POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review

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PURPOSE

- This Manual of Policies and Procedures (MAPP) and its attachment assist the review staff within the Center for Drug Evaluation and Research (CDER) on good review management principles and practices for submissions during the investigational new drug application (IND) phase of drug development, promote excellence in review science, and provide a consistent approach to the conduct and content of the IND review process.

- This MAPP describes CDER's goals for timely review of IND submissions, which will be implemented over time as resources permit.

- This MAPP and its attachment clarify the roles and responsibilities of CDER review staff in managing and facilitating review of IND submissions. This MAPP does not address the specific conduct or content of scientific reviews.

- This is one in a series of MAPPs designed to document good review practices (GRPs) for CDER review staff in accordance with MAPP 6025.1 *Good Review Practices.*

BACKGROUND

- By regulation, the IND is the process under which human trials of investigational drugs are conducted.[1] The regulations address procedures and timelines for submission and review of a new IND, including process and procedures to follow if the IND is placed on clinical hold. Required sponsor submissions to an IND and the importance of milestone meetings during the course of drug development are well described in the regulations, which have been further clarified in guidances and MAPPs.

- Although FDA regulations delineate the sponsor's responsibility to analyze and submit all information about a drug, FDA responsibilities are described primarily as responses to sponsor requests or as administrative actions. Most available guidances address process details (e.g., what the sponsor should submit and when), but do not describe timelines for CDER review of these submissions.

- Attachment 1 of this MAPP describes the underlying review goals of each IND submission, as the first step in a quality systems approach to drug review. However, it should be noted that CDER's resources are limited at present and these principles will be implemented over time as resources permit. Timely review of IND submissions with appropriate feedback to sponsors, while initially requiring an investment of time and resources, can result in greater efficiencies throughout the drug development process. Implementation of these principles could potentially improve the quality of marketing applications, allow more efficient review of new drug applications and biologics license applications, and improve first cycle approvals.

POLICY

- CDER review staff and managers will adhere to and consistently achieve the review management principles and practices detailed in Attachment 1 as resources permit.

- General policies regarding all GRPs are contained in MAPP 6025.1 *Good Review Practices* and apply to this MAPP.

RESPONSIBILITIES

- CDER review staff and managers will follow the responsibilities detailed in Attachment 1.

[1] See 21 CFR part 312.

PROCEDURES

- CDER review staff and managers will follow the procedures detailed in Attachment 1.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENT 1: Good Review Management Principles and Practices for Effective IND Development and Review

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1. INTRODUCTION

This document was prepared to assist review staff in the Center for Drug Evaluation and Research (CDER) on good review management principles and practices (GRMPs) for submissions during the investigational new drug application (IND) phase of drug development.[2] These principles are based on the collective experience of CDER staff and are intended to promote excellence in review science and a consistent approach to the conduct and content of the IND review process. This document also clarifies the roles and responsibilities of review staff in managing and facilitating review of IND submissions.

The GRMPs and fundamental values described in the guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products*, which discusses review standards for new drug applications (NDAs) and biologics license applications (BLAs) regulated in CDER, apply to the review of IND submissions.

The complexity and importance of material submitted to an IND will vary by therapeutic indication and development stage. Although review divisions retain the flexibility to determine the extent of review and feedback provided for each submission, it is important to articulate general principles, standards, and goals for review. Incorporation of these principles is intended to improve safety oversight and facilitate effective communication between CDER and sponsors to share information and perspectives at critical junctures in drug development. The goals of these interactions are to ensure studies and clinical trials of adequate design, to identify Critical Path opportunities, and, for drugs that are safe and effective, to increase the likelihood of a successful first-cycle action.

This document describes the IND review process for sponsors seeking approval of a drug, whether approval will be requested under 21 CFR part 314, subpart B (drug approvals); 21 CFR part 314, subpart H (accelerated approval (drugs)); 21 CFR part 314, subpart I (animal rule (drugs)); 21 CFR part 601, subpart C (biologics licensing); 21 CFR part 601, subpart E (accelerated approval (biologics)); or 21 CFR part 601, subpart H (animal rule (biologics)).

This document does not address the specific conduct or content of scientific reviews, such as the number of sampling time points needed for an adequate pharmacokinetic trial or the number of trials and level of evidence needed to support approval for a particular indication. A MAPP is being developed to assist staff in performing such reviews. This document does not alter existing Food and Drug Administration (FDA) processes or standards for scientific and regulatory decision making.

[2] For the purposes of this document, all references to *drugs* include both human drugs and biological products regulated within CDER unless otherwise specified.

The principles described herein apply to review of all INDs, including those from commercial sponsors, submissions from academic centers, the National Institutes of Health and other government agencies, and individual clinical sponsor-investigators. Best practices for review of IND submissions for new drugs are the focus, but the principles apply to the review of submissions of subsequent IND studies and trials of marketed drugs seeking additional marketing indications or evaluating safety, submissions for marketed unapproved drugs seeking initial approval, and IND trials.

The ability of CDER review staff and managers to adhere to and consistently achieve these review management principles depends on the availability of adequate resources (e.g., staffing, training, and information technology support). CDER also needs the full cooperation and participation of sponsors for effective implementation of the GRMPs. Therefore, this document describes best practices for CDER review staff, **which will be implemented over time as resources permit.** It is intended to describe CDER's *ultimate goals* for review timelines, but does not establish *actual* review timelines at this time.

Although this document describes CDER's current best practices, it should be appreciated that this process is dynamic. The best means of fulfilling these principles will evolve over time with feedback from sponsors and review staff. This document serves as initial documentation of what has been, and continues to be, an ongoing process improvement initiative.

2. BACKGROUND

The IND is the process under which human trials of investigational drugs are conducted. From CDER's perspective, the IND phase of drug development spans the time from submission of the first IND-related request (including submission of a pre-IND meeting request or an original IND) to the submission of a marketing application. It may extend beyond initial approval or licensure to include additional trials relevant to the drug's development and labeling. From the sponsor's perspective, drug development has a broader and longer time frame and is not limited to the IND phase because it also includes drug discovery and early work-up of compounds before IND submission and may include clinical trials conducted in other countries outside a U.S. IND.

Regulations address the procedures for a sponsor to submit, and for CDER to review, an original IND, including CDER's review timeline and the responsibilities of the sponsor and CDER if the IND is placed on clinical hold.[3,4] Required submissions to an IND and the importance of milestone meetings during the course of drug development are well

[3] See 21 CFR 312.1 through 312.42.

[4] See MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)*.

described in the regulations, which have been further clarified in guidances and MAPPs.[5,6,7]

The Prescription Drug User Fee Act (PDUFA)[8] and its subsequent reauthorizations and the Biosimilar User Fee Act of 2012 (BsUFA)[9] are intended to facilitate drug and biosimilar biological product development, respectively, by providing the FDA with additional resources to decrease application review times and to support the conduct of meetings with sponsors, in addition to other functions. Additional efficiencies depend on improving the quality of drug development during the IND phase, as articulated in "FDA's Critical Path Opportunities List."[10]

We can accomplish these efficiencies by actively describing and implementing best practices (e.g., in meetings and in timely responses to other sponsor submissions). Some best practices are outlined for the first time in this document. Many are listed in other published documents (such as International Conference on Harmonisation (ICH) guidances and the draft guidance for industry *Assessment of Abuse Potential of Drugs*)[11] and, as stated in the PDUFA Reauthorization Performance Goals,[12] many will be described in guidances that are under development.

Implementation of these principles is intended to lead to greater consistency within and across CDER review divisions, to minimize the conduct of studies/trials that are unlikely to produce useful information but unnecessarily consume sponsor and CDER resources, to encourage early termination of development for drugs unlikely to be safe or effective,

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[5] See the Food and Drug Administration Modernization Act of 1997 (http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/default.htm).

[6] See the guidances for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information*; *IND Meetings for Human Drugs and Biologics: Chemistry, Manufacturing and Controls Information*; *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized Therapeutic Biotechnology-Derived Products*; *Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products: Questions and Answers*; *End-of-Phase 2A Meetings*; *Formal Meetings Between the FDA and Sponsors or Applicants*.

[7] See MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)* and MAPP 6020.5 *Good Review Practice: OND Review Management of INDs and NDAs for Nonprescription Drug Products*.

