Guidance for Review Staff and Industry

Good Review Management Principles for PDUFA Products

Draft — Not for Implementation

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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)

July 2003
Procedural

Guidance for Review Staff and Industry

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Center for Biologics Evaluation and Research (CBER)

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 is intended to provide 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 (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).[2] 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 efficient and consistent management of application reviews. A key aspect of GRMPs is their emphasis on effective communication between the Agency and applicants throughout the drug and biologic product development and review processes.

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.

[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 ad Drug Administration.

[2] The Commissioner has announced a consolidation of the CDER and CBER review functions for therapeutic products. Once the consolidation has been completed, we will review those guidances affected by the transfer of functions for possible revision.

I. BACKGROUND

In conjunction with the June 2002 reauthorization of PDUFA, the FDA agreed to meet specific performance goals (PDUFA goals). These PDUFA goals are described in *PDUFA Reauthorization Performance Goals and Procedures*, an enclosure to a letter dated June 4, 2002, from the Secretary of Health and Human Services to Congress.[3] Under the PDUFA goals, CDER and CBER agreed to create this joint guidance for review staff and industry on good review management principles that apply to the first-cycle review of NDAs, BLAs, and efficacy supplements. These GRMPs clarify the roles and responsibilities of CDER and CBER review staff in managing the review process. The GRMPs also identify ways in which NDA and BLA applicants may help to enhance the effectiveness and efficiency of the review process. While the emphasis of GRMPs is on first-cycle reviews of PDUFA products, the principles generally pertain to all CDER and CBER reviews. This guidance is expected to lead to greater consistency and efficiency of the review process within individual review divisions, across review divisions, and between CDER and CBER.

The foundations of the GRMPs are the Agency's current best practices and goals for future review management improvements. These have evolved from a decade of review process innovations that began with the implementation of PDUFA in 1992. Under the PDUFA program, CDER and CBER have continuously improved review management for marketing applications to meet tightening review goals while maintaining FDA's traditionally high standards for review and approval of new drugs and biologics. Therefore, many GRMPs are currently in practice. Management and review capability enhancements have focused primarily on improving the planning and coordination of review team activities and on engaging applicants in productive communications during drug development (the Investigational New Drug Application (IND) phase) and marketing application review.

For review staff and managers to adhere consistently to these review principles, the FDA is dependent on the availability of adequate resources (e.g., staffing, and information technology). The FDA also needs full cooperation and participation by applicants for effective implementation of the GRMPs. This guidance provides information about the best practices demonstrated by applicants during PDUFA that serve to facilitate efficient application review (the *Applicant Focus* sections). The GRMPs also outline FDA's procedures (the *FDA Focus* sections) and objectives for communicating with applicants (the *Communication between FDA and Applicant* sections) 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 are strongly encouraged to be fully knowledgeable of the GRMPs as they interact with the FDA.

[3] 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 Committee on Energy and Commerce, House of Representatives. The PDUFA goals can be found at http://www.fda.gov/oc.pdufa/PDUFAIIIGoals.html.

Additional Agency documents are available and should be consulted 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. These documents provide more detail on specific CDER and CBER processes, expectations for review staff performance, and recommendations for industry.

III. OVERALL PRINCIPLES

This section highlights the universal themes of the GRMPs that underlie each stage of the review process for the FDA, applicants, and the communication between them.

A. FDA Focus

Optimally, a well-managed review process for an NDA or BLA begins with interactions between the applicant and the Agency's therapeutic review division having primary responsibility for regulatory actions on the product (review division) during the drug development (IND) phase and continues through the final action on the marketing application.

During the first review cycle, a well-managed review process allows sufficient time for careful regulatory decision making and, if needed, time to work with the applicant to attempt to resolve readily correctable deficiencies in the application. For applications that otherwise meet the standards for approval, the process 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, thereby eliminating additional unnecessary and inefficient review cycles. Such a well-managed review process fulfills the Agency's public health mission to make safe and effective drug and biologic products available to the public in a manner that is timely and makes most efficient use of the Agency's limited resources.

For an application found to have significant deficiencies in the required demonstration of safety, effectiveness, or product quality, thus precluding approval, a well-managed first-cycle review process provides the applicant with timely notification of such deficiencies. Often, timely notification of correctable deficiencies allows the applicant to begin the additional studies or corrective actions needed to address the deficiencies, reduce the number of review cycles prior to approval, and shorten the overall time to approval. In other cases, timely notification of the applicant regarding significant and potentially uncorrectable deficiencies in the marketing application may help inform applicant choices regarding whether to continue pursuit of product approval.

The GRMPs emphasize the importance of (1) a strong interdependence among the primary FDA review team, (2) frequent interactions between the primary review team and supervisory reviewers, and (3) the critical role of effective project management in the successful completion of the first-cycle review. This paradigm is based on thorough planning early in the review process and clear communication to move efficiently through the planned activities. A well-managed review process helps FDA staff to accommodate unanticipated events or findings that

may develop during the course of the review, using fewer resources in resolution of the issues and preventing the need for crisis management – which is inefficient and often error-prone – to meet PDUFA goals.

B. Applicant Focus

For NDA and BLA applicants, the GRMPs are intended to provide clarity and transparency into Agency processes and the expectation of consistently efficient management of the first-cycle review. It is important for applicants to understand that adhering to the GRMPs will not modify the first-cycle outcomes for applications with substantive scientific or regulatory deficiencies.

The applicant plays an essential role in optimizing review outcomes for an application. Central to PDUFA is the agreement that a complete application will receive a comprehensive and complete review within a specified time frame. Thus, a fundamental principle supporting an efficient first-cycle review process is for the applicant to provide the FDA with a complete application upon initial submission. A complete application should contain all required and expected information to support approval of the requested claims, labeling, and dosage forms. A complete application also means that the application is submitted in a readable, well-organized format. Submission of a complete application should essentially eliminate the need for unsolicited or unexpected amendments to the application during the review process. An application is not in keeping with this fundamental PDUFA principle if it meets the regulatory criteria for filing but lacks important information needed to complete the review and regulatory decision-making process, is disorganized, or does not conform to the recommended format for electronic submissions. Such an application contributes to inefficiency in the review process and may result in unnecessary and time-consuming, multiple-cycle reviews prior to approval.

The applicant is strongly encouraged to manage the drug development timeline in a manner that leads to submission of a complete application, with the exception of safety updates, for FDA review. Requests for the FDA to accept for review *planned* amendments that complete an application during the first-cycle review process should be minimized and should be discussed and agreed to in advance with the FDA (e.g., at the pre-NDA/BLA meeting). Such requests and agreements should generally be limited to situations when the FDA agrees that there is a valid public health urgency to expedite the availability of an important new product.

The FDA retains the authority to decide whether to review application amendments, solicited or unsolicited, submitted during the first review cycle. The FDA may decide to defer review of amendments to a subsequent review cycle for several reasons, including, but not limited to, significant application deficiencies that otherwise preclude approval of the application that are not addressed by the amendment, competing workload priorities, and limitations in resource availability. It has been FDA's experience that submission of a complete application leads to the most efficient review process and shortest approval time. In some cases, submitting a complete application may require a decision by the applicant to delay initial submission beyond a corporate target date. Such a delay in submission might ultimately result in an earlier approval date since a complete application might be approved at the end of the first review cycle and not require subsequent review cycles.

C. Communication between FDA and Applicant

The FDA recognizes the critical importance of effective and timely communication between the applicant and the review division throughout the drug development and review processes. Such communications allow the FDA to provide valuable guidance and advice regarding the applicant's drug development program and, during the review of a marketing application, to identify deficiencies that may require the applicant to submit additional analyses or data. The Agency believes that open communication of advice, guidance, and notification of deficiencies should occur at pivotal points during the drug development and review process (e.g., the end-of-phase 2 meeting, the pre-NDA/BLA meeting, and during the filing review) and on an as-needed basis. To ensure consistent communication, it is recommended that the FDA and applicants follow the general guidelines discussed in the following sections as they pertain to each phase of the first-cycle review process.

IV. PROCESS PRINCIPLES

This section builds on the overall principles of good review management and provides additional principles related to each phase of the first-cycle review: presubmission, application receipt, filing, review planning, review, advisory committee meetings, wrap-up and labeling, action, and preparation for any additional cycles of review.

