begin corrective actions, maximizes the chance for a first cycle approval, and shortens the overall time to approval when one or more review cycles are necessary. Timely notification of significant and potentially uncorrectable deficiencies in the marketing application may also influence product development decisions.

In general, few meetings with the applicant to provide feedback on the status of the review are warranted during the review process. However, meetings that offer productive communication opportunities for the FDA and applicants are described in subsequent sections of this guidance. Good review management is facilitated by applicants' submission of clear, concise background packages for such meetings.

Applicants are encouraged to use expeditious means of communication such as secure e-mail and teleconferencing, when appropriate.

- *The FDA will provide an official written regulatory action for each marketing application.*

The FDA will process and review all applications with the goal of issuing an official written regulatory action (e.g., refuse to file (RTF), approval, approvable, nonapproval, complete response letter) by the designated signatory authority for the Agency. The written regulatory action provides an official record of the Agency's review decision. The official written regulatory approval action contains important information on the Agency's basis for its decision and includes conditions of approval. Alternatively, the official written regulatory action documents the Agency's basis for a decision to refuse to file or not approve an application, as well as the information needed from the applicant to correct the identified deficiencies.

Although an applicant may voluntarily withdraw a marketing application at any time after it is submitted, it is generally preferred that the applicant not withdraw an application, so the Agency can issue an official written regulatory action documenting its review. FDA staff should not request or suggest that an applicant withdraw a pending marketing application except in the most unusual circumstances (e.g., the marketing application was submitted to the wrong center). In cases where an applicant voluntarily withdraws a marketing application in advance of an *adverse* regulatory action (e.g., RTF, nonapproval), the Agency will acknowledge the applicant's withdrawal of the application in writing. The withdrawal acknowledgment letter will generally include any deficiencies identified by the review division at the time the application was withdrawn.

- *FDA staff should not communicate to applicants the proposed or planned regulatory action before issuance of the official written regulatory action.*

A decision on the official regulatory action for an application can be made only after the signatory authority has completed review of the available information (e.g., from the action package and consultation with appropriate members of the review team and FDA management). Therefore, it is important that communication with the applicant during the review of an application be generally limited to requests for additional information (e.g., information request letters), conveyance of identified deficiencies that need to be corrected before the application can be approved (e.g., discipline review letters), and preliminary comments on draft labeling. FDA staff should make clear to the applicant that such communications are preliminary and that the official regulatory action for the application has not yet been taken. We discourage applicants from requesting that Agency staff speculate about the eventual official regulatory action. Such requests are premature and can lead to unnecessary tension in the communications between the applicant and the members of the review team.

Once the person responsible for making a decision on this application has made a decision on the official regulatory action, it is important to communicate this decision in writing to the applicant in the form of an official written regulatory action (e.g., RTF, approval, nonapproval, complete response). The review division should confirm by telephone that the applicant has received the official written regulatory action and document the call in the application file. 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. This assists the applicant in understanding the terms of an approval or the deficiencies identified, and what additional information is required to support approval.

IV. NDA/BLA REVIEW PROCESS

The NDA/BLA review process is divided into five phases: (1) filing determination and review planning; (2) review; (3) advisory committee meeting preparation and conduct; (4) action; and (5) post-action. The goals of each review phase are outlined below, with information on how applicants can best assist with review activities and the most useful type of communication between the FDA and applicants during each phase. A table accompanying the text for each review phase outlines each FDA review activity. Each table refers to procedural documents, including regulations, guidances, MAPPs, and SOPPs. A full understanding of each review phase requires integration of the content of both the appropriate text and table, as neither is a stand-alone descriptor of FDA review practice.

Adhering to prespecified internal timelines allows sufficient time to complete each review activity. The table associated with each review phase provides general timelines for important milestones. These timelines may require modification by the review division based on factors such as staffing, competing workload, and complexity of the application. Such deviations should be carefully considered, however, and any new internal timelines should be clearly communicated to the review team and applicant.

