
**Best Practices for
Communication Between
IND Sponsors and FDA
During Drug Development
Guidance for Industry and
Review Staff**

Good Review Practice

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

**December 2017
Procedural**

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Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff¹

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This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to describe best practices and procedures for timely, transparent, and effective communications between investigational new drug application (IND) sponsors² and FDA at critical junctures in drug³ development, which may facilitate earlier availability of safe and effective drugs to the American public. This guidance applies to communications between IND sponsors and FDA during the IND phase of drug development, including biosimilar biological product development (BPD). This guidance describes:

- FDA's philosophy regarding timely interactive communication with IND sponsors as a core activity
- The scope of appropriate interactions between review teams and IND sponsors
- The types of advice appropriate for IND sponsors to seek from FDA in pursuing their drug development programs
- General expectations for the timing of FDA response to IND sponsor inquiries

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

² For the purposes of this guidance, all references to *sponsors* include both sponsors and their authorized officials as described in 21 CFR 312.3 and 312.23(a)(1)(ix).

³ For the purposes of this guidance, all references to *drugs* or *drug products* include human drug products, including biological drug products, regulated by CDER and CBER, unless otherwise specified.

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- Best practices and communication methods to facilitate interactions between review teams and IND sponsors during drug development
- Expectations for appropriate methods, including the frequency, of such communications

This guidance does not apply to communications or inquiries from industry trade organizations, consumer or patient advocacy organizations, other government agencies, or other stakeholders not pursuing a development program under an IND.

Although this guidance describes FDA's current best communication practices, it should be appreciated that with additional feedback from sponsors and review staff processes may evolve further. As additional best practices are identified or established, this guidance may be updated.

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 FDA, review staff may depart from guidance documents only with appropriate justification and supervisory concurrence.

II. BACKGROUND

On July 9, 2012, the President signed the Food and Drug Administration Safety and Innovation Act, which includes the Prescription Drug User Fee Amendments of 2012 (PDUFA V). As directed by Congress in the Food and Drug Administration Amendments Act of 2007, FDA developed the proposed enhancements for PDUFA V in consultation with drug industry representatives, patient and consumer advocates, health care professionals, and other public stakeholders. These goals are described in "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017."⁴ Under the PDUFA V goals, FDA agreed to develop a dedicated drug development communication and training staff within the Center for Drug Evaluation and Research (CDER) and augment the Manufacturers Assistance and Technical Training Branch (MATTB) staff in the Center for Biologics Evaluation and Research (CBER) to focus on enhancing communication between sponsors and FDA during drug development.

CDER and CBER agreed to publish this joint guidance for industry and review staff on best practices for communication between sponsors and FDA during drug development. CDER and CBER gathered review staff best practices and incorporated input from interested parties to inform the content of this guidance.

The IND phase of drug development is the time during which human trials of investigational drugs are conducted. From FDA's perspective, the IND phase of drug development spans the time from the first IND-related submission (including a pre-IND or Biosimilar Initial Advisory (BIA) meeting request or an original IND) to the submission of a marketing application. The

⁴ <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>

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IND phase may also 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 is not limited to the IND phase because it also includes drug discovery and early development of compounds before IND submission and may include clinical trials conducted in other countries outside a U.S. IND.⁵

Each year, sponsors and FDA engage in thousands of communications, including meetings and teleconferences, during the IND phase of drug development. Because these communications are often opportunities to share information and provide critical advice (e.g., trial design, dose selection, analytical similarity assessment, nonclinical study requirements, manufacturing and facility issues), it is important that interactions be conducted efficiently and consistently, with clear, concise, and timely communication.

III. FDA'S PHILOSOPHY REGARDING COMMUNICATION WITH SPONSORS

Ideally, sponsors and FDA work collaboratively during the drug development process, having a shared public health goal of early availability of safe, effective, and high-quality drugs to the American public. In this process, sponsors and FDA have distinct roles and primary areas of responsibility.