[8] See http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

[9] See http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm.

[10] See http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077258.pdf.

[11] When final, this guidance will represent the FDA's current thinking on this topic.

[12] See http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm.

and to facilitate submission of a complete marketing application with quality information and well-designed/well-conducted nonclinical and clinical trials for review. These efforts could result in a greater likelihood of first-cycle approval and earlier availability of new safe and effective drugs to the American public.

3. PRINCIPLES

3.1 Fundamental Principle

The fundamental principle of IND review is that an interactive process between sponsors and CDER facilitates efficient and thorough development that increases the likelihood of submission of a complete marketing application, or alternatively, prompts early termination of a development program for an unsafe or ineffective drug.

3.2 Process and Review Principles

CDER review staff are encouraged to convey to sponsors the following process principles to facilitate preparation of high-quality submissions. CDER review staff are expected to adhere to the following review management principles.

- **The sponsor is responsible for a well-organized and complete submission**

  Complete and well-organized submissions can increase the efficiency of CDER review. CDER review staff should encourage sponsors to apply the following high-level content and formatting recommendations to IND submissions.

  – *Summary.*

    - All submissions should begin with an overall summary that provides sufficient information to allow CDER review staff to understand the regulatory and developmental context of the submission.

    - The summary, which usually comprises the first page of the submission, should list the objectives of the submission, identify what information and supporting data are attached, and include any questions the sponsor would like CDER to address in writing, *if workload permits*. Questions should include the regulatory context so that CDER review staff understand why the issue is important to choices made during drug development. For example, if a submission contains an adaptive trial design, this fact should be clearly identified in the initial summary, with a brief description of how this trial fits into the overall drug development plan, the issues on which the sponsor would like CDER feedback, and relevant data used to design the trial.

  – *Target product profile.* A target product profile, which is a concise version of the prototype product label, can be included and used to enhance

communication and promote a shared understanding of the drug development program by delineating the sponsor's goals.[13]

– *Supporting data.* Sufficient supporting data for the conclusions reached in the submission should be included. For example, submission of a new protocol with a new dosing regimen should be accompanied by a summary of the appropriate drug quality, pharmacokinetic, or exposure-response data used to support the change.

– *Description of pharmacogenomic-pharmacogenetic hypotheses.* Because clinical pharmacogenomics and biomarkers are increasingly used in drug development, a description of the hypotheses and specific aims (including exploratory aims) related to genetic determinants of drug response should be provided if applicable.

– *Statistical analysis plan.* Submission of a detailed statistical analysis plan (SAP) in the initial protocol submission for phase 3 protocols is not required by CDER regulations. However, review staff should strongly encourage sponsors to include the SAP in the initial protocol submission, because phase 3 protocols generally include a detailed section devoted to statistical methods that are closely linked to trial design.

– *Trial start date.* The anticipated trial start date and whether sponsors plan to wait for CDER feedback before trial initiation (although CDER feedback cannot be guaranteed) should be stated.

– *Marked-up copy.* Any protocol amendments should be marked (e.g., marked-up copy provided with deleted material in strike-out and new material underlined, as well as an unmarked copy).

A self-contained and complete submission allows CDER review staff to conduct a thorough review with efficient use of resources. For example, concise summaries of relevant data, with the date or link to relevant prior submissions and/or submission numbers, are preferable to citations of prior submissions alone.

- **The sponsor manages drug development and is responsible for soliciting CDER input**

  CDER recognizes that sponsors manage drug development and determine the nature and timing of submissions to the IND, but review staff should remind sponsors that there are important reasons for them to discuss development plans with CDER review staff and request advice. Scientific and regulatory recommendations during the drug development phase, either in response to

[13] See the draft guidance for industry and review staff *Target Product Profile — A Strategic Development Process Tool*. When final, this guidance will represent the FDA's current thinking on this topic.

submissions or during meetings, may result in more efficient and robust development programs.

CDER, with its broad experience, can help sponsors apply the general requirements of the law, regulations, and guidance recommendations to the specific drug under development in ways that may not be otherwise apparent to sponsors; explore the possibility of accelerated approval or special protocol assessment (SPA); recognize potential safety issues; recognize the potential need for drug scheduling; and help to ensure that sponsors perform all quality and nonclinical studies, clinical pharmacology, and clinical trials needed for a complete marketing or licensing application. CDER can also notify sponsors when studies/trials will not be required, conserving sponsor and CDER resources.

CDER review staff should encourage sponsors to identify problems or issues of concern in their submissions by describing them fully in submitted material and by soliciting CDER feedback. Sponsors run the risk of conducting an inefficient or inadequate development program and increasing the length of time to approval if they omit key information, do not clearly identify the regulatory and developmental intent of the submission, or provide insufficient detail before the time of submission of an NDA or BLA.

If sponsors request review of specific submissions, or include questions as part of a submission, review staff will notify sponsors whether they will be able to respond to sponsor requests for review and the anticipated timeline for providing the response. If review staff respond to such a request and request clarification, make recommendations, or identify a concern, they should encourage sponsors to reply promptly and completely. Prolonged delays in receiving responses to information requests or lack of response to reviewer recommendations, comments, or questions may delay CDER responses and lead to problems later in development.

- **CDER review staff are responsible for reviewing the content of the sponsor's IND submissions and providing advice on critical safety and efficacy concerns, even in the absence of a specific question from the sponsor**

  During review of IND submissions, CDER review staff may become aware that a quality, safety, or efficacy component critical for study/trial conduct or drug approval is missing; that the sponsor and CDER differ on the interpretation of the applicable statutory requirements; or that a development plan could be improved. CDER has the advantage of viewing the entire spectrum of drug development across different sponsors, indications, and drug classes. Without violating confidentiality, CDER review staff may be able to recommend better or more streamlined approaches (e.g., trial designs).

  Review staff should respond to a sponsor's specific question, as resources permit, but should also consider the implications of a submission in the absence of

questions, identifying problems and issues and providing high-level recommendations for important issues, as well as providing overall comments. For example, a sponsor may initiate phase 3 clinical trials without adequate attention to dose-response in earlier trials, may overlook a critical aspect in the choice of an endpoint or the patient population to be studied, may propose a trial design that is unlikely to succeed or be acceptable, may not use appropriate statistical approaches to deal with multiplicity, may not have appreciated potentially useful trial designs, or may not evaluate sources of variability in response among different populations.

At times, a sponsor's questions may focus on protocol details but not directly ask whether the overall trial design will support approvability. In such a case, the review division should outline the regulatory basis of approval and inform the sponsor of any critical trials that are missing or that use inappropriate endpoints (e.g., will not support approval). Similarly, review teams should comment on submitted studies or trials that are not deemed necessary to support approval. Reviewers also are responsible for applying all available guidance to the evaluation of a sponsor submission.

CDER supports public health goals by protecting subjects from participating in trials that are unlikely to support approval and by facilitating development so that beneficial drugs are available as soon as possible. Inefficient development may expose clinical trial subjects to unnecessary risk. Traditionally, CDER has used a proactive approach to respond to information provided in meeting packages and requests for SPA, and that approach should extend to review of other critical IND submissions as well, such as phase 2 dose-finding trials, phase 3 trials designed to support efficacy, and clinical trials to prove biosimilarity and/or interchangeability.

CDER review staff also should consider each part of a future marketing application during the IND phase and remind sponsors of their obligations at appropriate intervals. Although sponsors should be familiar with marketing application requirements, in practice they may inadvertently overlook required components, such as electronic submission formats, the requirements of the Pediatric Research Equity Act (PREA) (or request for a waiver or deferral), and the need to submit the number of subjects with safety and efficacy analyses by age, race, and gender in annual reports to the IND and in the marketing application.

Review staff also should encourage sponsors to submit requests for proprietary name review during the IND phase after drugs have completed phase 2 trials. Abuse and dependence issues should be considered early in development of a new drug so that all appropriate nonclinical and human studies are completed at the time of submission of the NDA and the data are supportive of the sponsor's proposal for scheduling the drug under the Controlled Substances Act (CSA), if

applicable.[14] The end-of-phase 2 (EOP2) meeting is frequently cited as the best forum for these reminders because it signifies the sponsor's expectation that a drug will proceed to phase 3 development and presumably to a marketing/licensing application. However, review staff should consider these elements throughout IND development, because it may be beneficial to communicate some reminders earlier in development, based on the type of development plan.