A. Presubmission

1. FDA Focus

a. FDA Input During Development

The FDA review staff should understand the critical importance of effective and timely communication between the review division and the applicant throughout the IND process. The FDA review staff are uniquely qualified to provide valuable scientific and regulatory advice to the applicant during the drug development phase. This advice can result in more efficient and robust drug development programs, furthering FDA's public health mission to make safe and effective drugs and biologics available to the American public in a timely manner. Effective communication between the FDA and the applicant during the IND phase can also lead to identification of potential filing and review issues that can then be addressed by the applicant before the application is submitted for review.

To provide the foundation for productive interactions with the applicant, FDA review staff should monitor closely each assigned IND to maintain a good working knowledge of the product characteristics, the proposed development strategy, and the applicant's proposed indication(s) for approval.

b. Milestone Meetings

Review divisions should also explicitly encourage the applicant to take advantage of end-of-phase 2 (EOP2) and pre-NDA/BLA meetings and use the program for special protocol assessment (SPA) when appropriate. The FDA guidance *Special Protocol Assessment* explains that the SPA process should particularly be encouraged when a study's design or endpoints are unique or when a study involves an indication or disease for which the FDA has not previously approved a drug or biologic product. Meetings during the IND phase and SPA submissions are invaluable opportunities for the review division and the applicant to review carefully and reach agreements about the drug development plan (EOP2 meeting and SPA) and the proposed content and format of the marketing application (pre-NDA/BLA meeting).

The pre-NDA/BLA meeting can be critical to creating a foundation for efficient review management. The meeting should focus on the format of a proposed application and on creating a shared understanding between the FDA and the applicant of an acceptable content to support initial planning for efficient review management. The pre-NDA/BLA meeting generally should be scheduled 6 to 12 months prior to the anticipated date for application submission. This timing of the pre-NDA/BLA meeting ensures that the applicant has accumulated sufficient information regarding the product development program to hold a productive discussion and that adequate time is available for the applicant to incorporate any advice from the review division before submitting the application for review. In preparing for the pre-NDA/BLA meeting, the review division should attempt to address any specific questions raised by the applicant in the meeting background package. The review division should also provide feedback regarding any major deficiencies or omissions identified in the proposed application based on the summary information provided by the applicant in the meeting background package.

c. Review Initiatives

New initiatives under the PDUFA goals, including enhanced preapproval attention to risk management by the FDA and the applicant, and two pilot programs to explore the continuous marketing application (CMA) concept, are underway and are the subject of separate guidances. The success of these initiatives will be highly dependent on effective presubmission interactions between review divisions and applicants and effective communication during the review process.

2. Applicant Focus

The Agency emphasizes that the quality and completeness of NDAs, BLAs, and efficacy supplements at the time of submission is critical to achieving an efficient first-cycle

review process for PDUFA applications. Numerous FDA guidances are available to provide information regarding the format and content of high-quality submissions, including electronic formats. This guidance is most relevant to submissions developed with appropriate presubmission activity. A primary mechanism for ensuring high-quality, complete applications is effective presubmission interactions between the FDA and the applicant.

a. Milestone Meetings

We recommend that the applicant take advantage of presubmission interactions with the review division. Such interactions can be critical to ensuring that an NDA or BLA application is complete at the time of submission. The FDA guidance document *Formal Meetings with Sponsors and Applicants for PDUFA Products* is available to provide additional information on meeting procedures with regard to EOP2 and pre-NDA/BLA meetings. The FDA guidance describing special protocol assessments is also available.

As noted in the previous section, emphasis should be placed on adequate preparation for EOP2 and pre-NDA/BLA interactions. Efficient management of FDA's review process is initially based on the presubmission information provided by the applicant, particularly during pre-NDA/BLA meetings. To facilitate good review management, it is recommended that the applicant present a clear, concise background package to inform the exchange of information. The applicant should submit the package in a timely fashion to allow for thorough review by the FDA. The pre-NDA/BLA meeting package should contain a comprehensive summary of all relevant data generated during the development program, identify pivotal trials and primary endpoints, and discuss all critical and potentially critical issues (i.e., any issues that may affect FDA's ability to review the application and/or approve the product).

The applicant is strongly encouraged to describe both the strengths and weaknesses of a proposed application. Weaknesses identified by the applicant and the Agency should be discussed during the pre-NDA/BLA meeting so that the FDA can advise the applicant how to address those weaknesses before application submission. If not identified and addressed prior to submission, some deficiencies might lead to a decision by the FDA to refuse to file the application or to unnecessary and time consuming multiple-cycle reviews. Effective presubmission communication between the applicant and the review division can often prevent such undesirable outcomes.

b. Risk Management Plan

Under the PDUFA goals, an applicant may choose to submit a risk management plan (RMP) as part of the pre-NDA/BLA meeting background package or as part of the marketing application. Applicants are encouraged to take advantage of this

new mechanism to initiate early discussions with the review division and drug safety reviewers regarding plans to minimize and manage the risks of new drug and biologic products after approval, thereby maximizing the benefit/risk ratio. The FDA is developing procedures and guidance to address the PDUFA goals related to risk management, and applicants should familiarize themselves with these documents as they become publicly available.

Between the pre-NDA/BLA meeting and the time of submission, the applicant is encouraged to inform the review division if plans for the content or format of the application change significantly. In addition, the applicant should provide the review division with updates regarding the timing of the planned submission. Such information is useful to the review division in assigning projects and effectively managing limited resources.

3. Communication between FDA and Applicant

If a CBER or CDER review division becomes aware of potentially serious deficiencies in a marketing application before it is submitted for review (e.g., at the pre-NDA/BLA meeting), the division should inform the applicant of the deficiencies in a clear and timely manner. The applicant should be advised that, if uncorrected, the deficiencies could result in a decision to refuse to file the marketing application, or if the application is fileable, may impair the division's ability to review and/or approve the application on the first cycle or on subsequent cycles.

During presubmission communication between the FDA and the applicant, the FDA should develop recommendations for the format and content of submissions based on the information provided by the applicant. These recommendations should be based on a clear rationale and documented appropriately. Their value to the applicant and ultimate impact on the first-cycle review are highly dependent on the applicant's interpretation and full disclosure to the FDA of the details and preliminary results of the applicant's development program. The FDA's recommendations are best followed in their entirety; partial adherence to FDA's recommendations may significantly undermine the potential benefit of presubmission communications.

B. Application Receipt Process (Prefiling)

1. FDA Focus

The application receipt process provides an important foundation for the subsequent application review, and the quality of its execution is key to the Agency's ability to complete an efficient review. During the application receipt process, the application content is assessed, and the application is assigned to the appropriate review team members. Review team roles and responsibilities are clarified during this process.

Upon receipt in the Central Document Room in CDER or the application review division in CBER, an NDA or BLA is assigned an application number. In some cases, a number can be assigned prior to submission if requested by the applicant. The submission is date-stamped on the day of receipt, and payment of any applicable user fee is due on that day. The application is then transferred to the review division document room (DDR) in CDER. Agency manuals delineate for FDA review staff the current policy and procedures for application processing.[4]

Once received in the review division, an application should be assigned to a regulatory project manager (RPM) as soon as possible. The RPM should determine whether the applicant has complied with all required user fee payments and, if so, the review clock starts the day of application receipt. An acknowledgement letter is generated to inform the applicant of the date of receipt and the assigned NDA or BLA number. If the applicant is in user fee arrears, the applicant should be notified. The review clock does not begin until the required fee is paid. Agency manuals delineate for FDA review staff the current policy and procedures regarding user fee payment.[5]

With the commencement of the review clock, multiple, simultaneous activities should begin promptly to maximize the time allotted for each activity.

a. Regulatory Project Manager Review

To ascertain the completeness of the application on its face, the RPM should conduct an administrative review, including ensuring that financial disclosure information has been provided by the applicant. Deficiencies identified during this review should be communicated to the applicant promptly to enable immediate correction if possible. Administrative issues can be sufficiently substantive to warrant a refuse-to-file action (e.g., when a significant section of the application is missing). This review is the NDA Regulatory Review in CDER and is finalized after the filing meeting with the attachment of filing meeting minutes.

b. Assignment of Review Team, Consultants, and Inspection Requests

i. Review Team

The primary review team should be assigned as soon as possible after receipt of a new application. Review team assignments are usually based on the reviewers

[4] CBER SOPPs 8401 *Administrative Processing of Biologics Licensing Application (BLA),* 8401.2 *Administrative Processing of Biologics License Application Supplement (BLSs),* and 8110 *Submission of Regulatory Documents to CBER,* and CDER MAPP 7600.7 *Processing an Electronic New Drug Application*.