- Sponsors' primary responsibilities are managing the overall development of their drugs (e.g., supporting well-designed and well-conducted nonclinical and clinical trials for approval while ensuring patient safety and drug quality), determining the nature and timing of regulatory submissions to their INDs, soliciting input and guidance from FDA during the course of their development programs, and providing well-organized and complete IND submissions (including amendments and supplementary information) to FDA for review.
- FDA's primary responsibilities with respect to INDs are, during all phases of investigation, to ensure the safety and rights of subjects, and, during phase 2 and phase 3, to help ensure that the quality of the scientific evaluation of a drug is adequate to permit the evaluation of the drug's effectiveness and safety.⁶ FDA also has the important responsibility of enforcing requirements related to good clinical practice (GCP) and human subject protections (HSP). FDA reviews IND submissions and takes regulatory actions (e.g., clinical hold) as appropriate. FDA review staff also play active roles during drug development by providing advice and feedback to sponsors on specific trials and overall development programs based on their review of IND submissions and in meetings conducted between sponsors and FDA. Finally, FDA promotes the advancement of regulatory science by authoring FDA and international guidances, conducting and

⁵ For more information on the use of information relating to foreign clinical trials in INDs and applications for marketing approval submitted to FDA, see the guidance for industry and FDA staff *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁶ 21 CFR 312.22

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participating in public workshops and public or private consortia, collaborating with academia, publishing in medical and trade journals, and presenting scientific and regulatory topics at professional conferences.

FDA believes that the timely review of IND submissions with appropriate feedback to sponsors can result in greater efficiency of the drug development process. At the sponsor's request, FDA will, if possible, provide advice on specific matters relating to an IND. Examples include providing advice on the adequacy of technical data to support an investigational plan, the design of a clinical trial, and whether proposed investigations are likely to produce the data and information needed to meet requirements for a marketing application.⁷ Because the complexity and importance of material submitted to an IND will vary by therapeutic indication and drug development stage, the review divisions retain the flexibility to determine the extent of review and feedback provided for each submission. For drugs developed under expedited programs, such as breakthrough therapy and fast track, sponsors receive more intensive guidance on an efficient drug development program with increased interactions and communications with FDA, including meetings.⁸

FDA believes that scientific and regulatory recommendations provided during drug development meetings with sponsors may result in more efficient and robust development programs. This philosophy is articulated in 21 CFR 312.47, 21 CFR 312.82, FDA's meetings guidances,⁹ CDER's Manuals of Policies and Procedures (MAPPs), and CBER's Standard Operating Policy and Procedures (SOPPs). Sponsors can request meetings with FDA at any time during drug development, and FDA strongly encourages sponsors to request the critical milestone meetings, and BIA or BPD meetings identified in the references cited above. FDA's decision to grant or deny meeting requests is resource-dependent and is based on the maturity of the drug's development at the time of the meeting request, taking into consideration the potential utility of the meeting. The procedures for requesting and conducting effective meetings between sponsors and FDA are fully described in the meetings guidances.

Timelines established by statute and/or regulation apply to the review of certain submission types (e.g., initial IND submissions) and CDER and CBER strive to review and provide timely feedback for other types of submissions that lack such required review timelines (e.g., a new phase 2 protocol under an active IND or a new clinical study protocol for products in the BPD program), as resources allow. CDER has documented its good review practices and principles

⁷ 21 CFR 312.41(b)

⁸ See CDER MAPP 6025.6 *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics* (<https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>) and CBER SOPP 8212 *Management of Breakthrough Therapy-Designated Products: Sponsor Interactions and Status Assessment Including Rescinding* (<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm506010.htm>).

⁹ See the guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* and *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

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during the IND phase of drug development in a MAPP.¹⁰ Incorporation of the principles outlined in the MAPP into IND review processes is resource-dependent and intended to improve safety oversight and facilitate effective communication between sponsors and FDA during drug development. The MAPP lists timelines for the review of and response to certain IND submissions, including recommended timelines where there is no required timeline (e.g., some safety-related submissions, drug development submissions without regulatory timelines where communication to the sponsor is often critical and recommended, and other submissions where communication with the sponsor may be needed). Although FDA review staff continually strive to meet the recommended review timelines for IND submissions described in the MAPP, they must balance this work with other critical public health responsibilities, including new drug application/biologics license application (NDA/BLA) review and oversight of drug safety.

FDA may at any time during the course of an IND communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information. Unless the communication is accompanied by a clinical hold order under 21 CFR 312.42, FDA communications with a sponsor under 21 CFR 312.41 are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to FDA.¹¹

IV. SCOPE OF INTERACTIONS BETWEEN THE SPONSOR AND THE REVIEW TEAM

Regulatory project managers (RPMs) oversee projects, processes, and programs. RPMs in CDER review divisions or CBER review offices are commonly referred to as review division RPMs. Other RPMs that operate in specific functional areas of FDA are sometimes referred to as process managers or program managers. Collectively, the review division RPMs and specific functional area RPMs are referred to as FDA RPMs.