For biosimilar biological product review, the objective of the development plan is not to independently demonstrate efficacy and safety. Instead, the objective is to demonstrate "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product."[15] Although these goals are not identical to the critical safety and efficacy concerns for the drug development, the same principles described in this section apply to interactions with sponsors and review of submissions intended to support demonstration that the molecule is structurally and functionally highly similar to a reference product, and therefore is likely to behave like the reference product with respect to efficacy and safety in a clinical setting.

- **Effective and efficient management of the review process for each component of the IND is primarily a CDER responsibility**

  Most IND submissions, except for those listed in Tables 1 and 4 in section 4., IND Review Process, do not have a mandatory review timeline, in contrast to PDUFA- and BsUFA-mandated review goal dates for NDAs and BLAs. Nonetheless, CDER is responsible for reviewing all IND submissions that it receives. A timely review is critical if any recommendations are to be useful to the sponsor. Review timelines are addressed in more detail in section 4., IND Review Process (see Tables 5 through 7). Prompt review can also protect subjects by decreasing unnecessary exposure to investigational drugs and can conserve CDER and sponsor resources by obviating the need for repeated correspondence cycles.

  Although CDER acknowledges its review responsibilities, it does not have unlimited resources to review all submissions with the highest level of scrutiny in short time frames. CDER review staff must prioritize their workload and evaluate individual submissions in the context of their place in drug development.

[14] See 21 CFR 314.50(d)(5)(vii). If the drug has a potential for abuse, the content and format of the application should include in the clinical section "a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act."

[15] Section 351(i)(2) of the Public Health Service Act.

When CDER review staff and their team leaders receive submissions for their assigned IND applications, they are responsible for screening the submissions to determine the extent of review needed, the need for consultation, and the prioritization for content review. For submissions without required responses, *CDER review staff will prioritize submission review based on: (1) relative importance to subject safety followed by (2) the importance of the submission to the sponsor's development program.*

After the initial review of safety issues, prioritization of the submission, based on the importance of the submission to the sponsor's development program, should be based on whether the sponsor submitted sufficient background information, regulatory context, and specific questions to permit an efficient and targeted review. An incomplete submission, a confusing submission (e.g., complex protocol amendment submitted only as an unmarked copy), or a submission lacking regulatory context (e.g., four phase 3 protocols submitted simultaneously in the absence of an EOP2 meeting) should be considered to be lower priority. In general, review of a phase 3 trial intended to support a marketing application, submitted after an EOP2 meeting, is likely to be assigned a high-priority review status, as are reviews of complex designs such as noninferiority or adaptive design trials. CDER review staff will consistently devote the highest level of scrutiny to aspects of a submission that affect subject safety and will prioritize remaining submissions accordingly.

A timely and thorough review is not necessarily synonymous with a lengthy written review; submissions may be evaluated that do not raise new issues and thus do not require further action. In this case, an electronic signature in CDER's electronic archive may adequately document the review. Issues may be addressed in written documents that evaluate selected, important protocol components appropriate for the development stage. A written assessment of a submission may consist of short, bulleted comments that address high-level issues.

In general, CDER review staff evaluate phase 1 and phase 2 protocols for subject safety considerations, characterization of exposure variability and response, development and adequacy of efficacy endpoint assessments (if relevant), and dose selection. Clinical pharmacology review staff may assess these submissions for broader considerations such as usefulness in defining exposure-response relationships, dose-finding, drug-drug or drug-food interactions, specific population trials, biomarker and pharmacogenomic evaluations for individualization of therapy, evaluation of relative bioavailability between the proposed drug and listed drug(s) for a 505(b)(2) application, identification of possible pharmacologically active metabolite(s), and potential immunogenicity for biologics. CDER review staff closely examine phase 3 trials for subject safety and to assess the adequacy of dose selection and trial design to support a marketing application. For biosimilar biological products, review staff should evaluate clinical trial protocols for subject safety consideration, and adequacy of

design, including enrolled population, endpoints and SAP, to support a marketing application.

Review divisions should be flexible in assigning resources to particular submissions. Time frames generally should be consistent with the recommendations outlined in Tables 5 through 7. Concerns that affect subject safety should be evaluated and communicated to the sponsor as soon as possible.

- **Effective IND review management is enhanced by CDER review team continuity**

  It is desirable for CDER to assemble a review team early and to maintain the team throughout the life cycle of the IND, if possible. Throughout the drug's development, from pre-IND through NDA/BLA submission, the team gains expertise with and an understanding of the data submitted for that drug that can facilitate prompt responses to submissions. Clear and careful reviews and detailed documentation of recommendations as needed in the electronic document archive is critical for ensuring accurate recall of past views and decisions, particularly if review team continuity cannot be maintained.

- **Good IND review management requires coordinated input from the entire CDER review team**

  Many submissions require coordinated evaluation by more than one review team member and consultants, as needed. A CDER review team generally consists of staff from multiple CDER offices, representing different disciplines and areas of expertise. For example, review staff from the Office of Surveillance and Epidemiology (OSE) may examine important safety submissions, as appropriate; staff from the Office of Pharmaceutical Science (OPS) provide expertise for drug quality submissions; Office of Clinical Pharmacology review staff evaluate human pharmacokinetic/pharmacodynamic data; the Office of Biostatistics evaluates statistical plans; staff from the Office of Counter-Terrorism and Emergency Coordination provide input on applications with a counterterrorism indication or that are submitted by the military; review staff from the Controlled Substance Staff review information related to abuse potential of drugs with central nervous system activity and whether the drug should be scheduled in the CSA.

  These reviewers are an integral part of the review team. Sometimes additional expertise is needed and other groups are consulted. Consultants can include consulting staffs in the Office of New Drugs (OND) Immediate Office (e.g., Study Endpoints and Labeling Development Team, Pediatric and Maternal Health Staff); review staff from other divisions, offices, or centers; a special government employee; or a subject representative.

Also, it is important for review staff to consider whether members of other CDER divisions and specialty teams and members of other centers, such as the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health, should be consulted, especially when drugs are developed for multiple indications or involve a combination product. Some examples include inviting the CDER Office of Compliance to attend pre-BLA meetings to prepare for licensing applications because of the complexities of manufacturing inspections for these products; the Office of Scientific Investigation may be consulted on quality risk management principles and quality management plans when they are included in the protocol. Information sharing should be an operational goal to improve the consistency of the CDER review process.

When more than one discipline reviews a submission, review team members should discuss any potential cross-disciplinary concerns, as needed. Recommendations should be collated and coordinated by the OND regulatory project manager (RPM), so that a single coordinated response, reviewed by review team members and appropriate managers, can be sent to the sponsor. The OND RPM should obtain assistance from review team members, as necessary, to resolve any conflicting recommendations. All relevant review team members should be copied on the response sent to the sponsor.

- **Information sharing between the sponsor and CDER review staff and within the CDER review team is critical**

  Effective management of IND review depends on CDER receiving full disclosure of all information about the drug from the sponsor, an *information-sharing* approach among CDER review staff and consultants, and effective detailed transmissions of concerns to the sponsor. Reviews and meetings are most useful when there is a diligent effort by both the sponsor and CDER review staff to identify problems and issues. For CDER advice to be useful, CDER should convey to the sponsor the importance of being candid when identifying problems and issues, particularly because CDER review staff generally do not have all primary data for review before the submission of the marketing application. CDER review staff should convey in detail to the sponsor the review team's concerns and reservations about trials and development plans. Information sharing allows CDER review staff and the sponsor to work together on optimal safeguards for subjects as well as optimal drug development plans.

  The OND RPM generally should be the point of contact for communication between the individual designated by the sponsor (i.e., regulatory affairs representative liaison for the sponsor's drug development team) and CDER review team members. In some circumstances, the OPS RPM may serve as a point of contact for communication related only to drug quality and the OSE Safety RPM may serve as a point of contact for the proprietary name review.

CDER review staff should share information with the sponsor as much as is advisable and legally permissible. CDER review staff have the advantage of reviewing data from multiple members of a drug class from different sponsors. CDER review staff are bound by confidentiality requirements with respect to other sponsors' data and plans, but to protect the public health review staff should consider class concerns (e.g., safety signals) that should be proactively investigated before submission of a marketing application for another class member. Similarly, review staff should provide feedback on clinical trial design issues and the analytical plan based on collective past experience.