[5] CBER SOPP 8406 *Verification of User Fee Data Sheet and Payment,* and CDER MAPP 6050.1 *Refusal to Accept Application for Filing from Applicants in Arrears*.

assigned to the IND for the product. However, in certain cases, new or additional reviewers may be assigned as dictated by workload, competing priorities, application complexity, or review discipline staffing.

In addition to the RPM, the review team comprises reviewers from the various disciplines that reflect the appropriate scientific content areas. Membership of the core team is dictated by the specific content of each application. The disciplines represented in core team membership typically include:

- Medical/clinical
- Pharmacology/toxicology (P/T)
- Chemistry, Manufacturing and Controls (CMC)
- Biometrics/statistical
- Clinical pharmacology and biopharmaceutics
- Clinical microbiology
- Bioresearch monitoring

ii. Consultants

Additionally, based on the content of each application, consults may be issued for additional review of any of the above disciplines. Other content areas that may require consultant input include:

- Environmental assessment (EA)
- Abuse potential (consulted to CDER's Controlled Substances Staff)
- Tradename, package insert (PI), patient package insert (PPI), MedGuide and other consumer information, and carton/container (consulted to the Division of Drug Marketing, Advertising and Communications (DDMAC) in CDER or the Advertising and Promotional Labeling Staff (APLS) in CBER

Procedures for issuing consults on risk management plans (RMPs) to the appropriate postmarketing drug safety staff in CDER and CBER are being developed as outlined in the PDUFA goals. Postmarketing drug safety staff from CDER (Office of Drug Safety, ODS) and CBER (Office of Biostatistics and Epidemiology, OBE) are expected to work in collaboration with the review division staff in reviewing RMPs and providing expert advice to applicants and the review divisions. The review division retains the ultimate responsibility for application approval decisions and for the type and scope of risk management tools to employ after approval.

The consult process may also involve seeking expertise from other review divisions, FDA centers, and in some cases, outside experts (e.g., special government employees from the professional community). Reviewers should identify the need for consultant input as early as possible in the review process so

the appropriate consultants can be identified promptly and, if necessary, screened for any potential conflicts of interest.

iii. Requests for Inspection

Requests for inspections of manufacturing facilities and research sites should be made early in the review cycle and, optimally, prior to the filing date. In CDER, manufacturing facilities are inspected based on an establishment evaluation request (EER) to the Division of Manufacturing and Product Quality (DMPQ). In CBER, the CMC facilities reviewer arranges with the Office of Compliance and Biologics Quality (OCBQ) for all necessary facilities inspections. Inspection of clinical, nonclinical, or biopharmaceutics research sites is conducted through consultation of the Division of Scientific Investigations (DSI) in CDER or the BioResearch Monitoring (BiMo) staff in CBER.

c. Designation of Review Priority

A decision regarding the review priority (i.e., *priority* or *standard*) for NDAs, BLAs, and efficacy supplements should be made as soon as possible following receipt of the application. The review division director, in consultation with the office director as appropriate, makes the review priority decision. The criteria for this decision are based on the therapeutic advantage potentially offered by a new drug or biologic product relative to marketed products. A decision regarding review priority should be made for every application submitted, regardless of whether the applicant has explicitly requested priority status. The decision should be based on the merits of the product and the application data and should not be contingent on internal FDA considerations such as competing workload or currently available resources in the review division or on whether the subject product was designated fast track during the development phase. Agency manuals delineate for FDA review staff the current policy and procedures for assigning review priority.[6]

In some instances, a preliminary designation of review priority may be made prior to submission. However, an official decision about review priority can be made only after the application is received for review. In some cases, a presubmission assessment of application review priority may be changed once the application is actually submitted for review. This can occur for several reasons including, but not limited to, failure of the clinical studies to demonstrate the expected advantage over existing therapy, or approval of other new therapies for the condition or disease prior to submission of the subject application. Once the decision is made to assign a priority review, that designation should not be changed during the first review cycle, regardless of findings during the review.

[6] CBER SOPP 8405 *Complete Review and Issuance of Action Letter*, and CDER MAPP 6020.3 *Priority Review Policy*.

The applicant should be informed of the review priority designation promptly following the decision, and the designation should be confirmed in writing not later than the filing date. The shortened review timeline for priority reviews under PDUFA requires even greater focus on GRMPs by the review division and the applicant to complete the review and decision-making process in a timely manner.

d. Determining Signatory Authority

A decision regarding the signatory authority for an application should be made as soon as possible following receipt of the application. Generally, the signatory authority for actions on an application for new molecular entities (NMEs) is delegated to the office level above the review division. This level of signatory authority for NMEs allows in-depth review by the Agency's more senior managers, often warranted by the novel issues presented in these submissions. This level of expertise comprises a significant knowledge base and promotes consistency in decision making with respect to NMEs. For a non-NME submission, the signatory authority for the action is generally delegated to the review division director. However, in certain situations, the signatory authority may be retained at the office level above the division (e.g., first-in-class switch from prescription to over-the-counter marketing).

e. Scheduling Filing Meetings

A filing meeting for the review team should be scheduled for all NDAs, BLAs, and efficacy supplements to allow the review team to determine whether the application is sufficiently complete to warrant filing for further review. This filing meeting should be scheduled to optimize the review process timelines. For example, sufficient time should be allotted before the meeting for the review team to conduct its filing review. However, the scheduling must also take into account the need for subsequent review time, particularly for a priority application. A priority review may benefit from a shortened filing review period to allow for more review time in a compressed review cycle.

The filing meeting for a standard application should be scheduled in time to finalize and communicate the filing decision by the 60-day filing date, often placing the filing meeting approximately 45 days after receipt of the application. This timing should allow the applicant sufficient time to resolve readily correctable filing issues identified by the review team that, if not addressed, might warrant a refuse-to-file decision.

2. Applicant Focus

To help ensure that the application receipt process proceeds smoothly, the applicant should prepare and submit an application in accordance with presubmission recommendations from the FDA, providing a complete application as previously discussed.

3. Communication between FDA and Applicant

Throughout the application receipt process and continuing throughout the entire review process, the RPM is the primary review team point of contact for the applicant. Channeling communication through this individual allows for well-coordinated responses, which promote efficient use of FDA resources and ensure that the entire review team is kept informed of issues and communications as they occur. The applicant is encouraged to direct inquiries regarding the status of the application to the assigned RPM rather than to individual members of the review team. Though inquiries from the applicant to the FDA during the application receipt process are generally unnecessary, the applicant is likely to receive communications from the FDA and should respond accordingly. When it is appropriate for the applicant to interact directly with a member or members of the review team, the RPM should arrange and, generally, participate in these interactions to capture action items and share information with other members of the review team.

During the application receipt process, the FDA will routinely convey readily correctable issues to the applicant in a timely manner as they are identified with the expectation that they should be addressed quickly. This will enable early communication of concerns and requests for additional information and provide the applicant with the opportunity to correct application deficiencies within a reasonable timeframe (e.g., before the filing meeting). We encourage communication with the applicant throughout the review process through secure e-mail, with electronic copies sent to the relevant members of the review team, the applicant staff, and the project manager.

C. Filing

1. FDA Focus

a. Preparation for Filing Meeting

The filing process for an NDA or BLA should bring the initial assessment of the application's content to a close and allow for a final determination about the filing of the application. The filing determination is based on the completeness of the submission for review and whether the application on its face contains the required information and format (21 CFR 314.101(a)(3)(d) and (e) and 21 CFR 601.2(a)). The filing decision is made by the review division director based on

input from the RPM, reviewers, and team leaders from each discipline, as well as relevant consultants and the office director, as appropriate. All refuse-to-file decisions should include consultations with the office director.

In preparing to make a filing recommendation to the review division director, reviewers from each discipline should conduct a preliminary review of materials submitted upon initial receipt of the application and any material subsequently requested and submitted prior to filing. The available information and the application format (e.g., pagination, table of contents) should be compared to the information and formatting required for filing under the appropriate regulations.