FDA RPMs communicate on FDA's behalf via written correspondence, email, fax, or telephone. FDA RPMs are also the primary contacts for facilitating the timely resolution of technical, scientific, and regulatory questions, conflicts, or communication challenges between sponsors and the review teams.

The review division RPM is the *primary* point of contact for communications between a sponsor and FDA during the life cycle of drug development. As a co-leader of the FDA review team, the review division RPM has comprehensive knowledge of the drug and its regulatory history.

However, there are limited circumstances during drug development when it is appropriate for sponsors to directly contact FDA RPMs other than the review division RPMs, such as contacting:

¹⁰ See CDER MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*.

¹¹ 21 CFR 312.41(c)

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- CDER's Office of Pharmaceutical Quality (OPQ) regulatory business process managers (RBPMs). They manage meeting requests, regulatory submissions, and other inquiries that are solely related to chemistry, manufacturing, and controls, including facility and product quality issues.
- CDER's Office of Surveillance and Epidemiology safety RPMs. They manage regulatory submissions and other inquiries related to proprietary names, biosimilar suffixes, human factors, and Sentinel/Active Risk Identification and Analysis assessments.
- CDER's Formal Dispute Resolution Project Manager. This person manages sponsor requests for resolving scientific and/or medical disputes that cannot be resolved at the division level.¹²

There are also limited circumstances when sponsors may use certain FDA points of contact for responses to basic or procedural drug development questions not directly linked to an existing or planned development program. These contacts may be in specific functional areas and serve as an alternative means to obtain general information or address issues that arise in the context of the regulatory process. The circumstances, contacts, and resources are described in detail in section VIII., Additional Contacts.

CDER and CBER are aware that at times sponsors wish to communicate directly with reviewers assigned to their INDs to expedite the exchange of information and to facilitate timely progress in their drug development programs. Such communications are strongly discouraged and sponsors should not directly contact FDA reviewers. It is critical that sponsor inquiries be directed to the appropriate FDA RPM to ensure that requests are appropriately communicated to and considered by the review team members, including supervisors as appropriate. CDER and CBER strive to provide timely and accurate advice and feedback to sponsors that represent the review teams' current thinking on the issue, and this is best accomplished by adhering to the communication procedures described above and throughout this guidance. Direct contact by sponsors with review team members may interrupt their work on other critical assignments and may lead to responses that have not been vetted by the appropriate members of the review teams and supervisors. The feedback and advice provided may thus not accurately or comprehensively capture FDA's thinking or be properly documented in the IND.

In rare cases, however, and with supervisory approval, it may be appropriate for FDA review team members to communicate directly with sponsors regarding specific, limited issues related to their drug development programs. In all such cases, the FDA review team member will document the conversation in a memorandum to the IND and provide a copy of that record to the appropriate FDA RPM for sharing with the rest of the FDA review team. Decisions to allow such limited direct contact between sponsors and FDA reviewers will be made on a case-by-case basis by FDA management and represent an exception to usual best practices.

¹² 21 CFR 10.75

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Independent consultants in the pharmaceutical field, whether working on behalf of specific sponsors or on their own behalf, who have basic drug development questions should use existing FDA resources listed in section VII.I, Resources for Sponsors, and/or the contacts listed in section VIII., Additional Contacts, if needed. An independent consultant working on behalf of a specific sponsor who seeks advice regarding the sponsor's drug development program should be authorized to do so in writing by the sponsor before initiating contact with FDA staff and should follow the procedures outlined above (i.e., direct requests to the appropriate FDA RPM).¹³

If a sponsor encounters challenges in obtaining timely feedback to inquiries to an FDA RPM, it should contact the project manager's next level supervisor (e.g., the review division's chief of the project management staff (CPMS) or branch chief). This generally results in timely resolution of the issue. If a sponsor continues to encounter challenges in obtaining timely feedback, it may wish to communicate with review team supervisors or division or office management officials. Such requests generally should be directed to the review division's CPMS/branch chief so they can be communicated appropriately to the requested official and a mutually agreeable time can be arranged for a conversation by telephone. It is helpful if the sponsor provides the review division's CPMS/branch chief with background information on the purpose of the request to assist in determining the proper official to handle the call and also to allow the FDA official to adequately prepare for the call to make most efficient use of the allotted time. All such communications will be documented by either the review division's CPMS/branch chief or the designated FDA official to the IND and shared, as appropriate, with other review team members.