CDER review staff should take the initiative to interact with other review team members throughout the review process. The frequent and open communication of perspectives, concerns, and insights can be an important vehicle for working as a team both to resolve concerns and to identify issues that need broader discussion. This is especially true when issues cross disciplines (e.g., when a clinical protocol raises important clinical pharmacology questions).

It is equally important that communication extend across CDER review divisions or across centers when appropriate; this is especially true when drugs have been submitted to different divisions for different indications or when combination product issues influence drug development. Depending on the nature of the communication (e.g., formal cross-division consultations), the OND RPM(s) should be involved to document and facilitate the interaction. Maintaining consistency in the recommendations sponsors receive from different divisions across CDER is an important aspect of the IND review process. However, it is important to understand that at times, when supported by risk versus benefit assessments for the targeted indication and population or other well-documented critical differences, CDER recommendations may differ.

CDER has certain memoranda of understanding in place with international regulatory bodies pursuant to which CDER review staff may exchange information with these entities.[16] When necessary, CDER review staff may discuss information from submissions with other regulators (e.g., Canada and Europe). Information sharing in these venues may facilitate detection of safety problems, improve study/trial designs, and help harmonize drug development.

- **Good IND review management requires documentation of the review process and timely communication to sponsors with a written rationale for CDER's recommendations**

  CDER review staff should respond to the sponsor's questions, supported by a rationale, and also provide feedback, when resources permit, on safety and efficacy concerns that have not been specifically identified by the sponsor. Documentation of a review can consist of an electronic signature, a brief written

[16] See http://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/default.htm.

summary, or a detailed, multipage document, depending on the type of submission and the issues it raises.

Submissions that do not require a written review are nonetheless evaluated by the review staff and the evaluation documented via the reviewer's signature in the electronic archive. Certain submissions may require a written review with appropriate team leader and/or supervisory review. Reviews should be archived (including those consisting of an electronic signature only), and comments (as needed) sent to the sponsor in a timely manner. The archive ensures documentation of and access to reviews, regardless of review staff turnover. Reviews document CDER's position in the event of a future disagreement or problem with a marketing application. CDER review staff should prioritize comments and clearly indicate those that are considered critical to the development program (i.e., deficiencies and clinical hold issues) and those that are recommended but not required (i.e., comments).

- **CDER will strive to support its critical drug development recommendations, unless substantial scientific issues essential to determining the safety or effectiveness of the drug are identified**

  The IND phase of drug development is a multiyear process, and CDER recognizes that new data will become available, and that scientific advances and changes in clinical practice may occur during this time. Although reviewers consider new information and revise recommendations as needed, CDER review staff should try to support and adhere to its prior critical recommendations. If CDER review staff change the recommendations, the changes should be based on new scientific information or advances in clinical practice that make earlier CDER recommendations about drug development irrelevant, inappropriate, or unethical. In such cases, review staff should inform sponsors in writing of this decision and the rationale behind the decision.

- **A quality system at CDER is desirable to maintain consistency in IND review, ensure appropriate follow-up, and identify best practices**

  A high-quality IND review, consistency in conduct of the review, and timeliness of the review are all important goals. CDER should continue to develop quality systems to facilitate timeliness and consistency and to identify and share best practices.

3.3 Scientific Advances and Professional Development

CDER review staff are expected to provide advice to sponsors that is commensurate with published scientific advances. The following review principle summarizes CDER's philosophy.

- **CDER review staff should maintain scientific and medical expertise to keep pace with new technology and new drug discovery mechanisms**

  CDER review staff are encouraged to participate in professional development, which includes the opportunity for physicians to practice in the clinic, for research scientists to work in the laboratory, and various opportunities for staff in other disciplines. CDER review staff also have the opportunity to attend continuing education classes both within and outside of the FDA, as well as professional meetings. Because scientific discovery moves quickly and technologic advances affect both drug discovery and drug development, CDER review staff are encouraged to keep pace with these initiatives to ensure effective and high-quality review of INDs and marketing applications.

4. IND REVIEW PROCESS

Sponsors who wish to conduct a clinical trial with an investigational drug in the United States must, by law, do so under an IND (unless exempted under 21 CFR 312.2(b),[17] or under 21 CFR 312.2(c) and 320.31(d) for bioavailability studies) or unless a waiver is obtained under 21 CFR 312.10.[18] This requirement is intended to ensure the safety of subjects (patients and healthy volunteers) and to ensure the adequacy of trials so that marketing/licensing applications contain well-designed clinical investigations that can support safety and effectiveness. These combined aims require attention both to the details of submitted studies and trials and to the scope of the investigations under the IND. At the same time, the sponsor is ultimately responsible for the nature and quality of all submissions in both INDs and marketing/licensing applications.[19] CDER's role is carried out through reviews of submissions, responses to questions posed by a sponsor, and meetings to further discussion and communication. CDER also may conduct inspections of sites and operations associated with an IND, including targeted inspections of select clinical trial manufacturing and clinical trial sites.

From CDER's perspective, there are three groups of submissions and activities under the IND:

1. An original IND and any associated regulatory actions, including clinical hold

2. Milestone meetings and other important meetings with the sponsor

[17] See the draft guidance for industry *Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND*. When final, this guidance will represent the FDA's current thinking on this topic.

[18] See 21 CFR 312.1 through 312.42.

[19] CDER recognizes that individual investigators who plan to develop drugs or conduct independent research with marketed drugs often lack experience with the content and format of IND submissions. A guidance is being developed to address those concerns.

3. Subsequent submissions or amendments to the IND that may be divided into:

    - Submissions with a specific regulatory-mandated timeline for review, such as an SPA

    - Significant submissions that directly affect safety, such as safety reports

    - Significant submissions that directly affect demonstration of efficacy, such as new clinical protocols or nonclinical toxicology or clinical pharmacology reports (e.g., dosing strategies) supporting clinical protocols

    - Other submissions, including annual reports, stability information, and nonclinical or clinical pharmacology final reports

    - Administrative submissions (e.g., notification of change in address, change in sponsor)

4.1 Original IND

The contents of an IND and the scope of the FDA's regulatory authority with respect to an IND are extensively described in regulations.[20] Because sponsors may proceed with the submitted clinical trial if they are not informed otherwise by the FDA within the specified time period, CDER must complete the initial safety reviews and make decisions on whether the proposed trial is safe to proceed by calendar day 30 after receipt of the submission.

Because review of a new IND focuses primarily on safety, CDER review divisions should hold an internal IND safety meeting, timed so that the division may provide requests to and receive responses from the sponsor for relatively easy fixes (e.g., minor protocol changes for added safety monitoring) that if not discussed might otherwise lead to a clinical hold. Given the 30-day time frame for the initial safety review, optimal timing of the internal IND safety meeting would be by calendar day 25. Such a meeting brings discipline review staff together with appropriate managers to identify any safety concerns raised during the IND review, or by broad experience within CDER, of safety problems associated with drugs in a similar pharmacologic or chemical class. CDER review teams should request consultations as early as practicable to allow sufficient time for consultants to review materials and attend the safety meeting. Early phase clinical trials submitted in a new IND should meet high standards for safety before they can be allowed to proceed.

If a clinical trial is not considered safe to proceed, it will be placed on clinical hold, with appropriate notification to the sponsor of the reason for the hold and the information required to lift the hold. Procedures for instituting a clinical hold and for reviewing and

[20] See 21 CFR 312.1 through 312.42.

acting on a response to clinical hold are described in FDA regulations and published MAPPs.[21]

Sponsors sometimes submit a new IND with clinical data obtained from extensive development outside of the United States and a later phase development protocol, such as a phase 2 or phase 3 protocol intended to support a marketing/licensing application. Sponsors may also submit a new IND with a complex clinical trial intended to support a new indication for a marketed drug in a new patient population where the risks and benefits of therapy differ from the approved indication. New INDs may also contain data intended to support approvals under section 505(b)(2) of the FD&C Act. In these and similar situations, sponsors may not necessarily request a pre-IND meeting, because, from their perspective, drug development already has been underway for some time. However, in these cases, CDER review staff generally should recommend submission of a pre-IND meeting request to discuss the sponsor's development program to ensure that the sponsor and the FDA are in agreement regarding the scope of existing data that may be used to support the application and the proposed later phase development trials.