The standard processes described below are subject to change as the FDA continues to identify and implement new best practices as part of developing a quality systems approach to the new drugs and biologics review and approval process.

A. Filing Determination and Review Planning Phase

1. Filing Determination

The primary goals of the filing process are to: (1) determine whether the submitted application meets the regulatory requirements for filing; (2) define the scope of review activity needed; and (3) identify major elements of the application that may pose concerns during the review. Reviewers of the INDs under which development of the product took place are assigned to review the NDA/BLA whenever possible. A review team is comprised of the assigned RPM and primary reviewers. Consultant input is sought when particular expertise not represented on the

review team is needed. In some cases, outside experts (e.g., special government employees) may participate in reviews.

The review division should convey to the applicant any significant deficiencies identified during the filing determination and ask the applicant to clarify or complete the application. In particular, it is important that potential RTF deficiencies be conveyed to the applicant as early in the review cycle as possible with a clear explanation of their potential impact on the review outcome. Based on the FDA's judgment at the filing meeting, substantive application deficiencies not corrected by the applicant may warrant an RTF action or may be conveyed to the applicant in the filing review issues letter. Applicants can facilitate the filing determination by promptly responding to FDA inquiries during the filing review.

2. Review Planning

Review planning also occurs during this phase to organize the associated review tasks, minimize review overlap among review disciplines, and establish an internal review timeline. Review planning activity can occur at the filing meeting to take advantage of the review team's collective input and obtain consensus on the review plan. Adherence to the review plan is critical to the efficiency and effectiveness of the review process and reduces the need for resource-intensive problem solving at the end of the review cycle.

Major review milestone timelines should be conveyed to applicants following review planning. It is important that applicants be aware that these timelines are flexible and subject to change based on division workload and other potential review issues (e.g., the need for submission of amendments). Significant changes to the review plan should also be conveyed to applicants as they arise. Often, changes in the review division's planned review timeline and review team activity can be made to optimize first cycle outcomes. Review planning is facilitated by applicants' provision of accurate timelines for the submission of planned amendments and safety updates.

Filing Determination and Review Planning Phase			
Timeline	**Activity**	**Reference[5]**	**Responsibility**
Day 0	**Application Receipt**		Central Document Room (CDER) or Document Control Center (CBER)
Days 0 – 14	**Assign RPM**		Chief, Project Management Staff (CPMS)
	Begin Regulatory Filing Review (including, but not limited to):	FDA Form 356h	RPM
	User Fee Payment Status	PDUFA, FDA Form 3397	
	Application Provision	FD&C Act 505(b)(1) and (2) 21 CFR 314.3	
	Pediatric Development	Pediatric Research Equity Act (PREA)	
	Financial Disclosure	21 CFR 54.5, FDA Forms 3454 and 3455	
	Orphan Drug Status	21 CFR 316	
	Patent Information/Certification (NDA)	21 CFR 314.53, FDA Form 3542a 21 CFR 314.50(i)	
	Debarment Statement	FD&C Act 306(k)(1)	
	Overview of Content and Format	21 CFR 314.50	
By Day 14	Acknowledge application receipt in writing		
	Assign Review Team, as needed		Review Discipline Team Leaders (CDER) Review Division Management (CBER)
	Medical/Clinical		
	Pharmacology/Toxicology (P/T)		
	Chemistry, Manufacturing, and Controls (CMC)		
	Biometrics/Statistical		
	Clinical Pharmacology and Biopharmaceutics		
	Clinical Microbiology		
	BioResearch Monitoring (BiMo)		
	Schedule Filing Meeting		RPM

[5] The references listed in this table are considered important to this topic, but are not all inclusive.