To streamline communications and have a mutual understanding of the preferences and expectations for sponsor and FDA communications during drug development, FDA recommends that sponsors and FDA RPMs, particularly the review division RPMs responsible for managing the applications, establish a mutually agreeable communication strategy. The communication strategy can be established early in the development program (i.e., around the time of IND submission) and adjusted at any time when there are outstanding issues (e.g., feedback on a new protocol) or modifications to the development program that might warrant more frequent or possibly less frequent interactions. A communication strategy might include the preferred method(s) (e.g., email versus telephone) and frequency of communications and/or approaches for managing information requests and responses (e.g., one request at a time versus bundled requests). As part of a communication strategy, sponsors and FDA should share contact information for alternative backups (e.g., the CDER review division CPMS or the CBER alternative project management staff) and the mutual expectations for the timing of responses to inquiries (see section VI., General Expectations for Timing of Communications).

A formal communication plan may be established for drug applications reviewed in the PDUFA Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs (the Program)¹⁴ and for biologic biosimilar applications reviewed under the Biosimilar User Fee Act (BsUFA). If established, the plan should be discussed and agreed to at the

¹³ 21 CFR 312.23(a)(1)(viii) describes the information to provide in an IND when a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization.

¹⁴ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327030.htm>

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presubmission meeting. The formal communication plan contains a mutually agreed-upon alternative approach to the timing and nature of interactions and information exchange between FDA and the sponsor. The formal communication plan should specify those elements of the Program that FDA and the sponsor agree are unnecessary for the application under review, if applicable.

For breakthrough therapy-designated drugs, FDA and the sponsor should establish a formal communication plan at the initial comprehensive multidisciplinary meeting. The plan includes the expectations on the timing and format of interactions and information exchange. As is the case for all drug development plans, the review division RPM is the primary point of contact.¹⁵

V. TYPES OF ADVICE THAT ARE APPROPRIATE FOR SPONSORS TO SEEK

During the life cycle of drug development, sponsors routinely solicit feedback from FDA on both scientific and regulatory issues. The breadth and frequency of advice sought can vary according to the experience of the sponsor, as well as the novelty and development stage of the proposed drug. During the IND phase of drug development, sponsors often solicit advice at critical junctures in their development programs. These topics include, but are not limited to the following:

- Regulatory (e.g., plans for submission of proprietary name requests, plans to defer or waive specific studies, development plans with other FDA centers (e.g., the Center for Devices and Radiological Health for combination products), applicability of an expedited program)
- Clinical/statistical (e.g., planned clinical trials to support effectiveness compared to a placebo or to demonstrate noninferiority to an active control, validity of outcomes and endpoints, trial size, enrichment designs)
- Safety (e.g., safety issues identified in nonclinical studies and early clinical trials, immunogenicity, size of the overall safety database, concerns related to particular populations, postapproval pharmacovigilance plans, risk evaluation and mitigation strategies (REMS), plans for human factors studies, issues related to evaluation of abuse potential)
- Clinical pharmacology and pharmacokinetics (e.g., dose selection and population, use in specific populations, drug-drug interactions)
- Nonclinical pharmacology, pharmacokinetics, and toxicology (e.g., genetic toxicology, reproductive and developmental toxicology, carcinogenicity, mechanism of action)
- Product quality (e.g., analytical similarity assessment, proposed shelf life and stability studies, delivery systems, characterization of drug substance/product, facility compliance)

¹⁵ See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

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with good manufacturing practices, comparability of lots used in clinical trials and commercial lots)

- Pediatrics (e.g., proposed pediatric development plan, dosing)

Because FDA resources are limited, sponsors are strongly encouraged to first seek answers to their scientific and regulatory questions from the multitude of resources available to them, such as the FDA resources described in section VII.I., Resources for Sponsors. Sponsors also can employ an independent consultant for assistance in conceiving strategic drug development and regulatory plans. Doing this allows both sponsors and FDA to conserve their respective resources to address the more complex and challenging drug development and regulatory science issues.

When soliciting feedback from FDA, sponsors should keep in mind the following:

- FDA policy positions are typically documented and described in FDA guidances, MAPPs, and SOPPs.
- Complex scientific and technical drug development questions should be directed to the FDA RPM, typically the review division RPM, via either a submission or through the formal meeting request process.
- General questions that cannot be answered by using existing resources can be directed to an FDA RPM, to the designated enhanced communication staff within each FDA center, or to CDER's Division of Drug Information (DDI) (see section VIII., Additional Contacts). Depending on the nature and complexity of the question(s), FDA will either respond to the question(s) or redirect the sponsor to an alternative pathway for receiving a response (e.g., other FDA subject matter expert, formal meeting request process).