If a sponsor submits an IND without having previously conducted a pre-IND meeting or if the IND contains complex submission materials, CDER review staff are still required to complete the safety review in 30 calendar days. Although CDER will determine whether the trial is safe to proceed in these cases, CDER review staff should notify the sponsor that CDER ordinarily will need more time to determine the trial's ability to fulfill regulatory requirements to demonstrate safety and effectiveness. The sponsor may then choose to request a meeting, such as an EOP2 meeting, or seek specific feedback on the protocol. CDER review staff should respond to these requests within the timelines mandated by PDUFA for meetings and/or in this document for submission review, as applicable.

In some cases, an IND is opened with a clinical protocol in which the dose and schedule of the drug do not represent a novel risk, based on other INDs with similar exposures or populations. In such cases, the sponsor can request a waiver of the 30-day waiting period, which the review division can grant at its discretion.

An IND is administratively assigned to the review division with expertise in the relevant therapeutic area. A sponsor can submit a new IND, complete phase 1 trials, and then plan to conduct phase 2 trials with the drug in several different therapeutic areas. For drugs that are not under development as biosimilars, it is at the discretion of the original review division as to whether the trials can be conducted under the original IND or should be conducted under a new IND (with a 30-day review clock) in the relevant division(s). For biosimilar product development, there is a single IND regardless of the number of conditions of use being studied. In this case, the IND is assigned to the review division that has oversight of the reference product and other relevant divisions should participate in a collaborative review process.

[21] See 21 CFR 312.1 through 312.42 and MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds).*

New IND submissions and their associated regulatory actions are summarized in Table 1.

Table 1. Original IND

Description	Timeline	Type of Evaluation	Communication With Sponsor
Original IND (21 CFR 312.40)[1]	• Less than 30 calendar days for initial safety review. • Written safety review if recommending clinical hold; completed in time to issue hold by calendar day 30. Issue hold letter within 30 calendar days of hold action. • Complete written review by day 60 if not recommending hold. Complete written review by day 30 if recommending hold.	• DARRTS safety review sign-off* • Written review by appropriate disciplines • Phone call followed by a letter for clinical hold	Required
Waiver for initial 30-day IND review (21 CFR 312.40(b))	Less than 30 calendar days	Written communication of decision by OND RPM or CPMS*	Required
Clinical hold response (21 CFR 312.42)[1]	30 calendar days for initial safety review and response	Written safety review by each discipline with hold issues (includes continued clinical hold responses and conversion from full to partial clinical hold)	Required
IND reactivation (21 CFR 312.45)	• 30 calendar days for initial safety review. • Written safety review by calendar day 30 if recommending clinical hold. Issue hold letter within 30 calendar days of hold action.	• Written review by appropriate disciplines • Phone call followed by letter for clinical hold	Required for hold

[1] See also MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)*
* DARRTS = Document Archiving, Reporting, and Regulatory Tracking System; CPMS = chief, project management staff

4.2 Milestone and Other Important Meetings

Milestone meetings occur at critical junctures in drug development and include pre-IND, end-of-phase 1 (EOP1), EOP2, and pre-NDA/BLA meetings. A sponsor also can request other types of meetings with CDER (e.g., drug quality meetings or an end-of-phase 2A meeting). Meetings provide an important formal forum for the sponsor to present information to CDER review staff and for CDER review staff to provide specific and targeted advice to the sponsor about subsequent development and regulatory requirements. For this reason, CDER review staff should encourage the sponsor to submit clearly worded questions so that CDER understands the purpose of the meeting. Tables 2 and 3 summarize some of the topics that are frequently considered in the major IND milestone meetings.[22]

Table 2. Critical IND Milestone Meetings — Nonbiosimilars Development

Meeting	Examples of Topics to Consider	Comments	Reference
Pre-IND	• Animal studies to support human testing • Phase 1 trial design • PSP* • CMC issues for certain drug types,* such as biotechnological drugs, biological drugs, natural products, complex dosage forms, and drug-device combinations that could affect safety • Bioequivalence trials to support marketing applications • Unapproved drugs • Animal and human abuse liability information or drug control issues	**Not routine; consider using for the following situations:** • NME* • Critical to public health to have effective and efficient drug development plan (counter-terrorism) • New IND with substantial early development outside the United States or with adequate and well-controlled trials to support new indication (functions as EOP2 meeting) • 505(b)(2) applications	• 21 CFR 312.82 • Pre-IND consultation program Web site[1] • Guidance for industry *IND Meetings for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information*

continued

[22] For additional information, see relevant ICH guidances for industry and the following guidances for industry: *Formal Meetings Between the FDA and Sponsors or Applicants*; *End-of-Phase 2A Meetings*; *IND Meetings for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information*; and the draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants* (when final, this guidance will represent the FDA's current thinking on this topic).

Table 2, continued

Meeting	Examples of Topics to Consider	Comments	Reference
EOP1	• Phase 2 controlled trials, including safety and efficacy • Pediatric studies • EOP2 for accelerated approval • Optimal dose selection, identification of populations for phase 3 trials • Adaptive trial designs • Adequacy of supporting nonclinical data • Proposed studies/trials to support evaluation of abuse potential • Adequacy of data quality measures	• For accelerated approval drugs (subparts E and H), functions as EOP2	• 21 CFR 312.82(b) • 21 CFR part 312, subpart E • 21 CFR part 314, subpart H or I • 21 CFR part 601, subpart E or H • Guidance for industry *End-of-Phase 2A Meetings*
EOP2	• Phase 3 trial design (including dose selection and endpoint selection) • Adequacy of safety database • Pediatric studies, including studies required under PREA and Written Requests issued under the Best Pharmaceuticals for Children Act • Additional information needed to support NDA/BLA • Context for SPA submission • Adequacy of supporting nonclinical data • Adequacy of supporting clinical pharmacology data • Adequacy of supporting abuse-related data • Use of data standards for submission	• Should be held before phase 3 trials begin. • Evaluate need for pediatric studies, pediatric formulation. • Initial PSPs must be submitted within 60 days after an EOP2 meeting. Division must meet with sponsor to discuss or provide written comments on the plan within 90 days after submission. PeRC must review the PSP.* • Generally must have EOP2 meeting to submit SPA for adequate and well-controlled trial intended to support approval.	• 21 CFR 312.47(b)(1)(i) • PREA • FDAMA* • 1997 PDUFA goals • Guidance for industry *Special Protocol Assessment* • FDASIA[2,]*

continued

Table 2, continued

Meeting	Examples of Topics to Consider	Comments	Reference
Pre-NDA/ BLA	• Identify unresolved issues • Identify trials to support quality, safety, and efficacy in NDA/BLA • Pediatric studies • Summarize data • Data format and presentation • Initiate drug name review • NMEs • Preliminary discussions of risk management plans, postmarketing studies or trials • Quality information and inspection considerations, including the identification of manufacturing facility(ies) and readiness for inspection • Outline of data to be submitted for abuse potential assessment and drug scheduling • For NMEs/original BLAs, agreements on the contents of a complete application and late submission application components (up to 30 days after original submission) (the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs)	• If development was straightforward, formatting • If not, determine whether outstanding issues require additional data or studies/trials that may affect the fileability of future submission	• 21 CFR 312.47b(2) • PREA • Guidances for industry: – *IND Meetings for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information* – *Formal Meetings Between the FDA and Sponsors or Applicants* • PDUFA V Reauthorization Performance Goals and Procedures; Fiscal Years 2013 Through 2017[3]

[1] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm.
[2] See http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm20027187.htm.
[3] See http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.
* PSP = pediatric study plan; CMC = chemistry, manufacturing, and controls; NME = new molecular entity; PeRC = Pediatric Review Committee; FDAMA = Food and Drug Administration Modernization Act of 1997; FDASIA = Food and Drug Administration Safety and Innovation Act of 2012

