Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications

Guidance for Industry and Review Staff

Good Review Practice

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) the Office of New Drugs at 301-796-0700 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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

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Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
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Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
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Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications Guidance for Industry and Review Staff[1]

Good Review Practice

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to industry and review staff on good review management principles and practices (GRMPs) for the review of new drug applications (NDAs), biologics license applications (BLAs), or efficacy supplements/supplements with clinical data.[2] This guidance applies to *human drug applications* (as defined in section 735(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)) and *biosimilar biological product applications* (section 744G(4) of the Public Health Service Act (PHS Act)). The goal of GRMPs is to ensure that the review process is managed in a consistent and efficient manner, thereby decreasing the number of review cycles necessary for approval and enhancing patients' timely access to important therapies. This guidance also clarifies the roles and responsibilities of review staff in managing the review process and identifies ways in which applicants may support an efficient and robust review process. Successful implementation of the GRMPs is crucial to FDA's mission of protecting and promoting the public health.[3]

This guidance revises the guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products* issued in April 2005. After it has been finalized, this guidance will replace the April 2005 guidance. Significant changes in this revision reflect:

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

[2] Going forward, the Office of Pharmaceutical Quality generally will use the term *assessment* in place of *review*. Assessment means the process of both evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination.

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

- Advances in the Prescription Drug User Fee Act (PDUFA) program and the implementation of the Biosimilar User Fee Act (BsUFA)

- Evolution of GRMPs to support additional regulatory programs such as breakthrough therapy, the Program for Enhanced Review Transparency and Communication for NME (New Molecular Entity) NDAs and Original 351(a) and 351(k) BLAs (*the Program*), and risk evaluation and mitigation strategies (REMS)

- A consolidated focus on the fundamental values and operational principles that serve as the foundation for the GRMPs

In general, FDA's guidance documents 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. Although guidance documents do not legally bind the FDA, review staff may depart from guidance documents only with appropriate justification and supervisory concurrence.

II. BACKGROUND

The GRMPs are comprised of the fundamental values and operational principles described in this guidance. Originally established under PDUFA III in 2002, FDA's implementation of GRMPs is periodically updated to reflect the ongoing evolution of statutory and regulatory requirements as well as innovations that become part of FDA's review process for marketing applications. FDA continues to work to improve management of marketing applications to meet challenging review goals, while maintaining the highest standards for the evaluation of product safety, effectiveness, and quality.

III. FUNDAMENTAL VALUES

FDA seeks the highest levels of quality in submitted applications, Agency reviews and processes, and final regulatory decisions. Quality can be achieved by applying the fundamental values of accountability, communication, and consistency, which serve as the foundation for the GRMPs. Successful implementation of the GRMPs is dependent on the fulfillment of these values in the execution of policies and processes to ensure that high-quality regulatory decisions are made in a consistent and timely manner. FDA staff must apply the appropriate statutes and regulations in their review of specific applications. FDA staff are also expected to be current on the latest scientific advances and patient perspectives and apply this knowledge in their work. Critical thinking that is grounded in current scientific knowledge is an irreplaceable component of marketing application review and supports successful implementation of the GRMPs.

- **Accountability**

FDA is accountable to the American public for helping to ensure the safety, efficacy, and quality of new drug and biological products. FDA is also accountable for a high-quality and efficient review process that produces timely and informed decisions. In addition, review staff are responsible for implementing the GRMPs and associated policies and processes. Applicants are accountable for the quality and completeness of their applications, including optimal use of product development resources. The quality of submitted applications is vital to achieving timely and science-based regulatory decisions. This shared accountability to the public, including patients who participate in clinical trials, is critical to the implementation of the GRMPs by review staff and applicants.