Reviewers should be aware that the reasons for refusing to file an application are limited to those specified in the regulations (21 CFR 314.101(d) and (e)) and that many issues or concerns identified during the filing review do not warrant a decision to refuse to file the application. Agency manuals delineate for FDA review staff the current policy and procedures regarding refusal to file and application.[7] The review issues identified during the filing review are nonetheless important as they may provide an early signal to the reviewer of an area that requires particular attention during the subsequent review, or an area that requires the applicant to conduct additional analyses or provide additional data. Potentially substantive deficiencies that do not merit a refuse-to-file action should be noted and captured as filing review issues and communicated to the applicant as required under the PDUFA goals (see below). Reviewers should discuss the findings from their filing review with their team leader or supervisor prior to the filing meeting and should be prepared to present to the review team their discipline's position on the application's fitness for filing. In many instances, it may be useful for each discipline to document the filing process decisions in a brief filing review.

b. Filing Meetings

As previously stated, a filing meeting should be held in time to meet the 60-day filing determination and to support efficient subsequent review timelines. The filing meeting is often held approximately 45 days after receipt of a standard review application, but in some cases, the review team should consider compressing the receipt/filing process.

At the filing meeting, reviewers from each discipline should discuss the relevant content of the application and present an overview including:

- A summary of the submitted material

[7] CBER SOPPs 8404 *Refusal to File Procedures for Biologic License Applications* and 8404.1 *Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest),* and CDER MAPP 6010.5 *NDAs: Filing Review Issues.*

- Special development or approval issues, if any (e.g., use of Subpart H or E)
- A description of any required materials that were omitted from the submission
- Specific deficiencies that may warrant a refuse-to-file decision
- Other substantive deficiencies that appear to have been inadequately addressed by the applicant and potentially have significant impact on the ability to complete the review or approve the application
- Issues that potentially merit advisory committee input

Although most inspection or consult requests assignments are made prior to the filing meeting, consideration should be given at the filing meeting whether additional requests are warranted.

c. Communication of Deficiencies

Although communication with the applicant regarding application content is recommended prior to the filing meeting (e.g., to correct minor application deficiencies), additional issues may nevertheless be identified during the filing meeting. If these issues are substantive and prohibit further review of the application, a decision should be made regarding whether the deficiency is readily correctable by the applicant and whether the review division has time to review the adequacy of corrections in advance of the 60-day filing date. If the deficiencies appear to be readily correctable, the division should promptly notify the applicant of the deficiencies and establish a date by which the applicant must satisfactorily respond to avoid a refuse-to-file decision. If the reviewers believe that the deficiencies are not readily correctable by the applicant, or if the applicant fails to respond satisfactorily to notification of refuse-to-file issues, the specific refuse-to-file deficiencies should be conveyed to the applicant in a letter signed by the review division director (see next section).

Requests for additional information from the applicant and filing review issues raised during the filing meeting should be communicated to the applicant. Specifically, filing review issues should be conveyed to the applicant by letter, telephone conference, facsimile, secure e-mail, or other expedient means within 14 calendar days after the 60-day filing date as specified in the PDUFA goals. Agency manuals delineate for FDA review staff the current policy and procedures regarding the filing review issues requirement of the PDUFA goals.[8]

d. Refuse to File

Applications that are substantially deficient on their face do not merit further expenditure of FDA review resources. In this instance, a refuse-to-file letter

[8] CBER SOPPs 8404 *Refusal to File Procedures for Biologic License Applications* and 8404.1 *Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest),* and CDER MAPP 6010.5 *NDAs: Filing Review Issues.*

should be issued by the review division director as required under 21 CFR 314.101 and 601.2(a). Complete information regarding the specific deficiencies in the application that warrant the refuse-to-file decision and an explanation of how the application can be corrected should be conveyed to the applicant in the refuse-to-file letter. Additional information is available in the CDER guidance *Refusal to File,* and Agency manuals delineate for FDA review staff the current policy and procedures regarding refusal to file an application (see footnote 7).

2. Applicant Focus

Various types of application deficiencies may be identified during the filing process, and the applicant should be aware of the available responses to each and the potential effect of those responses on the FDA review process. Specific information requests from the FDA should be addressed expediently to facilitate the review. The applicant should be aware that amendments containing responses to filing review issues identified by the FDA and communicated according to the PDUFA goals may or may not be reviewed by the FDA during the first review cycle. The applicant can address refuse-to-file issues in a variety of ways (21 CFR 314.101 and 601.2(a)), including a request for an informal conference with the review division and filing over protest.

3. Communication between FDA and Applicant

The purpose of the filing process is for the FDA to identify application deficiencies quickly, determine the potential impact of these deficiencies on the Agency's ability to complete its review, and convey the outcome of this process to the applicant. It is essential that the FDA clearly communicate to the applicant the rationale used to arrive at these conclusions and their projected implications.

Officials at the FDA should not request or suggest to an applicant that the applicant withdraw a pending marketing application except in the most unusual circumstances (e.g., the marketing application was submitted to the wrong FDA center). If, during the filing review of a submitted marketing application, the Agency identifies serious deficiencies that may warrant a refuse-to-file action, the applicant should be informed of these deficiencies in a timely manner, generally no later than day 45 of the filing review. The Agency should advise the applicant that the deficiencies, if uncorrected, could result in a refuse-to-file decision and offer the applicant a reasonable opportunity to correct the deficiencies, if possible. Communication to the applicant that failure to correct a deficiency in the application may result in a refuse-to-file decision should only occur with concurrence from the review division director. Informal communication methods can be used (e.g., telephone call, facsimile) for timely communication of such deficiencies to the applicant. However, a record of all such communication must be included in the FDA's application file for the record.

D. Review Planning

1. FDA Focus

Planning for the entire review process should occur early in the review cycle to organize the associated review tasks, minimize review overlap among review disciplines, and build an understanding of team responsibilities. In most cases, the initial review planning activity should be combined with the filing meeting to take advantage of the convened team's collective input and to obtain consensus for the proposed review plan and specific timelines. The planning activity should involve development of and commitment to a specific and detailed timeline for completion of the various tasks necessary for the review. The timeline should be based on the PDUFA performance goals, workload and staffing in the review division and consultant divisions, and the complexities of the application. The timeline should incorporate planning for efficient completion of the following activities:

- Periodic team progress check-ins and updates to share information and adjust the review timeline based on interim events
- Team or sub-group interaction on particular scientific or regulatory issues
- Secondary review as appropriate
- Tertiary or higher level reviews and/or briefings as appropriate
- External consultant reviews and/or briefings as appropriate
- Advisory committee meeting as appropriate

The extent to which the team is able to plan accurately the amount of time needed for review, as well as to anticipate the type of interactions needed to resolve potential issues, is a primary determinant of an efficient review process. Resolve by the review team to meet the agreed upon milestones can minimize the need for end-of-cycle, resource-intensive problem solving activity and inefficient crisis management.

2. Applicant Focus

An applicant can best support the planning process by providing accurate projected timelines for response to information requests and submission of expected amendments (e.g., safety updates). Failure to meet projected timelines has a systemic impact on the FDA review process, reaching beyond the intended submission's discipline-specific material.

3. Communication between FDA and Applicant

In planning for the review process, the FDA is committed to managing efficiently the communication of concerns to the applicant and the timing of applicant responses. The applicant should not expect to be apprised of all interim timelines for internal FDA processes, but will be involved by the FDA in planning activities that clearly require applicant input, such as an advisory committee meeting.

E. Review

1. FDA Focus

a. Management of Review Process

For optimal review efficiency, primary and secondary reviewers (e.g., team leaders, branch chiefs, and first-line supervisors) should observe the timelines and interim goals for review progress established during the planning process. Primary and secondary reviewers are responsible for managing their individual workloads to accommodate the schedules of multiple projects. Any difficulties in this regard (e.g., if major unanticipated issues arise during the conduct of the review) should be discussed immediately between the primary and secondary reviewers and other review team members, particularly the RPM. Efforts should be made to resolve the issues without altering the review plans, if possible. In some cases, additional review personnel will be assigned to the application, or reviewer workloads will be adjusted. Any changes to the planned timeline for the review should be communicated among the entire review team and discussed with the signatory authority for the application.

b. Levels of Review

The planning process should anticipate the need for timely review, concurrence, and sign-off by multiple levels of reviewers. Communication between primary and secondary reviewers should be ongoing throughout the review process. The primary review team members should be allotted sufficient time to conduct individual reviews, while keeping their secondary reviewers informed of their progress and findings. Rapid communication of unanticipated findings is essential, particularly for issues that affect multiple review disciplines or that could delay arrival at a final action determination.

i. Primary and Secondary Review

Secondary reviewers should discuss review progress and findings with the appropriate division director, who in turn should keep the office director informed. This can occur during regular administrative rounds to review pending applications and at other times, as necessary. Requests should be made as early in the review process as possible when Center level input is needed.