VI. GENERAL EXPECTATIONS FOR TIMING OF COMMUNICATIONS

FDA recognizes that timely and effective communication during the IND phase of drug development provides sponsors with information they seek to inform the design of studies and trials, as well as product quality information, intended to support approval of a future marketing application. FDA staff therefore try to respond to sponsor questions promptly, while balancing FDA public health priorities and other work obligations. Note that responses to safety-related inquiries will be prioritized higher than other inquiries in alignment with FDA's previously stated primary responsibilities with respect to INDs.

During the course of these collaborative interactions, sponsors sometimes pose questions to FDA that they perceive as simple or clarifying questions with the expectation that only minimal time will be needed for an FDA response. However, what may appear to the sponsor to be simple or clarifying questions may be more complex and necessitate significant review and communication among review team members, including internal meeting(s), before an answer can be provided. For example, questions that involve interpretation of regulations and statutes, or application of

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existing FDA policy to novel circumstances, are often complex (*not simple*) and therefore demand significant vetting and response time. Similarly, questions involving combination products usually demand additional time to solicit and consider feedback from multiple FDA centers and offices. In all cases, FDA needs to take a thoughtful approach to answering sponsor questions both efficiently and comprehensively, particularly when the questions could have an important effect on critical decisions in development programs or that represent FDA views related to the evidence that will be used to support marketing.

Complex scientific/technical, policy, or regulatory questions are best posed to FDA in either requests for formal meetings or in formal submissions. Traditionally, FDA has taken a collaborative approach to responding to questions included in meeting packages and in submissions, according to their respective prespecified timelines as follows:

- **Meetings.** Communications that involve sharing results and information at critical milestones during drug development or at the appropriate stage of development for a biosimilar product, or are necessary for a stalled development program to proceed, are best addressed in formal meetings between FDA and sponsors (e.g., face-to-face meeting, teleconference, or written response only (WRO)). Timelines for FDA feedback to sponsors via the formal meeting process are described in the PDUFA and BsUFA agreements¹⁶ and in FDA's formal meetings guidances.¹⁷ This FDA feedback includes: preliminary comments, final meeting minutes, and responses to questions posed in WRO requests.
- **Submissions.** Hundreds of supporting documents might be submitted to an IND during its life cycle that require varying degrees of review and for which communication with the sponsor may be needed. Some submissions have regulatory-mandated timelines for reviewing and providing feedback to the sponsor that are described by statute or regulation (e.g., some safety-related submissions, complete response to clinical hold¹⁸) while other submissions have FDA-established goals for review and feedback (e.g., in a MAPP). These latter submission types include some safety-related submissions, drug development submissions without regulatory timelines where communication to the sponsor is often critical and recommended (e.g., a new protocol or protocol amendment), and other submissions where communication with the sponsor may be needed.

For all other sponsor inquiries that are received via telephone, email, or in a submission without a prespecified review timeline described in a MAPP and include specific questions for FDA's consideration, the FDA RPM will strive to *acknowledge* such communications via telephone or email within 3 business days of receipt by the FDA RPM. FDA's acknowledgment will:

¹⁶ See <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm> or <https://www.fda.gov/forindustry/userfees/biosimilaruserfeactbsufa/default.htm>.

¹⁷ See the guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* and *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

¹⁸ 21 CFR 312.42(e)

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- Include the response itself, if available within the acknowledgment time frame;
- Include an estimated time frame for division response to question(s);
- Inform the sponsor that its question(s) involve consultation with other FDA parties (e.g., policy questions where legal input is necessary, questions about combination products where other centers or offices are involved) and therefore an estimated response time frame will be forthcoming;
- Recommend that the sponsor submit a formal meeting request (e.g., face to face, teleconference, or WRO); or
- Recommend that the sponsor contact another specialized functional area in FDA (e.g., import/export, orphan products or rare diseases, pediatric therapeutics)

Similarly, sponsors should:

- Acknowledge receipt of FDA's information requests (written or otherwise)
- Provide the appropriate FDA RPM with an estimated response time

Because sponsor delays in responding, or lack of response, to FDA information requests can negatively affect later development, it is equally important for sponsors to respond completely and promptly to FDA requests.