Table 3. Critical IND Milestone Meetings — Biosimilars Development

Meeting	Examples of Topics to Consider	Comments	Reference
Biosimilar Initial Advisory meeting	• Manufacturing process information (including planned methodology and assay validation) • Sufficient comparative characterization data with the reference product for the FDA to make a preliminary determination whether the product is appropriate for 351(k) pathway • Development plan including conducted and planned trials • Description of planned analytical similarity exercise • Summary of data from any conducted trials	• Similar in intent to the pre-IND meeting in Table 2	• Biosimilar Biological Product Authorization Performance Goals and Procedures; Fiscal Years 2013 Through 2017[1] • Draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*
Biosimilar BPD Type 1 meeting*	• Dispute resolution meetings • Meetings to discuss clinical holds in which a response to hold issues has been submitted but the FDA and the sponsor agree that development is stalled and a new path forward should be discussed • SPA meetings that are requested by sponsors or applicants after FDA receipt of SPA • Meetings to discuss an important safety issue, when such an issue is identified and the FDA and the sponsor or applicant agree that the issue should be discussed	• Meeting necessary for an otherwise stalled biosimilar development program to proceed	• Biosimilar Biological Product Authorization Performance Goals and Procedures; Fiscal Years 2013 Through 2017[1] • Guidances for industry: – Draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants* – Draft guidance for industry and review staff *Formal Dispute Resolution: Appeals Above the Division Level*[2] – Guidance for industry *Special Protocol Assessment* • 21 CFR 10.75, 312.48, and 314.103

continued

Table 3, continued

Meeting	Examples of Topics to Consider	Comments	Reference
Biosimilar BPD Type 2 meeting	• Specific issue or questions (e.g., proposed trial design or endpoints) for an ongoing biosimilar development program • May include substantive review of summary data, but not full reports As needed: • Pediatric assessment • Risk management plans, postmarketing studies or trials	• Meeting to discuss a specific issue or questions where the FDA provides targeted advice for an ongoing biosimilar BPD program • Sponsor may request as many BPD Type 2 meetings as warranted by developmental needs	• Biosimilar Biological Product Authorization Performance Goals and Procedures; Fiscal Years 2013 Through 2017[1] • Draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*
Biosimilar BPD Type 3 meeting	• Substantive review of full reports • FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product based on information submitted • FDA advice regarding additional trials, including design and analysis As needed: • Pediatric assessment • Risk management plans, postmarketing studies or trials	• In-depth data review and advice meeting for an ongoing BPD program • Sponsor may request as many BPD Type 3 meetings as warranted by developmental needs	• Biosimilar Biological Product Authorization Performance Goals and Procedures; Fiscal Years 2013 Through 2017[1] • Draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*

continued

Table 3, continued

Meeting	Examples of Topics to Consider	Comments	Reference
Biosimilar BPD Type 4 meeting	• Data format and presentation • Identify unresolved issues, residual uncertainty • Quality information and inspection considerations, including the identification of manufacturing facility(ies) and readiness for inspection As needed: • Pediatric assessment • Risk management plans, postmarketing studies or trials • Outline of data to be submitted for abuse potential assessment and drug scheduling	• To discuss the format and content of a biosimilar biological product application or supplement submitted under 351(k) of the PHS Act* • Similar in intent to the pre-NDA/BLA meeting in Table 2	• Biosimilar Biological Product Authorization Performance Goals and Procedures; Fiscal Years 2013 Through 2017[1] • Draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*

[1] See http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf
[2] When final, this guidance will represent the FDA's current thinking on this topic.
* BPD = biological product development; PHS Act = Public Health Service Act

It is the sponsor's responsibility to outline the purpose of the meeting in the meeting request. The sponsor should provide adequate and relevant information in the briefing document to support the purpose of the meeting. After a meeting is requested and granted, CDER should remind sponsors that it is their responsibility to provide additional detail about the purpose of the meeting in the meeting briefing document. The sponsor generally asks whether specific studies or trials, clinical or nonclinical, will be sufficient in design and quality to support the drug development stage discussed at the meeting. There may be other purposes, such as discussion and planning for risk management of an identified safety concern.

CDER should also remind sponsors to submit a limited number of specific questions that directly summarize their concerns about the drug and development program, and to provide sufficient data to support the questions being asked. It is the responsibility of CDER review staff to ensure that the meeting purpose is understood in advance, to share preliminary responses to questions raised in the meeting package with the sponsor in advance of the meeting, to determine whether other important discussion points not considered by the sponsor should be raised at the meeting, and to consider the components of a complete application and remind the sponsor of these components at

appropriate stages during development. CDER review staff document these discussions in meeting minutes and share them with the sponsor.

Meeting requests, packages, scheduling, preparation, conduct, and documentation (meeting minutes) are described in other guidances. The timelines are described in PDUFA and BsUFA agreements.[23]

4.3 IND Submissions and Amendments

After an IND is opened, hundreds of supporting documents may be submitted to the IND during its life cycle. To date, CDER has not had formal expectations for the extent and timeliness of review of most of these submissions. The types of IND submissions and amendments can be separated into four categories as follows:

1. Submissions with a specific regulatory-mandated timeline (e.g., SPAs) or an FDA-established timeline (e.g., review of proposed pediatric study requests)

2. Safety-related submissions (e.g., initial telephone safety reports or 7- or 15-day reports, where communication with sponsors may or may not be needed)

3. Drug development submissions without regulatory-mandated timelines where communication to the sponsor is often critical and recommended (e.g., new nonclinical, clinical, or protocol changes/amendments)

4. Other submissions that may overlap any of the preceding three categories and where communication with the sponsor may be needed (e.g., general correspondence, final reports, annual reports, drug quality amendments)

The following tables list recommended timelines for evaluating these submissions, separated into the four categories listed above. The tables list the primary discipline responsible for each submission, but other disciplines may be consulted or provide secondary review. The tables reflect review goals, which may be adjusted depending on the complexity of the submitted material, staff resources, competing workload priorities, and other factors.

CDER must adhere to regulations and it takes its responsibilities seriously. Thus, CDER consistently completes reviews of the submissions listed in Tables 1 and 4 on time. Similarly, scheduling meetings (and preparing for meetings by reviewing submitted meeting packages (see Tables 2 and 3)) occurs according to goal dates agreed on under PDUFA and BsUFA. Traditionally CDER has had a high rate of accomplishing goal dates. CDER also has consistently considered safety-related submissions to be a top priority, and the targeted dates listed in Table 5 are based on standard practice.

[23] See http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm or http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm.

Presently, CDER does not have the resources to meet all listed timelines, and must balance this work with other responsibilities, including NDA/BLA review and oversight of postmarketing safety. Meeting all the dates specified in Tables 6 and 7 cannot be accomplished at present. However, CDER has selected several high-priority submissions from these tables and will work toward implementing the goal date over the next several years for these submission types. The high-priority submissions include new phase 2/3 adaptive trial designs, new phase 3 protocols, and postmarketing requirement protocols (for required postmarketing studies and trials that concern complex designs or statistical assessments).

In addition, CDER has a new program intended to expedite drug development. Section 506(a) of the FD&C Act provides for designation of a drug as a breakthrough therapy "if the drug is intended, alone or in combination with 1 or more other drugs, to treat a *serious or life-threatening disease or condition* and *preliminary clinical evidence* indicates that the drug may demonstrate substantial improvement over *existing therapies* on 1 or more *clinically significant endpoints*, such as substantial treatment effects observed early in clinical development."[24] CDER intends to expedite the development and review of a breakthrough therapy by, where appropriate, intensively involving senior managers and experienced review staff in a proactive collaborative, cross-disciplinary review. Where appropriate, CDER also intends to assign a cross-disciplinary project lead for the review team to facilitate an aggressive timeline and efficient review of the development program. Submissions for a drug designated as a breakthrough therapy should be considered high priority and managed accordingly.