Filing Determination and Review Planning Phase			
Timeline	**Activity**	**Reference**	**Responsibility**
Days 0 – 45 (30)[6]	**Request Consults (most frequently used)**		From Review Team
	Claims of Categorical Exclusion		To Office of New Drug Chemistry (ONDC) or Office of Biotechnology Products (OBP) (CDER) To Division of Manufacturing and Product Quality (DMPQ) (CBER)
	Environmental Assessments (EAs)		To OPS Environmental Scientist (CDER) To DMPQ (CBER)
	Trade name, carton/container labels, labeling, packaging, drug delivery device (working model), package insert (PI), patient package insert (PPI), MedGuide and other consumer information, as needed		To Office of Drug Safety (ODS) (CDER) To Division of Drug Marketing and Communication (DDMAC) (CDER) To Advertising and Promotional Labeling Branch (APLB) (CBER) To Office of Compliance and Biologics Quality (OCBQ) (CBER)
	Postmarketing Risk Management Plan (RMP)		To ODS (CDER) To Division of Epidemiology (DE) (CBER)
	Abuse Potential	CDER MAPP 4200.3, *Consulting the Controlled Substance Staff on Abuse Liability, Drug Dependence, Risk Management, and Drug Scheduling*	To Controlled Substances Staff (CDER)
	Pregnancy Labeling		To Pregnancy Labeling Team (CDER) To OCBQ (CBER)
	Health-Related Quality of Life (HRQL) and Patient-Reported Outcomes (PROs)		To Study Endpoints and Labeling Development Team (CDER) Review Team (CBER)

[6] The number in parentheses indicates modification of timeline for priority status reviews.

Filing Determination and Review Planning Phase			
Timeline	**Activity**	**Reference**	**Responsibility**
	Identify Inspection Actions		From Review Team
	Submit Establishment Evaluation Request (EER) and request inspections (for NDA)		ONDC or OBP (CDER) DMPQ (CBER)
	Coordinate Preapproval Inspections (PAI) for BLAs	21 CFR 601.20(d)	DMPQ (CDER) DMPQ or Product Reviewer (CBER)
	Request investigation of clinical, nonclinical, and biopharmaceutics research sites		To Division of Scientific Investigation (DSI) (CDER) To BiMo (CBER)
Days 0 – 45 (30)	**Applicant Orientation Presentation (optional)**		For Review Team
	Designate Priority Review Classification/Status (Priority or Standard)	CBER SOPP 8401, *Administrative Processing of Biologics License Applications,* SOPP 8405, *Complete Review and Issuance of Action Letters* CDER MAPP 6020.3, *Priority Review Policy*	Review Division Director Office Director
	Conduct Filing Review		Review Team
	Review completeness and adequacy of submission	21 CFR 314.101 21 CFR 601.2(a)	
	Identify any RTF issues	21 CFR 314.101(d) and (e)	
	Identify any filing review issues	CBER SOPP 8401.3, *Filing Action: Communication Options* CDER MAPP 6010.5, *NDAs: Filing Review Issues*	
	Identify any special development or approval issues	21 CFR 314 Subpart H or I 21 CFR 601 Subpart E or H	
	Identify omissions from the submission		
	Identify need for AC input		
	Identify potential for postmarketing commitments	FDA Modernization Act of 1997 (Section 130)	
	Convey Potential RTF Issues to Applicant		RPM

Filing Determination and Review Planning Phase			
Timeline	**Activity**	**Reference**	**Responsibility**
	Identify Signatory Authority		
	NME NDA and BLA		Office Director/Deputy
	Non-NME NDA		Review Division Director/Deputy Office Director (in special circumstances)
By Day 45 (30)	**Hold Filing Meeting**		Review Team Consultants
	Discuss filing review		
	Make filing recommendations		
	Make Filing Decision	CBER SOPP 8404, *Refusal to File Procedures for BLAs* CDER guidance *Refusal to File*	Review Division Director Office Director (consulted for RTFs)
By Day 45 (30)	**Conduct Planning Meeting (with Filing Meeting where possible) to Plan for and Schedule:**		Review Team
	Periodic team progress check-ins		
	Mid-cycle review meeting		
	Team or subgroup interaction on particular issues		
	Primary review completion		
	Secondary (team leader or branch chief) review		
	Review division director, or higher level, review		Review Team
	Consult review input		
	Advisory committee meetings		
	Internal briefings for signatory authority		
	Wrap-up (integration of review, consult, and inspection input)		
	Preapproval safety conference (CDER)	CDER MAPP 6010.1, *NDAs: Preapproval Safety Conferences*	
	Preapproval facility inspections (BLAs)		
	Labeling negotiation		
	Issuance of action letter by PDUFA goal date		