The secondary reviewer finalizes the primary reviews from each discipline with secondary sign-off. Before a primary review is completed and entered into the division archive, the secondary reviewer should review the final draft and offer comments and suggestions to the primary reviewer regarding the technical completeness and accuracy of the review. The primary and secondary reviewers

should discuss any differences of opinion regarding the review findings, conclusions, and recommendations and attempt to resolve such differences before the primary review is completed.

It is generally expected that secondary reviewers will write their own brief review to summarize the discipline review and to note their findings, conclusions, and recommendations regarding the application. In some cases (e.g., no disagreement between the primary and secondary reviewers and a well-written executive summary by the primary reviewer), it may not be necessary for the secondary reviewer to write a separate review. Agency manuals delineate for FDA review staff the current policy and procedures for documenting reviews by secondary and tertiary levels of review.[9]

ii. Resolution of Difference in Scientific Judgement

If a primary reviewer and team leader are unable to reach agreement on one or more important finding, conclusion, or recommendation, the primary reviewer should proceed by entering his or her signed review into the division archive. The secondary reviewer should then sign the review to indicate that it has been accepted as a complete review. That signature should include a comment referring to the secondary review, in which any differences between the primary and secondary reviewers' opinions should be explained. Agency manuals delineate for FDA review staff the current process for scientific dispute resolution among reviewers at various levels of the organization.[10]

iii. Division Director and Office Director Review

The division director of the review division responsible for the original application or supplement is also generally expected to write a brief summary review of the application following a review of the various discipline primary and secondary reviews and a discussion with the review team. The division director's review should clearly explain the basis for the final action on the application. In addition, the division director's review should discuss elements of the reviews that presented particularly challenging scientific or regulatory issues, and those that prompted differences of opinion between the primary and secondary reviewers or among reviewers across scientific disciplines. When the office director over the division is the signatory authority for the application, the division director's review should recommend resolution for differences of opinion and for final action.

[9] CDER MAPP 6020.8 *Action Packages for NDAs and Efficacy Supplements*.

[10] CBER SOPP 8006 *Resolution of Differences in Scientific Judgment in the Review Process*, and CDER MAPP 4151.1 *Resolution of Disputes: Roles of Reviewers, Supervisors and Management–Documenting Views and Findings and Resolving Differences*.

If not documented adequately in primary or secondary reviews, the division director should discuss issues that will need to be attended to in the postapproval period (e.g., postmarketing commitments, risk management). The division director should also describe how input from an advisory committee, if held, was factored into the action. In some cases (e.g., efficacy supplements in which there are no disagreements among the primary and secondary reviewers and the division director), a division director's written review may not be necessary.

The final action on an application with office director signatory authority generally merits a written summary review by the office director. This summary review should discuss any disagreements noted at lower review levels and clearly document final decisions regarding these issues.

c. Interdisciplinary Communication

Complex review issues often require close coordination among review staff from multiple disciplines. Resolving these issues can be a resource-intensive activity that must be efficiently managed for timely completion of the review. Interaction among review disciplines is encouraged throughout the course of the review to identify and address multidisciplinary issues as early as possible. Joint reviews, most commonly written by medical and biometric and/or statistic reviewers, can facilitate coordination of the review process and save time.

Review team meetings should be held as scheduled during the planning process. These meetings provide a forum for identifying multidisciplinary issues and sharing them with the entire review team. Separate working meetings and informal interactions among reviewers should be coordinated with the reviewers and the RPM, involving team leaders or supervisors as needed. Any multidisciplinary issue that may affect the review timeline established during the planning process should be communicated to the entire team, including the team leaders and the review division director, as soon as it is identified.

d. Use of Information Request and Discipline Review Letters

Information request (IR) and discipline review (DR) letters are communications that can be used by the FDA during a well-managed review to provide an applicant with the opportunity to correct some types of deficiencies in an application and address questions raised during the review process.

i. IR Letters

IR letters are issued prior to completion of a discipline review and are used to identify the need for additional data or request clarification of submitted documents to facilitate completion of the review. An IR letter may address concerns from more than one discipline and may be sent as a secure e-mail

communication provided a copy of the letter is captured in the review division files.

ii. DR Letters

DR letters provide applicants with feedback and preliminary conclusions from one review discipline following the completion of that review through the secondary reviewer level. The review division director does not generally review DR letters before they are issued, and any deficiencies or requests for additional data or analyses contained in a DR letter do not represent final Agency action on the application. The DR letter gives the applicant early notification of issues raised in a discipline review. In some cases, it may be appropriate for the applicant to respond to the deficiencies noted by submitting an amendment during the first-cycle review.

DR letters should generally be sent to the applicant once a discipline's review is completed at the team leader or secondary reviewer level. Agency staff should make every effort to adhere to agreed upon timelines for completion of reviews to facilitate issuing DR letters as early in the review cycle as possible and to provide the applicant with timely feedback on the application. However, when the discipline review is completed only shortly before the PDUFA goal date (e.g., 1 or 2 weeks) or shortly before planned comprehensive action prior to the PDUFA goal date, it may not be an efficient use of FDA resources to send a DR letter. In such cases, it is generally most efficient to include any substantive deficiencies identified by the discipline review in the action letter for the application. A decision regarding whether to send the DR letter in such cases should be discussed with the review division director. The review division director's decision should be based on an analysis of the overall status of the application review and the most efficient way to complete the review within the PDUFA goals. Consideration should be given to the seriousness of the identified deficiencies and the expected time required for the applicant to respond satisfactorily, knowledge of any other serious deficiencies that might prevent approval of the application on the first cycle, competing division workload priorities, and division resource allocation.

The review division will decide whether it is appropriate to review amendments submitted during the first-cycle review or defer review to a subsequent review cycle based on the division's workload and priorities and the review timeline with respect to the nature of the deficiencies. It may not be possible to accommodate correction of major application deficiencies during the first review cycle. Further information on IR and DR letters is available in the FDA guidance *Information*

Request and Discipline Review Letters Under the Prescription Drug User Fee Act.[11]

e. Amendment Submissions

Application amendments generally will be reviewed during the first cycle when they are likely to contribute to finalization of reviews. The division's workload and priorities, and the review timeline and nature of the deficiencies addressed in the amendment also are critical to deciding whether to review them during the first cycle. Responses to IR letters are generally reviewed during the first-cycle review if they are submitted in a timely fashion following the request to the applicant. The review division retains the authority to determine whether to review amendments that contain material that should have been included with the initial application submission, responses to communication of the FDA filing review issues or DR letters, or other amendments originating with the applicant. A prior agreement may be reached between the division and the applicant regarding amendment submission and review for an application with a compelling public health basis for accommodating late submission of required material.

Under PDUFA, major amendments submitted during the last three months of the first-cycle review might lead to a three-month extension of the review clock. The review division retains the authority to determine whether to extend the review clock in response to such amendments. In making this decision, the review division should consider the contents of the amendment, the status of each discipline's review for the application, the division's workload and staffing, and the likelihood that review of the major amendment could lead to approval of the application during the first-cycle review. For example, the review division should generally not extend the review clock if a major amendment addressing issues identified in a DR letter is submitted during the last three months of the review cycle when the application is not approvable due to another discipline's identification of major deficiencies that cannot reasonably be corrected by the applicant within the new extended review timeline. In this scenario, the review division should take a timely action, deferring review of the major amendment to the next review cycle.

2. Applicant Focus

Applicants can best contribute to efficient first-cycle review by initially providing a complete application, submitting planned amendments (e.g., safety and stability updates) on a timely basis, and quickly and completely responding to IR letters and other requests for information. Applicants should consult the FDA guidance *Information Request and*

[11] Additional information for FDA review staff is available in CBER SOPP 8401.1 *Issuance and Review of Responses to Information Requests and Discipline Review Letters to Pending Applications*.