[24] 21 U.S.C. 356(a)

Table 4. IND Submissions With Regulatory-Mandated or FDA-Established Timelines (Corresponds to Submission/Amendment Category 1)

Description	Timeline	Type of Evaluation	Communication With Sponsor
Treatment IND/ treatment protocol[1,2]	Less than 30 days for complete review. CDER-established interim dates: • Day 19 after receipt for discipline review • Day 21 for team leader reviews • Day 26 for division director • Day 30 for office director 30 days to send acknowledgement letter. Issue hold letter within 30 calendar days of hold action.	Written review by appropriate discipline(s) Treatment IND/Protocol Executive Summary Review[3]	Required: Acknowledgement letter from CDER to sponsor for IND and protocol(s) Hold letter required if the IND/protocol is put on clinical hold
Single patient IND[2,4]	Up to 30 days	Brief written review	Required: Acknowledgement letter from CDER to sponsor Hold letter required if the IND is put on clinical hold
Single patient protocol[2,4]	Up to 30 days	Brief written review	Hold letter required if the protocol is put on clinical hold
Emergency IND or protocol[2,4,5]	Immediately	Brief written review	Acknowledgement letter from CDER to sponsor
Intermediate-size access IND[2,6]	Up to 30 days	Brief written review	Required: Acknowledgement letter from CDER to sponsor Hold letter required if the IND is put on clinical hold
Intermediate-size access protocol[2,6]	Up to 30 days	Brief written review	Hold letter required if the protocol is put on clinical hold

continued

Table 4, continued

Description	Timeline	Type of Evaluation	Communication With Sponsor
Request to charge[7]	30 days for complete review and response	Clinical evaluation	Required
Request for SPA[8]	45 days for review and response	Written review by appropriate discipline(s) (including consult with appropriate OPS reviewer for updated drug information) or Exec CAC meeting minutes*	Required
Pediatric exclusivity, PPSR[9,]*	120 days for response. Must be reviewed internally by PeRC before issuance.*	Written review by appropriate discipline(s), issued as an FDA Written Request or notification of an inadequate or incomplete PPSR	Required
Pediatric exclusivity, amendment to request for studies[9]	120 days for response. Must be reviewed by PeRC if substantive changes.	Written review by appropriate discipline(s), issued as pediatric revised or reissued Written Request	Required
Initial PSP[10,]*	90 days for initial response. Must be reviewed internally by PeRC before issuance. Additional 90 days to reach agreement with sponsor on agreed initial PSP.	Meeting with appropriate disciplines and sponsor, or written review by appropriate discipline(s) if meeting is not necessary, for initial response	Required
Agreed initial PSP[10]	30 days for response. Must be reviewed by PeRC before issuance.	Written response	Required
Amendment to agreed initial PSP[10]	90 days for initial response. Must be reviewed internally by PeRC before issuance. Additional 90 days to reach agreement with sponsor on agreed initial PSP	Meeting with appropriate disciplines and sponsor, or written review/response by appropriate discipline(s) if meeting is not necessary for initial response Further negotiations and revisions needed	Required
Agreed amendment to initial PSP[10]	30 days for response. Must be reviewed by PeRC before issuance.	Written response	Required
Fast track designation request[11]	60 days for response	Letter to the sponsor denying or granting fast track status. Fast track form — medical reviewer to complete.	Required

continued

Table 4, continued

Description	Timeline	Type of Evaluation	Communication With Sponsor
Breakthrough designation request	60 days for response	Letter to the sponsor denying or granting breakthrough status	Required
Proprietary name review (submitted to the IND)[12]	180 days for response	Written review	Required
Request for formal dispute resolution[13]	30 days for response	Letter to the sponsor from the office or center director/deputy	Required

[1] See 21 CFR 312.320
[2] See 21 CFR 312.305
[3] See MAPP 6030.6 *INDs: Processing Treatment INDs and Treatment Protocols.*
[4] See 21 CFR 312.310
[5] See 21 CFR 312.310(d)
[6] See 21 CFR 312.315
[7] See 21 CFR 312.8
[8] See the guidance for industry *Special Protocol Assessment*, MAPP 7412.1 *Management of CDER Carcinogenicity Assessment Committee (CAC) and Executive CAC*, and the Biosimilar Biological Product Authorization Performance Goals and Procedures; Fiscal Years 2013 Through 2017 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf).
[9] See the guidance for industry *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*.
[10] See http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm20027187.htm.
[11] See the guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review*.
[12] See MAPP 6720.2 *Procedures for Handling Requests for Proprietary Name Review* and the Biosimilar Biological Product Authorization Performance Goals and Procedures; Fiscal Years 2013 Through 2017 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf).
[13] See the draft guidance for industry and review staff *Formal Dispute Resolution: Appeals Above the Division Level*.
* CAC = Executive Carcinogenicity Assessment Committee; PPSR = Proposed Pediatric Study Request; PeRC = Pediatric Review Committee; PSP = pediatric study plan

Table 5. Safety-Related Submissions (Corresponds to Submission/Amendment Category 2)

Description	Recommended Timeline	Type of Evaluation	Communication With Sponsor
Unexpected fatal or life-threatening suspected adverse reaction reports	1 day	Written documentation of the call (OND RPM) or electronic archiving of emails/faxes and any advice or recommendations (in consultation with medical reviewer)	Inherent
IND safety report	Up to 15 days	Written review if needed, or electronic sign-off that "Safety report was reviewed and did not identify new safety concerns or items that required additional action" (medical reviewer)	As needed
Follow-up to an IND safety report	Up to 30 days	Written review if needed, or electronic sign-off that "Safety report was reviewed and did not identify new safety concerns or items that required additional action" (medical reviewer)	As needed
Thorough QT trial reports[1]	Review division should send consult within 2 weeks of receipt; IRT will provide written response within 45 days of receipt*	Written consult by IRT	As needed

[1] See MAPP 6020.14 *Interdisciplinary Review Team for QT Studies*
* IRT = Interdisciplinary Review Team

Table 6. IND Drug Development Submissions (Corresponds to Submission/Amendment Category 3)[25,26]

Description	Recommended Timeline	Type of Evaluation	Communication With Sponsor
QUALITY			
Quality information	OND RPM, quality (OBP/ONDQA) RPM,* quality reviewer should screen within 30 days of receipt to determine priority status and level of review: • 60 days priority • 180 days standard	Written review as needed	As needed
Quality: Response to information request	OND RPM, quality (OBP/ONDQA) RPM, quality reviewer should screen within 30 days of receipt to determine priority status and level of review: • 60 days priority • 180 days standard	Written review as needed	As needed
NONCLINICAL			
Nonclinical information: Priority amendments, supporting new clinical protocols (general, genetic, reproductive toxicology reports) Standard (toxicology studies by routes of administration other than planned clinical route, pharmacology, abuse/dependence)	Reviewer/team leader should screen within 7 business days of receipt to determine priority status and level of review: • Priority amendments: preliminary evaluation within 14-30 days; review up to180 days • Standard: within 6-12 months	• Written review for priority • Written review as needed for nonpriority	As needed
New animal protocol (excluding SPA)	Up to 60 days	Written review if CDER feedback is requested	As needed

continued

[25] The ability of review staff and managers to adhere to the recommended review timelines depends on the availability of adequate resources (e.g., staffing, information technology support) and the completeness and quality of the submissions CDER receives.

[26] Discipline-specific *information* submissions in Table 6 exclude protocols, which have separate listings.

Table 6, continued

Description	Recommended Timeline	Type of Evaluation	Communication With Sponsor
Carcinogenicity information	Reviewer/team leader should screen within 7 business days of receipt to determine priority status. Within 6-12 months.	Written review	As needed
Nonclinical: Response to information request	Reviewer/team leader should screen within 7 business days of receipt to determine priority status and level of review. Up to 90 days.	Written review as needed, or electronic sign-off that "Response reviewed and satisfactorily addresses CDER's information request."	As needed
CLINICAL PHARMACOLOGY[1]			
Clinical pharmacology information:	Reviewer/team leader should screen within 7 business days of receipt to determine priority status and level of review		
High priority: (1) Submissions where input on use of quantitative drug development methods can be influenced	Up to 60 days	Written review	Required
(2) Decision-making by CDER or the sponsor will be based on clinical pharmacology review	Up to 60 days	Written review	Required
Standard	Up to 180 days	Written review as needed	As needed
Clinical pharmacology: Response to information request	Up to 90 days	Written review as needed	As needed
CLINICAL			
Clinical information	Reviewer/team leader should screen within 7 business days of receipt to prioritize and determine level of review. Safety-related: within 15 days. Other: up to 180 days.	Written review as needed	As needed