Filing Determination and Review Planning Phase			
Timeline	**Activity**	**Reference**	**Responsibility**
By Day 60	**Inform Applicant of a Priority Designation in Writing**		RPM
	Communicate Filing Determination to Applicant, if RTF	21 CFR 314.101(a)(3) CBER SOPP 8404, *Refusal to File Procedures for Biologic License Applications;* SOPP 8404.1, *Procedures for Filing an Application When the Applicant Protests an RTF Action (File Over Protest)*	Review Division Director (for RTF)
By Day 74	**Communicate Filing Review Issues to Applicant**	CDER MAPP 6010.5, *NDAs: Filing Review Issues*, CBER SOPP 8401.1, *Issuance and Review of Responses to Information Requests and Discipline Review Letters to Pending Applications*	RPM

B. Review Phase

During this phase, primary reviewers conduct a review of the application, sharing findings on a regular basis with secondary and other supervisory reviewers, reviewers of other disciplines, and consultants. In some instances, joint reviews are conducted between reviewers of the same or different disciplines.

Reviews are finalized with sequential signatory steps that document the action on an application. While primary reviewers are expected to seek and consider input from secondary reviewers, the primary review conclusions and recommendations represent the opinion of the primary reviewer. A primary review is considered final only after it has been reviewed and signed by the secondary reviewer. In CDER, secondary reviewers write their own brief reviews to summarize the discipline review and note their own recommendations for the application. These written secondary reviews are optional in CBER, except when the secondary reviewer does not agree with the findings or conclusions of the primary reviewer.

Applicants may receive additional information requests as a result of ongoing reviews and are encouraged to respond promptly and completely to such requests. During the first cycle, the division ordinarily reviews all amendments solicited by the Agency during the review, and any amendments to the application previously agreed upon (e.g., during the pre-NDA/BLA meeting). Substantial amendments submitted late in the review cycle may, however, be reviewed in a subsequent cycle, depending, in part, on other identified application deficiencies. The review division attempts to review all other amendments during the first review cycle, but may not be able to, or may decide not to do so in some instances (e.g., when the content of such an amendment does not address a known deficiency in the application). We strongly encourage applicants to submit complete applications, making later amendments unnecessary unless requested by the review division.

Under the PDUFA provisions, submission of a major amendment during the last 3 months of a review may trigger a 3-month extension of the review clock. The Agency decides whether to extend the review clock in response to such amendments. This decision is based on a variety of factors (e.g., content of the amendments, FDA workload and resources, existence of other known deficiencies that may affect approval and have not been addressed by the amendment), but the underlying principle is to consider the most efficient path toward completion of a comprehensive review that addresses application deficiencies and leads toward a first cycle approval when possible.

Review Phase			
Timeline	**Activity**	**Reference**[7]	**Responsibility**
Begin at time of assignment	**Conduct Review**		Review Team Consultants Signatory Authority, as needed
	Interaction of primary and secondary reviewers		
	Interdisciplinary interaction		
	Team meetings		
	Issue IR Letter or other requests for information, as needed		
By End of Month 5 (3)	**Mid-Cycle Meeting**		
	Update on progress and findings of all reviews, consults, and inspections		
	Define need for additional interaction with applicant related to labeling, risk management, postmarketing commitments		
	Revise review plan, if needed		
	Brief signatory authority		
By End of Month 8 (5)	**Complete Primary Review**		Review Team

[7] The references listed in this table are considered important to this topic, but are not all inclusive.