Although FDA's accountability generally has been measured as compliance with targeted goal dates, with emphasis on the efficiency of first cycle reviews, FDA strives to establish better metrics for evaluating the timely analysis and critical thinking on which regulatory decisions are based. For example, FDA also holds itself accountable for the timely completion of critical review work not included in FDA's annual performance reports, such as notification to applicants regarding issues identified during FDA's initial review of applications, notification to applicants of planned review timelines early in the review process, and internal timelines that govern other important aspects of FDA's regulatory work (e.g., labeling supplement review).[4]

- **Communication**

Communication that is clear, complete, and concise is key to ensuring transparency and clarity during marketing application review. Transparency ensures that all stakeholders understand FDA's regulatory processes and policies. Transparency also ensures that applicants are informed of review progress and allows for both applicants and review staff to anticipate and respond to potential issues and plan for next steps. Clarity allows FDA to understand the applicant's assessment of the benefits and risks of a product as described in the marketing application. Clarity also allows the applicant to understand the reasoning behind a given regulatory action. Communications necessary to achieve transparency during an ongoing review are expected to contain the highest possible degree of clarity.

- **Consistency**

Consistent application and support of the GRMPs by review staff and applicants are critical to the overall success of the marketing application review process. FDA staff can exercise flexibility within the process when a thorough assessment of an individual situation justifies doing so. Process changes that become generally accepted as new best practices will be documented and shared for broader implementation.

[4] BsUFA includes annual performance goals regarding notification to applicants of issues identified during FDA's initial review of applications and notification to applicants of planned review timelines early in the review process for first cycle review of supplements with clinical data. More information on BsUFA performance goals can be found at https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm.

IV. OPERATIONAL PRINCIPLES

FDA's goal is to execute an effective, efficient, and thorough review process that ensures high-quality regulatory decisions. The following operational principles are essential elements that serve to achieve that goal. They are expected to remain stable despite changes in other factors (e.g., regulatory, economic, scientific), but the processes that stem from them may need to adapt and respond to scientific advances and evolving public health needs.

- **A well-designed and executed product development phase facilitates submission and efficient review of a high-quality marketing application**

Effective interaction between FDA and applicants during product development is critical to maximizing first cycle marketing application review efficiency.[5] Execution of a high-quality development program is the applicant's responsibility. However, there are important reasons for applicants to discuss development plans with FDA and consider the review team's feedback. Review staff can provide valuable scientific and regulatory advice to the applicant, including helping advise applicants on the level of evidence needed to demonstrate the product's safety, efficacy, and quality. Applicants should seek such feedback from FDA well in advance of the submission of a marketing application to help ensure a more efficient and robust development program.

Open communication between FDA and applicants should occur at pivotal points during product development. This communication can lead to identification of potential filing and review issues that the applicant should address before submission of a marketing application. Development milestones should be marked with meetings between FDA and applicants to exchange ideas on development program status and planning.[6] Applicants should also promptly inform review divisions of circumstances that arise during development that may affect product approval (e.g., inability to carry out agreed-upon protocols, new nonclinical or clinical safety concerns, manufacturing problems). Taking timely and appropriate action on this information can help prevent deficiencies that could cause FDA to refuse to file an application or result in additional review cycles.

Several regulatory approaches exist to facilitate product development and interactions with FDA to address important public health needs. Examples include breakthrough therapy designation, regenerative medicine advanced therapy designation, and fast track designation for products that

[5] For the purposes of this guidance, the term *applicant* includes any sponsor of an investigational new drug application or applicant for an NDA or BLA under section 505 of the FD&C Act or section 351(a)/351(k) of the PHS Act.

[6] These meetings include, but are not limited to, pre-investigational new drug application, end-of-phase 1, end-of-phase 2, and pre-NDA/BLA meetings for PDUFA, and biosimilar biological product development Type 2, 3, and 4 meetings for BsUFA. The following draft guidances for industry provide information on meeting procedures: *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* and *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products.* When final, these guidances will represent the FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

address an unmet medical need in the treatment of a serious condition.[7] Special protocol assessments can be used to reach agreement with FDA about the design of certain types of protocols.[8] Applicants are encouraged to review the relevant regulatory approaches and discuss their potential use with FDA early in development to support a high-quality and efficient product development phase.