continued

Table 6, continued

Description	Recommended Timeline	Type of Evaluation	Communication With Sponsor
Clinical: Response to information request	Reviewer/team leader should screen within 7 business days of receipt to prioritize and determine level of review. Up to 90 days.	Written review for safety (including abuse/dependence) concern as needed, or electronic sign-off that "Response reviewed and satisfactorily addresses CDER's information request."	As needed
BIOMETRICS			
Biometrics information	Up to 60 days	Written efficacy or safety review if submission addresses statistical aspects of phase 3 clinical protocol	As needed
Biometrics: Response to information request	Up to 90 days	Written efficacy or safety review as needed, or electronic sign-off that "Response reviewed and satisfactorily addresses CDER's information request."	As needed
Statistical analysis plan	Up to 60 days	Written review	As needed
PROTOCOLS			
Thorough QT protocols[2]	Review division consults IRT within 2 weeks of receipt;* IRT completes review within 2 weeks of consult receipt	Written review by IRT Written communication to sponsor by review division	Required
New phase 1 protocol	Up to 30 days	Written safety review as needed by appropriate discipline(s)	As needed

continued

Table 6, continued

Description	Recommended Timeline	Type of Evaluation	Communication With Sponsor
New phase 2 protocol	Reviewer/team leader should screen within 7 business days of receipt to determine priority status; potential clinical hold issues; and need for consult to quality, clinical pharmacology (including pharmacogenomics and pharmacometrics), or other disciplines. Up to 60 days.	Written safety and/or efficacy review by appropriate discipline(s): • As needed for dose-response phase 2 or proof-of-concept studies/trials (clinical pharmacology) • Required for: – Sponsor states trial is intended to support accelerated or full approval – Novel trial design, endpoint, or other *new* element • Recommended if requested by sponsor and workload permits	As needed
New phase 2-3 adaptive trial design	Up to 60 days	Written review as needed by appropriate discipline(s)	As needed
New phase 2-3 abuse potential protocol with statistical analysis plan	Up to 90 days	Written review(s)	As needed
New phase 3 protocol (excluding SPA)	Reviewer/team leader should screen within 7 business days of receipt to determine priority status and need for consult to quality, clinical pharmacology (including pharmacogenomics or pharmacometrics), or other disciplines. Up to 60 days.	• Written safety and efficacy review by appropriate discipline(s) if trial is intended to support approval, novel endpoints • Recommended if requested by sponsor and workload permits	As needed (required if intended to support approval; as workload permits if requested by sponsor)
Clinical trial intended to support a demonstration of biosimilarity (excluding SPA)	Reviewer/team leader should screen within 7 business days of receipt to determine priority status and need for consult to quality, clinical pharmacology (including pharmacogenomics or pharmacometrics), or other disciplines. Up to 60 days.	Written review by appropriate discipline(s)	As needed

continued

Table 6, continued

Description	Recommended Timeline	Type of Evaluation	Communication With Sponsor
Pediatric protocol (part of Written Request or PREA)	60 days	Written safety or efficacy review by appropriate discipline(s)	Required
Postmarketing study/clinical trial protocol	Up to 60 days	Written safety and efficacy review by appropriate discipline(s), including assessment of whether it will fulfill stated objectives, as needed	As needed
Protocol change	30 days for safety; up to 60 days for development concerns	Written review by appropriate discipline(s) for: • Safety concerns • Change in analysis plan for phase 3 trial • Major change in design element	As needed

[1] See MAPP 5100.3 *OCP Prioritization, Triage, and Review Process for INDs and Pre-INDs*.
[2] See MAPP 6020.14 *Interdisciplinary Review Team for QT Studies*.
* OBP/ONDQA = Office of Biotechnology Products/Office of New Drug Quality Assessment; IRT = Interdisciplinary Review Team

Table 7. Other Submission Types (Corresponds to Submission/Amendment Category 4)

Description	Recommended Timeline	Type of Evaluation	Communication With Sponsor
General correspondence	Up to 6 months	As needed by relevant discipline(s)	As needed
Annual report (to be replaced by DSUR* per ICH E2F[1])	OBP/ONDQA:* Screen contents within 2 months. Review within 12 months. Other disciplines: Screen contents within 14-30 days. Review within 6 months.	Written review as needed, or electronic sign-off that "Annual report was reviewed and did not identify new concerns that required CDER action."	As needed

continued

Table 7, continued

Description	Recommended Timeline	Type of Evaluation	Communication With Sponsor
Study/Trial final report	Screen within 14 days. Review within 60-120 days.	Written review as needed (and see below), or electronic sign-off for phase 1 or early phase 2 trials that "Trial was reviewed and did not identify new concerns that required CDER action." Targeted brief written review of critical elements generally needed for phase 3 trials, important phase 2 trials (e.g., dose selection; possible use for accelerated approval).	As needed
Rolling review designation	60 days	Letter denying or granting request	Required
Change of sponsor/change of address/transfer obligation	Up to 60 days	Letter (RPM/CPMS*)	Required
IND inactivation	Up to 30 days	Letter (RPM)	Required
IND withdrawal	Up to 30 days	Letter (RPM)	Required

[1] See the ICH guidance for industry *E2F Development Safety Update Report*.
* DSUR = development safety update report; OBP/ONDQA = Office of Biotechnology Products/Office of New Drug Quality Assessment; CPMS = chief, project management staff

5. GLOSSARY OF ACRONYMS

BLA	biologics license application
BPD	biological product development
BsUFA	Biosimilar User Fee Act of 2012
CDER	Center for Drug Evaluation and Research
CMC	chemistry, manufacturing, and controls
CPMS	chief, project management staff
CSA	Controlled Substances Act
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DSUR	development safety update report
EOP1	end-of-phase 1
EOP2	end-of-phase 2
Exec CAC	Executive Carcinogenicity Assessment Committee
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act of 2012
GRMPs	good review management principles and practices
ICH	International Conference on Harmonisation
IND	investigational new drug application
IRT	Interdisciplinary Review Team
NDA	new drug application
NME	new molecular entity
OBP	Office of Biotechnology Products
OND	Office of New Drugs
ONDQA	Office of New Drug Quality Assessment
OPS	Office of Pharmaceutical Science
OSE	Office of Surveillance and Epidemiology
PDUFA	Prescription Drug User Fee Act
PeRC	Pediatric Review Committee
PHS Act	Public Health Service Act
PPSR	Proposed Pediatric Study Request
PREA	Pediatric Research Equity Act
PSP	pediatric study plan
RPM	regulatory project manager
SAP	statistical analysis plan
SPA	special protocol assessment

6. REFERENCES[27]

Draft guidance for industry *Assessment of Abuse Potential of Drugs*[28]

Draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*[29]

Draft guidance for industry *Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND*[30]

Draft guidance for industry and review staff *Formal Dispute Resolution: Appeals Above the Division Level*[31]

Draft guidance for industry and review staff *Target Product Profile — A Strategic Development Process Tool*[32]

Guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized Therapeutic Biotechnology-Derived Products*

Guidance for industry *Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products: Questions and Answers*

Guidance for industry *End-of-Phase 2A Meetings*

Guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review*

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

[27] Guidances for industry can be found on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. MAPPs can be found on the Manual of Policies and Procedures Web page at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

[28] When final, this guidance will represent the FDA's current thinking on this topic.

[29] When final, this guidance will represent the FDA's current thinking on this topic.

[30] When final, this guidance will represent the FDA's current thinking on this topic.

[31] When final, this guidance will represent the FDA's current thinking on this topic.

[32] When final, this guidance will represent the FDA's current thinking on this topic.

Guidance for industry *IND Meetings for Human Drugs and Biologics: Chemistry, Manufacturing and Controls Information*

Guidance for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information*

Guidance for industry *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*

Guidance for industry *Special Protocol Assessment*

Guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products*

ICH guidance for industry *E2F Development Safety Update Report*

MAPP 5100.3 *OCP Prioritization, Triage, and Review Process for INDs and Pre-INDs*

MAPP 6020.5R *Good Review Practice: OND Review Management of INDs and NDAs for Nonprescription Drug Products*

MAPP 6020.14 *Interdisciplinary Review Team for QT Studies*

MAPP 6030.1 *IND Process and Review Procedures (Including Clinical Holds)*

MAPP 6030.6 *INDs: Processing Treatment INDs and Treatment Protocols*

MAPP 6720.2 *Procedures for Handling Requests for Proprietary Name Review*

MAPP 7412.1 *Management of CDER Carcinogenicity Assessment Committee (CAC) and Executive CAC*