Review Phase			
Timeline	**Activity**	**Reference**	**Responsibility**
Variable	**Secondary Sign-Off**	CBER SOPP 8006, *Resolution of Differences in Scientific Judgment in the Review Process* CDER MAPP 4151.1, *Resolution of Disputes: Roles of Reviewers, Supervisors, and Management — Documenting Views and Findings and Resolving Differences* CDER MAPP 6020.8, *Action Packages for NDAs and Efficacy Supplements*	
Variable	**Issue DR Letters, as appropriate**	FDA guidance, *Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act*	

C. Advisory Committee Meeting Phase

The review division, in consultation with the office director, may decide to convene an advisory committee (AC) meeting. A review division may seek AC input, for example, when: (1) the application is for a new molecular entity (NME), especially if it is the first member of a new class of drug; (2) the clinical study design used novel clinical or surrogate endpoints; (3) the application raises significant issues on the safety and/or effectiveness of the drug or biologic; or (4) 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 hold an AC meeting should be made and communicated to the applicant early in the first cycle review process.

The FDA and the applicant should work together during AC meeting planning to share issues and avoid redundant presentations. Applicants are strongly discouraged from submitting amendments that contain significant new data after the review division has sent the FDA background package to the AC members and the applicant, because this does not allow the review division sufficient opportunity to review and consider the new data before the meeting. There are also strict timelines for clearance of background packages for public dissemination before the meeting, so the FDA is not able to accommodate applicant requests for changes in FDA background materials, other than to correct factual errors (e.g., issuance of an errata sheet).

Based on the discussions at the AC meeting and committee recommendations, the FDA may ask an applicant to submit additional data or analyses for review. We encourage applicants to provide these amendments in a timely manner.

Advisory Committee Meeting Phase (if needed)			
Timeline	**Activity**	**Reference[8]**	**Responsibility**
Begin when need for AC meeting is identified	**Plan AC Meeting**		Review Team Consultants, as needed FDA Advisors and Consultants Staff
Variable	Formulation of questions for AC		
By 2 weeks before AC meeting	Disseminate and disclose applicant and FDA background materials[9]		
By End of Month 8 (5)	**Conduct AC Meeting**	FDA guidance, *Implementation of Section 120 of the Food and Drug Administration Modernization Act of 1997 — Advisory Committees*	
Variable	**Follow-Up to AC**		
Within 2 weeks after AC meeting	Internal meeting to integrate AC input into review outcomes and request or conduct additional analyses		Review Team
With Action	Confidential memo to AC to announce action and interpretation of AC input		Review Division Director

[8] The references listed in this table are considered important to this topic, but are not all inclusive.

[9] The following draft guidances are references for this activity: CDER draft guidance *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*; and CBER draft guidance *Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of Biologic Products and Convened by the Center for Biologics Evaluation and Research Beginning on June 1, 2001*. Once finalized, these draft guidances will represent the FDA's current thinking regarding these topics.

D. Action Phase

1. Wrap-Up

The outcomes of all review activity are integrated during wrap-up, the first part of the action phase. An internal meeting facilitates the development of a comprehensive understanding of the safety, efficacy, and quality of the proposed product and a preliminary decision on the regulatory action. Consideration should be given to critical elements such as risk management, major labeling issues, and postmarketing commitments.

2. Labeling

Review wrap-up determinations help form the basis for labeling discussions with the applicant to complete the labeling for products whose approval can be anticipated (i.e., approval and most approvable actions). Since essential labeling discussions by necessity occur 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. Adherence to the review timeline, including completion of primary and secondary reviews well in advance of the PDUFA goal date, allows time to resolve labeling content issues and avoids crisis management of these issues near the PDUFA goal date.

Applicants can support labeling discussions by not submitting large amounts of new data in support of proposed labeling text, and by clearly explaining their basis for changes from the review division's recommended labeling language. Applicants are discouraged from printing labels for commercial distribution before receipt of an approval letter, because the label can change until it is approved. Labels printed in advance of the actual receipt of an approval letter are done so at the applicant's risk.