Consistent with the PDUFA and BsUFA agreements,[9] which are fundamental to the success of FDA's regulatory programs, when a complete application is submitted to FDA, FDA's goal is to conduct a complete review of the application within a specified time frame. A complete application contains all information needed to support the claims in the final labeling, and is submitted in a readable, well-organized, electronic format. Omission of important or relevant information can lead to a refusal to file action or requests for additional information. Applicants are strongly encouraged to respond promptly and completely to FDA's requests for additional information. During the first review cycle, FDA ordinarily reviews all amendments to an application solicited by FDA and any amendments that were previously agreed upon (e.g., during the presubmission meeting). FDA attempts to review all other amendments during the first review cycle, but may not be able to, or may decide not to do so in some instances (e.g., when the content of such an amendment does not address a known deficiency in the application). FDA's decision to review an amendment, and whether the amendment should extend the review clock, is based on identifying the most efficient path to completing a comprehensive review that addresses application deficiencies and leads toward a first cycle approval when possible.

Finally, as FDA's overall regulatory workload has increased over time, advance notice from sponsors regarding an expected marketing application submission allows review teams to plan ahead and helps ensure that adequate resources are available for a timely and rigorous review of the application. FDA strongly recommends that sponsors provide review teams with early notice of anticipated marketing application submissions.

- **Planning is crucial to good review management**

The submission of a marketing application shifts the primary responsibility in the review process to FDA, whose obligation is to determine whether a submitted application meets the statutory and regulatory requirements for approval. Review planning should be grounded in the team's knowledge of the development program, with the goal of identifying key focus points for the upcoming review. The team should also establish review timelines specific to the application under review. This helps to ensure efficiency and consistency during the review cycle.

Review planning also promotes identification of potential safety issues, so their optimal management can be adequately discussed during the review cycle. This is particularly important

[7] More information on these programs can be found in the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics.*

[8] As discussed in the guidance for industry *Special Protocol Assessment*.

[9] More information on PDUFA and BsUFA, including the commitment letters, is available at https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ and https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm, respectively.

in the case of safety issues that might require a REMS. REMS can be complex programs that take time to design and implement. Therefore, such work should begin as soon as a serious safety issue that may require a REMS is identified. Ideally, this occurs during product development, giving the review team and applicant ample time to plan for managing the safety issue. When major safety signals warranting discussion are identified by FDA during the application review, the review team should notify the applicant promptly.

Review teams should also inform applicants about major elements of the internal review timeline and promptly communicate any significant changes in the review timeline to applicants to ensure a transparent review process. Applicants should note that some flexibility in the review of the application is needed and changes to the review plan are possible. A well-managed review process helps FDA staff to accommodate and adequately consider unanticipated events and findings. It also takes into account ongoing workload and other public health priorities.

- **Timely and frequent review team collaboration is critical to good review management**

The review team's scientific assessment of an application and regulatory decision-making is a collaborative process. Open lines of communication among reviewers are critical to an efficient and thorough review. Review team members should communicate frequently to ensure that issues affecting multiple disciplines are shared early and that their implications are fully understood. The team should also engage with supervisory personnel early and often to ensure alignment on the approach to review and to maintain awareness of issues identified during the review cycle.

An effective review team maintains a strong interdependence among its members to support a collaborative and rigorous review. Review teams consist of members from many different disciplines. They may also consult representatives from other intra- or inter-center disciplines or review divisions. This underscores the need for efficient communication and teamwork during the review.