Discipline Review Letters Under the Prescription Drug User Fee Act regarding these types of communication.

The RPM is the primary review team point of contact for the applicant throughout the review process, and questions regarding review status should be referred to this individual. Because it may impede efficient review time-management, direct contact with the primary reviewers or others with designated sign-off authority is generally discouraged unless requested by the FDA.

3. *Communication between FDA and Applicant*

Under 21 CFR 314.102 and PDUFA meeting management policy, applicants can request meetings during the review process as an opportunity to receive feedback regarding the application review status and deficiencies. The FDA will evaluate meeting requests based on whether the meeting is likely to serve a useful purpose warranting the time and resources required to prepare for and conduct the meeting (e.g., whether the meeting has the potential to resolve significant application deficiencies or issues and further review of the application).

Requests for meetings primarily focused on *status updates* generally are not an efficient use of the review division's limited time and resources and may actually slow the review process because of the need for preparation. Such meeting requests ordinarily will be denied. More efficient means of providing the applicant with an update on the application review status should be used (e.g., a telephone call between the RPM and the applicant). Routine conveyance by the FDA of interim review process timelines and speculative action dates is discouraged.

F. Advisory Committee Meetings

1. FDA Focus

The FDA may determine that it is appropriate to present certain applications to an expert Advisory Committee (AC) for review and discussion.[12] The decision regarding whether to present an application to an AC generally is made by the review division in consultation with the office director early in the first-cycle review process. A number of reasons may prompt a review division to seek AC input including, but not limited to: (1) the application is for an NME or a new class of drug; (2) the clinical study design used novel clinical or surrogate endpoints; (3) the application raises significant issues regarding safety and/or effectiveness of the drug or biologic; or (4) the application raises significant public health questions regarding the role of the drug or biologic in the treatment or prevention of a disease.

[12] ACs provide independent advice and recommendations to FDA on scientific and technical matters related to the development and evaluation of products regulated by the Agency. Although an AC provides recommendations to the Agency, final decisions are made by the FDA.

a. Planning

Once determined to be necessary, an AC meeting becomes an integral part of the review process. The timing of the AC meeting and all attendant activity should be managed to promote optimal completion of the first-cycle review. Enough time must be allotted for the various discipline reviewers to complete detailed preliminary reviews before the AC meeting. Sufficient time must also be allowed after the AC meeting to consider the advice from the committee, complete reviews, make a decision about the application, and reach agreement with the applicant on labeling within the PDUFA review timeline. The review division should work with FDA's Advisors and Consultants staff to schedule the meeting at the most appropriate time in the review cycle, giving consideration to the availability of the appropriate expert consultants. In general, an AC meeting for a standard review should be scheduled no later than 2 months before the PDUFA review goal date. An AC meeting for a priority review should be scheduled no later than 1 month before the PDUFA review goal date. The applicant should be notified when it is determined that an AC meeting will be needed and should be consulted during the scheduling process.

A MAPP and SOPP articulating the roles and responsibilities of FDA staff in preparation for an AC meeting are currently being developed. Those documents will include further details regarding the timing and content of background packages for distribution to AC members and the procedures for public release of redacted background packages in advance of the AC meeting.

Information about applicants' preparations for AC meetings is available in FDA draft guidances.[13] CDER and CBER are developing additional guidances for industry about the advisory committee process.

b. Conduct

The procedures followed at the AC meeting (e.g., discussion and voting) are described in the FDA guidance *Implementation of Section 120 of the Food and Drug Administration Modernization Act of 1997 – Advisory Committees*.

To maximize the value of the feedback and advice provided by the AC meeting, it is important that the review division carefully develop the questions the AC will

[13] 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 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.* Once finalized, these draft guidances will represent FDA's current thinking regarding these topics.

be asked at the meeting. The questions should be designed to address the division's most important issues regarding the application and, in general, should be written to allow for a clear vote to be taken and recorded. The questions for the committee should generally be provided to the AC members and the applicant with the background package from the review division so they can prepare to address these issues at the meeting. In some cases it may be necessary initially to provide the committee members with draft questions. However, the final questions should be provided to the committee and applicant as far in advance of the actual meeting as feasible. The review division should consult with the office director and, when appropriate, the chair of the AC in developing the final questions.

The review division's presentation at the AC meeting should be focused on the major issues and questions on which the division is seeking advice and feedback from the committee and invite all AC member viewpoints. The review division's presentation should explain the importance of the committee's input in making the Agency's final regulatory decision about the application following the AC meeting. A neutral presentation that invites all AC viewpoints does not preclude the division from highlighting concerns about the application or presenting preliminary conclusions regarding the data contained in the application. To maximize the amount of time available for public input and committee discussion, the division's presentation to the committee should be developed to avoid unnecessary overlap and redundancy with the applicant's presentation. This goal can best be accomplished if the review division and the applicant work together and share information and presentations in advance of the meeting. This type of cooperation can help eliminate surprises at the meeting for either the division or the applicant and allows for a productive review and discussion of the issues by the committee.

c. Follow-up

The review team should expeditiously evaluate and incorporate AC input and recommendations into subject reviews to prevent delay in the overall progress of the review. To facilitate this, the review team should meet after the AC meeting to review the AC input and determine its implication for the pending reviews and decision-making process. Representation from the various review sign-off authority levels should be included in the follow-up meeting.

It is also important that the review division keep the AC members informed regarding regulatory decisions and actions that occur on an application that has been presented to the AC. For an application that is subsequently approved in the same review cycle as the AC meeting, the division should provide the members of the committee with a copy of the approved labeling along with a brief memorandum from the review division director summarizing the division's

actions and rationale. Such communication should occur on the day the application is approved or as soon thereafter as feasible.

For an application not approved in the same review cycle as the AC meeting, particularly in cases where the division's action was at odds with the AC's recommendations, the review division should inform the chair of the AC about the regulatory action. The division should also send a brief memorandum to those members who participated in the meeting. The memorandum should outline the regulatory action taken and provide a brief description of the rationale for such action. AC members should be reminded of the confidential nature of such communications. The review division should also plan to discuss the basis for the division's action with the committee in a closed session during a future meeting of the AC.

2. Applicant Focus

Information about the exchange of information prior to AC meetings is available in FDA draft guidances (see footnote 12). To facilitate the complex and time-sensitive logistics necessary to hold an AC meeting, the applicant should adhere to the timelines and procedures outlined in the guidance or reach agreement with the FDA on alternative timelines. The applicant should coordinate interactions regarding preparations for an AC meeting with the appropriate personnel in the Advisors and Consultants Staff and with the RPM in the review division.

The applicant is encouraged to share the planned presentation for the AC meeting with the review division as far in advance of the meeting as feasible to facilitate meeting efficiency and avoid surprises at the meeting. The review division can then develop its presentation to the committee to avoid redundancy by limiting its presentation to areas in which FDA's interpretation differs from that of the applicant. The review division generally will share its presentation with the applicant in advance of the AC meeting. Given the timeline and the division's need to modify its presentation based on a review of the applicant's presentation to avoid redundancy, the division may not be able to provide its presentation to the applicant until a few days prior to the meeting. The applicant is strongly discouraged from submitting amendments containing significant new data after the review division's background package has been sent to the AC members and the applicant. Such amendments do not allow the review division sufficient time to consider the new data or include it in the background packages that are provided to the AC members in advance of the meeting.

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. The applicant should provide these amendments in a timely manner for the review to proceed efficiently toward a final action on the application within the PDUFA timeline.

3. Communication between FDA and Applicant

The goal of communication between the FDA and the applicant in preparation for and during AC meetings is to create an environment of thorough, neutral deliberation based on available data. Although new viewpoints regarding the data may surface at any time in the process, it is intended that none of the parties pose or be subjected intentionally to previously undisclosed concerns. This goal can best be achieved when both the applicant and the division adhere to the timelines for submission of background packages to the committee and share their presentations with one another in advance of the meeting. It is generally useful for the applicant and the review division to discuss the plans and logistics for the AC meeting well in advance of the meeting date and to develop a mutually agreeable timeline for sharing presentations.