3. Signatory Review Documentation

When the review division director in CDER has signature authority for an application, the team leader from each review discipline should write a summary of the basis for the recommended action from that discipline. In CBER, the review discipline branch chief will write a summary of the basis for the recommended action from that discipline only if he or she disagrees with the findings or conclusions of the primary reviewer (see Section IV.B., Review Phase). The division director of the responsible office should also write a summary to document the basis for the regulatory action, taking into account the input from the entire review team. The division director summary should describe the resolution of difficulties or disagreements and clarify any issues that need attention during the postapproval period. In some instances, particularly when there has been little disagreement during the review process, the medical team leader in CDER, or the review team leader in CBER, may write the summary of the basis of the recommended action from the multidisciplinary perspective. The division director should document concurrence with the team leader's statement as part of the signatory process, or document in writing the basis for nonconcurrence, if necessary.

When the office director has signature authority, the previously described documentation is warranted as well as an additional written summary review by the office director.

4. Regulatory Action

The goals of the regulatory action and FDA policy on communicating regulatory actions are described in Section III.B., Operational Principles. The FDA processes and reviews marketing applications with the goal of completing the review and issuing an official written regulatory action by the PDUFA goal date. It is important that any communication with the applicant before the official regulatory action makes it clear that a decision has not yet been made, and there should be no speculation on the nature of the final action.

Action Phase			
Timeline	**Activity**	**Reference[10]**	**Responsibility**
By End of Month 8 (5)	**Wrap-Up Meeting**		Review Team Consultants Signatory Authority
	Integrate outcomes of reviews, consults, inspection reports, and AC input		
	Consider need for center level input (e.g., Regulatory Briefing)		
	Internal Briefings for Signatory Authority, as needed		
4 Weeks Before Approval Action	**Preapproval Safety Conference (for NMEs in CDER)**	CDER MAPP 6010.1, *NDAs: Preapproval Safety Conferences*	Review Team ODS
	Initiate Compliance Check Request (BLAs)		RPM
Begin 3 Weeks Before Division Sign-Off	**Labeling Discussions (for Approval and Approvable Actions)**		Review Team Consultants, in CDER: ODS DDMAC Study and Endpoints Labeling Team Consultants, in CBER: OBE APLB OCBQ
	Apply labeling review checklist	CBER SOPP 8412, *Review of Product Labeling*	
	Meeting/teleconference with applicant and/or secure e-mail exchange of proposed labeling		
	Finalize labeling based on data	FD&C Act, section 502 21 CFR Part 201	Review Team Signatory Authority
	Finalize dependent materials (PPI, MedGuide)		Review Team Consultants
	Negotiation of Postmarketing Commitments, if needed		
	Negotiation of Risk Management Program, if needed		

[10] The references listed in this table are considered important to this topic, but are not all inclusive.

Action Phase			
Timeline	**Activity**	**Reference**	**Responsibility**
By 6 (4-6) Weeks Before Action	**Compile Action Package**	CBER SOPP 8401, *Administrative Processing of Biologics License Application (BLA)*; SOPP 8405, *Complete Review and Issuance of Action Letters* CDER MAPP 6020.8, *Action Packages for NDAs and Efficacy Supplements*	RPM
	Draft Action Letter with Conditions of Approval (for Approval Actions)	Approval: 21 CFR 314.105 21 CFR 601.4(a)	
	Draft Action Letter with Comprehensive List of Deficiencies (for Actions Other than Approval)	NDA Approvable: 21 CFR 314.110 NDA Not Approvable: 21 CFR 314.120 BLA Denial of License: 21 CFR 601.4(b)	RPM
	Circulate and Review Action Package and Letter		Review Team Signatory Authority
	To primary reviewers (and consultants, as needed)		
	To secondary reviewers (when signatory authority is the Division Director) OR To Division Director (when signatory authority is the Office Director)		
By 3 (2-3)Weeks Before Action	To signatory authority, with revision as needed		
By PDUFA Goal Date	**Action**		Signatory Authority
	Archive signed letter		RPM
	Send official copy to applicant (by facsimile, secure e-mail, or postal service)		
	Verify and document applicant receipt		
	Distribute approval information (for approval action)	CBER SOPP 8106, *Submission of Product Approval Information for Dissemination to the Public* CDER MAPP 4520.1, *Communicating Drug Approval Information* CDER MAPP 4520.2, *Providing General Consumer Information on NMEs on CDER's Web Site*	

E. Post-Action Phase

During the post-action phase, the Agency and applicants should focus on learning from the successful aspects of the review process and identifying other aspects of the review process that could benefit from future improvement.