- **Effective communication between the review team and applicant is imperative**

Applicant involvement in the review process is important to good review management and helps to ensure transparency and clarity. During the review, the team should promptly communicate significant review issues to the applicant. Timely notification of issues allows the applicant to begin corrective actions, maximizes the chance for a first cycle approval, and may shorten the overall time to approval when additional review cycles are necessary. Applicants can also serve as a resource to the review team in understanding the contents of a marketing application. Communication between applicant representatives and the review division regulatory project manager (RPM) is the most effective and timely mechanism for interaction. Applicants are encouraged to work with RPMs to establish a clear communication strategy.[10]

[10] More information on best practices for communication with FDA during drug development can be found in the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development.*

For new molecular entity NDAs and original 351(a) and 351(k) BLAs, FDA and industry have formalized effective communication practices using the review model known as the Program. This communication strategy is described in the PDUFA and BsUFA commitment letters.[11] The goals of the Program align with those of the GRMPs: to promote the efficiency and effectiveness of the first review cycle and minimize the number of review cycles necessary for approval so that patients have timely access to safe, effective, and high-quality therapies. To accomplish this, the Program includes meetings at key points during the review cycle. Applicants and the review team can also choose to agree on a formal communication plan that can be customized to best meet the specific needs of an application. The Program reflects FDA's commitment to maximize transparency, flexibility, and communication for the most innovative and complex products reviewed by FDA.

It is important that communication with the applicant during the review of an application be generally limited to questions about the contents of an application, requests for additional information, conveyance of identified review deficiencies that need to be corrected, and preliminary comments on draft labeling.[12] FDA staff should not communicate to applicants the proposed or planned regulatory action before issuance of the official written action. Applicants should not request that FDA staff speculate on the eventual official regulatory action.

- **Clear and concise documentation of the scientific review and regulatory decision ensures a thorough and informative record of FDA's regulatory actions**

FDA issues an official written regulatory action for each marketing application. This document represents the official record of FDA's decision. FDA's written review documentation of an approval action contains important information on FDA's basis for its regulatory decision and includes other requirements of the applicant such as postmarketing requirements. In the case of a refuse-to-file or complete response action, FDA's official communication to the applicant contains the information needed to correct the identified deficiencies. The review division should confirm that the applicant has received the official written regulatory action.

Although an applicant may voluntarily withdraw a marketing application at any time for various reasons, it is generally preferred that this not occur following the application's filing so that FDA can complete its review and issue a regulatory action.[13] If an applicant voluntarily withdraws a marketing application in advance of an adverse regulatory action, the withdrawal acknowledgment letter generally includes any deficiencies identified by the review division at the time the application was withdrawn.

[11] More information on PDUFA and BsUFA, including the commitment letters, is available at https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ and https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm, respectively.

[12] FDA staff should make clear to the applicant that such communications are preliminary and that the official regulatory action for the application has not yet been taken.

[13] FDA staff should not request or suggest that an applicant withdraw a pending NDA/BLA except in the most unusual circumstances (e.g., the NDA/BLA was submitted to the wrong center).

An additional goal of documentation is to reflect FDA's scientific evaluation of an application. Documentation should not summarize the work that occurred over the course of a review, nor should it reiterate content that is found in the submission. Documentation should describe FDA's scientific assessment of the submission and highlight the most important issues that led to the regulatory action. Because these documents serve as the official record of FDA's review, it is crucial that documentation is clear, concise, and comprehensive.

V. NEW PRODUCT REVIEW PROCESS

The fundamental values and operational principles described above serve as the foundation for application review and are expected to remain relatively constant over time. However, the review process must be able to nimbly adapt to scientific advances in product development, evolving patient perspectives, and other factors that cannot always be anticipated. More resources concerning FDA's review process are listed below; these resources reflect FDA's goal of building in flexibility to allow the review process to evolve over time while also preserving the values and principles of the GRMPs. It should be noted that review processes in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) may diverge slightly at times; however, both processes are fully aligned with to the fundamental values and operational principles described above.

A. CDER's New Product Review Process

CDER's review process is described in the CDER 21st Century Review Process Desk Reference Guide, available at https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf. Additional detail on specific processes (e.g., meetings, advisory committees) can be found on the Good Review Practices (GRP) website, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ucm092893.htm.

B. CBER's New Product Review Process

CBER's review process is described on the Industry (Biologics) web page available at www.fda.gov/biologicsbloodvaccines/resourcesforyou/industry/default.htm.