G. Wrap-Up and Labeling

1. FDA Focus

The outcome of reviews and input from all review disciplines, consultants, inspections reports, and the AC should be integrated near the end of the review cycle to formulate an aggregate understanding among the review team and to inform decision-making at tertiary review levels. This wrap-up function is often most efficiently conducted in a meeting that includes all relevant internal review staff. The need for Center level input on the final decision should be discussed at this juncture. In addition, this meeting can be used to identify the requisite parameters for the subsequent labeling negotiation.

Negotiation with the applicant about final labeling content is an essential part of the first-cycle review for products that are to be approved or that are considered otherwise approvable. Communications such as IR and DR letters should convey concerns to the applicant throughout the review cycle regarding the data and the proposed labeling contained in the application. The planning process should also anticipate communication events with the applicant for labeling negotiation. The negotiation should be implemented well in advance of the final action goal date and should not impede timely completion of the first-cycle review.

As part of completing their reviews, primary reviewers and consultants from CDER's Office of Drug Safety (ODS), and Division of Drug Marketing, Advertising and Communications (DDMAC) and from CBER's Office of Biostatistics and Epidemiology (OBE) and Advertising and Promotional Labeling Staff (APLS) should consider the applicant's proposed labeling and recommend any changes that might more accurately reflect the data and review conclusions. It is recommended that review teams schedule internal labeling meetings starting well in advance of the PDUFA goal date to facilitate the discussion of labeling content and identify major labeling issues. Early communication of potential labeling issues to the applicant is encouraged following secondary review and division or office level input, as warranted. The division should remind the applicant that such labeling comments are preliminary and that the labeling is

not final until it has been reviewed and approved by the signatory authority as part of the approval letter.

2. Applicant Focus

The labeling negotiation should be a collaborative activity with the FDA, based on a mutual understanding of FDA's interpretation of the submitted application. The content of the discussions cannot be thoroughly anticipated in advance for either the FDA or the applicant. Ready access to the applicant's staff facilitates the efficient management of the negotiation process. Significant delays for internal consultations can deter efficient completion of the negotiation process. Submission of materials requested by the FDA, including promotional material amendments, should be timely and responsive to discussions held with the FDA. Applicants are discouraged from printing labels for commercial distribution prior to receipt of an approval letter, because the label is not considered approved by the FDA until then. Labels printed in advance of the actual receipt of an approval letter can contain differences from the final approved label and may have to be destroyed.

3. Communication between FDA and Applicant

It is important that there be clear communication between the review division and the applicant during the labeling negotiations. The review division should communicate to the applicant the reasons for requested changes from the applicant's proposed language for the label in addition to providing the applicant with new text. This approach should improve the efficiency of communication by decreasing the number of back-and-forth negotiations between the division and the applicant. Similarly, the applicant should clearly explain in the response to the review division the basis for changes from the review division's recommended labeling language. Since the labeling discussions occur near the end of the review cycle, it is important that applicants not submit large amounts of new data to the review division in support of proposed labeling text. In some cases, however, the applicant and review division might need to reach agreement based on the material submitted in the application, but subsequently (i.e., after approval) the applicant might need to submit a labeling supplement containing new data to support a labeling change. All labeling content must be adequately supported by data (21 USC 352).

H. Action

As part of PDUFA goals, the FDA has committed to conduct a complete review and provide the applicant with a complete action on applications within specified timelines. Agency actions at the end of the application review can be to approve the application for marketing (21 CFR 314.105 and 601.4(a)) or to provide the applicant with a comprehensive list of deficiencies that must be addressed before the application may be approved.

For NDAs, if the application is not approved following the first-cycle review, the applicant may receive either an approvable letter (21 CFR 314.110) or a nonapprovable letter (21 CFR 314.120). An approvable letter generally indicates that the application can be approved pending the resolution to FDA's satisfaction of issues listed in the letter. Deficiencies that may need to be corrected before an approvable application can be approved range from labeling comments to completion of additional clinical trials. A nonapprovable letter generally indicates that the application is more seriously deficient and cannot be approved without significant additional work, or that the application is unlikely to be approved.

For BLAs, an application that is not approved receives a complete response letter listing all the deficiencies to be corrected to FDA's satisfaction before the application can be approved.

Under the PDUFA goals, the FDA was directed to eliminate the use of approvable and nonapprovable letters and implement use of complete response letters. The FDA is working to amend its regulations since these letters are currently defined in the Code of Federal Regulations for new drug applications.

1. FDA Focus

The FDA's primary focus in reaching a decision and taking action on an application at the end of the first-cycle review is to determine whether the application as submitted and amended meets the statutory requirements for approval. In general, the review divisions and offices should identify and resolve minor deficiencies in an application that otherwise meets the statutory standards for approval during the first-cycle review. This allows the new drug to be approved on the first cycle, which is the most efficient use of FDA resources, avoiding unnecessary multiple-cycle reviews and allowing public access to the new drug in a timely manner.

It is very important that the review staff adhere to the review plan and timelines throughout the review so the reviews are complete and the action package for a decision is presented to the signatory authority in a timely manner. Late completion of reviews and late arrival of the complete action package to the signatory authority places undue time pressure on this important portion of the review process. Such delay can lead to unnecessary multiple-cycle reviews due to the inability to identify and resolve all the deficiencies in the application before the PDUFA goal date. In general, the action package should be completed and available to the signatory authority no later than 2 weeks before the PDUFA goal data for a priority application and no later than 3 weeks before the PDUFA goal date for a standard application. All reviews, consults, and inspection reports should be complete and archived in the division files before a final action is taken on an application.

Once the signatory authority receives the action package, he or she should conduct a careful review of all information to reach a preliminary decision about the appropriate

action. If the signatory authority reaches a preliminary decision that is different from that recommended by the review team or the division, he or she should meet with the review team or division promptly to discuss and resolve any differences of opinion. It is often necessary to have additional labeling negotiations with the applicant following review of the action package by the signatory authority. This should not preclude preliminary discussions and agreements on the labeling by the review team and the division in advance of the action package being submitted to the signatory authority. The review team and division should always remind the applicant of the preliminary nature of such labeling discussions and agreements and emphasize that the labeling is not final until the application is approved. Agency manuals delineate for FDA review staff the current policy and procedures for the action stage of the review process.[14]

a. Action Package

The action package for an application contains final reviews for all disciplines, along with copies of consults and inspection results for the application, and various administrative forms and copies of correspondence between the FDA and the applicant regarding the application. The RPM should begin to assemble the action package on receipt of the application and continue to add new components to it throughout the review process.

b. Finalization of Reviews and Consults

It is important that review team members and consultants manage their work so that their reviews are completed within the timelines developed by the review team as part of the planning process. Late completion of one or more reviews, consults, or inspections causes significant time pressure at the end of the review cycle. Such delay can compromise the amount of time available for the signatory authority to complete review of the action package, for labeling negotiations, and for other activities necessary to complete the review process. This results in the need for crisis management to meet the PDUFA goal and represents an inefficient use of FDA resources that could lead to unnecessary multiple-cycle reviews and could potentially lead to a compromised final decision process.

c. Draft Action Letter and Circulation

The RPM should develop a draft action letter as the reviews are completed based on the preliminary assessment by the review team of what the final action should be. If approval is anticipated, the draft action letter should specify all the conditions of approval, including labeling text, any postmarketing study commitments, and any restrictions on distribution of the product when warranted. Further guidance is being developed to address initiatives specific to

[14] CBER SOPP 8405 *Complete Review and Issuance of Action Letters*, and CDER MAPP 6020.8 *Action Packages for NDAs and Efficacy Supplements.*

postmarketing study commitments addressed in the Food and Drug Administration Modernization Act of 1997 (Section 506 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 356), including engagement of the review division with the applicant in defining the need, scope, and timing of study completion.

If the application is not expected to be approved on the first cycle, the draft action letter should list all the deficiencies identified by the reviewers that must be remedied prior to approval and should also specify how the applicant is expected to respond to each deficiency.