For actions other than approvals, it is optimal to direct activities toward improving outcomes for subsequent review cycles by creating a clear understanding on the part of both the FDA and the applicant of deficiencies and the expected responses. This can be accomplished by scheduling a post-action teleconference or meeting to discuss the deficiencies. A presubmission meeting between the review division and the applicant can also be scheduled to discuss the applicant's planned response to the action letter and help avoid incomplete responses. Applicants can help optimize the outcome of subsequent review cycles by responding clearly and completely to issues identified in the action letter.

Post-Action Phase			
Timeline	**Activity**	**Reference**[11]	**Responsibility**
After PDUFA Goal Date	**Meet or Discuss with Applicant**		Review Team Signatory Authority Consultants
	Lessons learned		
	Clarify deficiencies and expected responses (actions other than approvals)	21 CFR 314.102(d) CBER SOPP 8405.1, *Procedures for the Classification of Resubmissions of an Application for a Product Covered by PDUFA* CDER MAPP 6020.4, *Classifying Resubmissions of Original NDAs in Response to Action Letters* FDA guidance, *Formal Dispute Resolution: Appeals Above the Division Level*	
	Dispute Resolution (when necessary, can occur throughout review process)	21 CFR 314.103 FDA guidance, *Formal Dispute Resolution: Appeals Above the Division Level*	

[11] The references listed in this table are considered important to this topic, but are not all inclusive.

V. IMPLEMENTATION AND EVALUATION

The GRMPs are based in part on the Agency's current best practices. Implementation activity, including reviewer training and performance evaluation, began in October 2003 and will continue with additional training on this guidance.

In accordance with commitments under the reauthorization of PDUFA, an independent expert consultant under contract with the FDA will carry out the performance evaluation. The consultant, with input from the FDA and the public, will be responsible for developing an evaluation study design that identifies key questions, data requirements, data collection plans, and planned analyses in accordance with the PDUFA goals.

APPENDIX A: GLOSSARY OF ACRONYMS

AC	Advisory Committee
APLB	Advertising and Promotional Labeling Branch (CBER)
BiMo	Bioresearch Monitoring Branch (CBER)
BLA	Biologics License Application
BLS	Biologics License Supplement
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMA	Continuous Marketing Application
CMC	Chemistry, Manufacturing, and Controls
CPMS	Chief, Project Management Staff
DDMAC	Division of Drug Marketing, Advertising, and Communications (CDER)
DE	Division of Epidemiology (CBER)
DMPQ	Division of Manufacturing and Product Quality
DR	Discipline Review
DSI	Division of Scientific Investigations (CDER)
EA	Environmental Assessment
EER	Establishment Evaluation Request
EOP2	End-of-Phase 2
FDA	U.S. Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GRMP	Good Review Management Principles and Practices
HRQL	Health-Related Quality of Life
IND	Investigational New Drug Application
IR	Information Request
MAPP	Manual of Policies and Procedures (CDER)
NDA	New Drug Application
NME	New Molecular Entity
OBE	Office of Biostatistics and Epidemiology (CBER)
OBP	Office of Biotechnology Products (CDER)
OCBQ	Office of Compliance and Biologics Quality (CBER)
OCPB	Office of Clinical Pharmacology and Biopharmaceutics (CDER)
ODS	Office of Drug Safety (CDER)
ONDC	Office of New Drug Chemistry (CDER)
PDUFA	Prescription Drug User Fee Act
PI	Package Insert
PPI	Patient Package Insert
PREA	Pediatric Research Equity Act
PRO	Patient-Reported Outcome
P/T	Pharmacology/Toxicology
RMP	Risk Management Plan
RPM	Regulatory Project Manager
RTF	Refusal to File
SOPP	Standard Operating Policies and Procedures (CBER)

SPA	Special Protocol Assessment
U.S.C.	U.S. Code

APPENDIX B: REFERENCED GUIDANCES, MAPPS, AND SOPPS

The guidances for industry, MAPPs, and SOPPs for FDA staff referenced in this document are listed below. This is not a comprehensive list of available information from CDER and CBER. Consult the following CDER and CBER Web pages for additional information:

http://www.fda.gov/cder/guidance/index.htm
http://www.fda.gov/cber/guidelines.htm

Presubmission

FDA Guidances

- *Formal Meetings with Sponsors and Applicants for PDUFA Products*
- *Special Protocol Assessment*
- *Continuous Marketing Application: Pilot 1*
- *Continuous Marketing Application: Pilot 2*

Filing Determination and Review Planning Phase

FDA Guidance

- *Refusal to File*

CBER SOPPs

- 8401 *Administrative Processing of Biologics Licensing Application (BLA)*
- 8401.1 *Issuance and Review of Responses to Information Requests and Discipline Review Letters to Pending Applications*
- 8401.2 *Administrative Processing of Biologics License Application Supplement (BLSs) [Except Blood, Blood Components, and Source Plasma]*
- 8401.3 *Filing Action: Communication Options*
- 8110 *Submission of Regulatory Documents to CBER*
- 8406 *Verification of User Fee Data Sheet and Payment*
- 8405 *Complete Review and Issuance of Action Letters*
- 8404 *Refusal to File Procedures for Biologic Licensing Applications*
- 8404.1 *Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest)*

CDER MAPPs

- 7600.7 *Processing an Electronic New Drug Application*
- 6050.1 *Refusal to Accept Application for Filing from Applicants in Arrears*
- 6020.3 *Priority Review Policy*
- 6010.5 *NDAs: Filing Review Issues*

- 4200.3 *Consulting the Controlled Substance Staff on Abuse Liability, Drug Dependence, Risk Management, and Drug Scheduling*

Review Phase

FDA Guidance

- *Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act*

CBER SOPPs

- 8006 *Resolution of Differences in Scientific Judgment in the Review Process*
- 8401.1 *Issuance and Review of Responses to Information Requests and Discipline Review Letters to Pending Applications*

CDER MAPP

- 4151.1 *Resolution of Disputes: Roles of Reviewers, Supervisors, and Management — Documenting Views and Findings and Resolving Differences*

Advisory Committee Meeting Phase

FDA Guidance

- *Implementation of Section 120 of the Food and Drug Administration Modernization Act of 1997 — Advisory Committees*

CBER Draft Guidance

- *Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of Biologic Products and Convened by the Center for Biologics Evaluation and Research Beginning on June 1, 2001*

CDER Draft Guidance

- *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*

Action Phase

CBER SOPPs

- 8405 *Complete Review and Issuance of Action Letters*
- 8106 *Submission of Product Approval Information for Dissemination to the Public*
- 8412 *Review of Product Labeling*

CDER MAPPs

- 6010.1 *NDAs: Preapproval Safety Conferences*
- 6020.8 *Action Packages for NDAs and Efficacy Supplements*
- 4520.1 *Communicating Drug Approval Information*
- 4520.2 *Providing General Consumer Information on NMEs on CDER's Web Site*

Post-Action Phase

FDA Guidance

- *Formal Dispute Resolution: Appeals Above the Division Level*

CBER SOPP

- 8405.1 *Procedures for the Classification of Resubmissions of an Application for a Product Covered by the Prescription Drug User Fee Act (PDUFA III)*

CDER MAPP

- 6020.4 *Classifying Resubmissions of Original NDAs in Response to Action Letters*