The draft action letter should be circulated to all members of the review team and their team leaders and supervisors for review and concurrence before being forwarded along with the action package to the signatory authority. Depending on the review and decisions made by the signatory authority, additional revisions to the draft action letter may be necessary before it is ready for signature. Any such revisions should be circulated to the appropriate members of the review team to ensure that they are informed about the proposed changes to the draft action letter and have an opportunity to make corrections or suggest changes before the final decision is reached.

d. Timing of Sign-Off with Signatory Authority

Once the signatory authority has completed his or her review and consultations with the review team and upper management as appropriate, the action letter conveying the decision to the applicant should be completed in a timely manner and in advance of the PDUFA goal.

e. Process for Conveyance of Action

When the signatory authority has made the final decision regarding action on the application, the action letter should be signed and archived in the division files and a copy sent to the applicant by facsimile. The RPM should call the applicant to document their receipt of the action letter and should document the receipt confirmation in the action package. Agency manuals delineate for FDA review staff the current policy and procedures regarding the distribution of approval information to the public.[15]

2. Applicant Focus

The primary focus for the applicant during the end of the review leading up to the action decision should be to respond in a timely manner to any requests for information or new

[15] CBER SOPP 8106 *Submission of Product Approval Information for Dissemination to the Public*, and CDER MAPP 4520.1 *Communicating Drug Approval Information.*

proposed labeling from the review division. Based on the nature of communications between the applicant and the review division throughout the review process (e.g., IR letters, DR letters, labeling negotiations), it should be reasonably clear to the applicant whether the application may be headed toward approval or whether another review cycle will be needed to address the Agency's concerns. It is generally not an efficient use of Agency resources during this final critical period to be responding to frequent and redundant inquiries from the applicant. There should generally be only one point of contact, the RPM, between the applicant and the review division to ensure consistency of communication and to avoid misunderstandings.

The FDA guidance *Formal Dispute Resolution: Appeals Above the Division Level* provides additional information regarding the appeal of FDA actions under 21 CFR 314.103.

3. Communication between FDA and Industry

The FDA will process and review all submitted marketing applications in a manner consistent with the goal of issuing an official written regulatory action (e.g., refuse-to-file, approval, approvable, nonapproval, complete response) within the timelines specified in the regulations and the PDUFA goals. The FDA believes that the integrity and transparency of the review process are best served by issuing an official written regulatory action following an appropriate review of the application. The official written regulatory action, signed by the designated signatory authority, provides an official record of the Agency's decision following review of the marketing application. The official written regulatory action contains important information regarding the basis for the Agency's approval decision in cases where the application is approved, or when the Agency's decision is to refuse to file or not approve an application, complete information regarding that decision and the information needed to correct any deficiencies identified.

Although an applicant may voluntarily withdraw a marketing application at any time after submitting it for review, the FDA believes it is generally preferable for the Agency to issue an official written regulatory action documenting its review rather than for the applicant to withdraw the application. When an applicant voluntarily withdraws a marketing application in advance of an *adverse* regulatory action (e.g., RTF, nonapproval), the FDA will acknowledge the applicant's withdrawal of the application in writing. The withdrawal acknowledgement letter will generally include the deficiencies identified by the review division at the time the application was withdrawn.

A decision regarding the official regulatory action for an application is made only after the signatory authority for the application completes his or her review of the available information (e.g., action package) and consults with appropriate members of the review team and management. Therefore, communication with the applicant during the review of the application should generally be related to requests for additional information (e.g., information request letters), deficiencies identified during review that might need to be corrected before the application can be approved (e.g., discipline review letters), and

comments regarding draft labeling. When communicating deficiencies identified during the review and comments on draft labeling, review divisions should make clear to the applicant that the findings are preliminary and that a decision has not yet been made regarding the official regulatory action for the application.

Once the signatory authority for the application makes his or her decision regarding official regulatory action for the application, the decision should be communicated in writing to the applicant as an official written regulatory action (e.g., refuse-to-file, approval, nonapproval, complete response) in a timely and appropriate manner. The information may be of a highly sensitive nature and may have significant impact on the financial markets for publicly held companies. The review division should confirm by telephone the applicant's receipt of the official written regulatory action and include a record of this in the application file (e.g., a notation on the fax transmittal form), clearly recording the timing of notification to the applicant.

Following receipt of an action letter, the applicant may wish to hold a brief telephone conference with the principal signatory in the office and/or review division to ensure full understanding of the decision. Additional provisions are described in the following section for communications to assist an applicant in planning a resubmission.

I. Cycles of Review

1. FDA Focus

A review process subsequent to the first-cycle review should also be managed efficiently. Resources should be allocated based on the projected content of the applicant's response and deficiencies identified during the review process. Agency manuals delineate for FDA review staff current PDUFA goal dates for resubmissions.[16]

2. Applicant Focus

An applicant can help optimize any review process subsequent to the first-cycle review by responding to the issues identified by the review division in the first action letter. Complete responses that target the areas of concern help speed closure on additional cycles. Resubmission priorities are identified for FDA review staff in Agency policy manuals (see footnote 15).

3. Communication between FDA and Applicant

An end of review conference, described in 21 CFR 314.102(d), provides the applicant with the opportunity to meet with the FDA reviewing officials following issuance of an

[16] CBER SOPP 8405.1 *Procedures for the Classification of Resubmissions of an Application for a Product Covered by the Prescription Drug User Fee Act*, and CDER MAPP 6020.4 *Classifying Resubmissions of Original NDAs in Response to Action Letters.*

approvable, nonapprovable or complete response letter. This meeting is recommended if the applicant has questions regarding the identified deficiencies and to support further development and submission planning.

V. IMPLEMENTATION AND EVALUATION

As previously discussed, the GRMPs are based in part on the Agency's current best practices. Additional implementation activity, including reviewer training and performance evaluation, could begin as early as October 1, 2003 if the guidance is finalized, or later when the final guidance becomes available.

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 will have the responsibility, with input from the FDA and the public, to develop an evaluation study design that identifies key questions, data requirements, and a data collection plan in accordance with the PDUFA goals.

APPENDIX A: GLOSSARY OF ACROMNYMS

AC	Advisory Committee
APLS	Advertising and Promotional Labeling Staff (in CBER)
BiMo	Bioresearch Monitoring Staff (in CBER)
BLA	Biologics License Application
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
DDMAC	Division of Drug Marketing, Advertising and Communications (in CDER)
DMPQ	Division of Manufacturing and Product Quality (in CDER)
DR	Discipline Review
DSI	Division of Scientific Investigations (in CDER)
EA	Environmental Assessment
EER	Establishment Evaluation Request
EOP2	End of Phase 2
FDA	U.S. Food and Drug Administration
GRMP	Good Review Management Principles
IND	Investigational New Drug Application
IR	Information Request
MAPP	Manual of Policies and Procedures (for CDER)
NDA	New Drug Application
NME	New Molecular Entity
OBE	Office of Biostatistics and Epidemiology (in CBER)
OCBQ	Office of Compliance and Biologics Quality (in CBER)
ODS	Office of Drug Safety (in CDER)
PDUFA	Prescription Drug User Fee Act
PI	Package Insert
PPI	Patient Package Insert
P/T	Pharmacology/Toxicology
RMP	Risk Management Plan
RPM	Regulatory Project Manager
SOPP	Standard Operating Policies and Procedures
SPA	Special Protocol Assessment

APPENDIX B: REFERENCED GUIDANCES, MAPPS AND SOPPS

The guidances for industry and 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. It is recommended that the following CDER and CBER Web Pages be consulted for additional information:

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

Pre-Submission

FDA Guidance

- *Formal Meetings with Sponsors and Applicants for PDUFA Products*
- *Special Protocol Assessment*

Application Receipt Process (Pre-Filing)

CBER SOPP

- 8401 *Administrative Processing of Biologics Licensing Application (BLA)*
- 8401.2 *Administrative Processing of Biologics License Application Supplement (BLSs)*
- 8110 *Submission of Regulatory Documents to CBER*
- 8406 *Verification of User Fee Data Sheet and Payment*
- 8405 *Complete Review and Issuance of Action Letters*

CDER MAPP

- 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*

Filing

FDA Guidance

- *Refusal to File*

CBER SOPP

- 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 MAPP

- 6010.5 *NDAs: Fling Review Issues*

Review

FDA Guidance

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

CBER SOPP

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

CDER MAPP

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

Advisory Committee Meetings

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*

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

FDA Guidance

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

CBER SOPP

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

CDER MAPP

- 6020.8 *Action Packages for NDAs and Efficacy Supplements*
- 4520.1 *Communicating Drug Approval Information*

Cycles of Review

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*