Note that although FDA will attempt to adhere to all established or estimated response timelines, FDA may not always be able to meet these timelines. If unexpected complex issues arise during the review of a submission, FDA will provide an answer when it is fully developed, rather than adhering to a timeline when doing so may provide incomplete information to a sponsor. The timing of FDA response may also be negatively affected if the review team experiences an unexpected shift in work priorities or team staffing. In these cases, the FDA RPMs fully intend to keep sponsors apprised of changes to the estimated response timeline. When sponsors encounter delays in obtaining an FDA response to questions for which they have solicited feedback, the following stepwise approach should be taken:

- Contact the appropriate FDA RPM, typically the review division RPM, for a status update after the expected amount of time for FDA response has passed (e.g., the timelines described in a MAPP);

Or

Contact the appropriate FDA RPM, typically the review division RPM, for a status update after the estimated response time has passed (i.e., the estimated FDA-response date communicated to the sponsor previously)

- Contact the appropriate FDA RPM's next level supervisor for assistance in eliciting a response from the FDA RPM

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- Contact the appropriate division or office management officials for assistance in eliciting a response from the FDA RPM's next level supervisor
- Contact CDER's Enhanced Communication Team (ECT) or CBER's Ombudsman for assistance should the division or office management officials fail to respond

VII. BEST PRACTICES AND COMMUNICATION METHODS

Effective and timely communication between FDA and sponsors promotes understanding of mutual goals and is invaluable to the drug development process. Central to this is the ability to communicate clearly, both verbally and in writing, inside and outside the formal meeting format. It is also important that FDA and sponsors have a common understanding of terms and phrasing used in communications with each other, and that they are used consistently by both parties. In FDA communications related to INDs, as a best practice FDA staff will:

- Use words such as *shall*, *must*, *required*, or *requirement* to convey a statutory or regulatory requirement.
- Use the following words to communicate advice (e.g., on trial design), comments, or current thinking: *advisable*, *critical*, *important*, *may be appropriate*, *should*, *consider*, *discourage*, *encourage*, *prefer*, *recommend*, *suggest*, or *urge*. Because FDA has the advantage of viewing the spectrum of drug development data and information across sponsors, indications, and drug classes, FDA is able to communicate advice to sponsors with that expertise in mind, while upholding commercial confidentiality.

The IND phase of drug development is typically a multiyear process, and FDA recognizes that new data will become available and that scientific and regulatory advances and changes in clinical practice may occur during this time. Because sponsors are ultimately responsible for managing the overall development program for their proposed drugs, sponsors should monitor for advances in the field and/or changes in FDA guidance, and inquire if those changes may necessitate changes in prior FDA recommendations for their development programs. Although FDA reviewers consider new information and revise recommendations as needed, they try to support and adhere to their prior critical recommendations when appropriate. Changes in recommendations are expected to be based on new scientific or safety information or advances in clinical practice that make earlier FDA recommendations outdated, inappropriate, or unethical. In such cases, review staff via the FDA RPMs should inform sponsors in writing of these changes and the rationale behind the changes.

Both FDA and sponsors use various communication methods to focus discussions to effectively exchange information and resolve issues. Because there are different business cultures, communication styles, preferences, and documentation needs, there is no single best communication method. Rather, there are best practices that enhance each method. For example, telephone communication between a sponsor and the FDA RPM may be more effective than email for time-sensitive matters. A best practice would be to follow up after the telephone

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call with a written communication (e.g., email, submission, correspondence) so that there is documentation of decisions, agreements, or action items that arose during the interaction.

The best practices and communication methods described within this section are intended to identify means of exchanging information in ways that permit efficient, timely, and targeted review of and response to sponsors' questions. Communication via any of these methods (except meetings where numerous attendees participate) should be conducted via the FDA RPM, typically the review division RPM, rather than FDA reviewers, team leaders, or senior management to ensure that the advice is appropriately vetted and documented.

A. Formal Meetings Between FDA and Sponsors

Meetings are useful in resolving questions and issues raised during the life cycle of drug development. There are important reasons for sponsors to discuss development plans with FDA. FDA can provide valuable scientific and regulatory advice, resulting in more efficient and robust development programs. FDA can also help sponsors understand the evidence that will be necessary to demonstrate effectiveness, safety, highly similar or no clinically meaningful differences, and product quality. It is critical for sponsors to ascertain FDA's views on the applicable statutory and evidentiary requirements well in advance of submission of a marketing application to ensure an efficient development program.

Meetings between FDA and a sponsor at critical junctures in drug development can be especially helpful in minimizing wasteful expenditures of time and resources and thus in speeding the drug development and evaluation process.

These milestone meetings under PDUFA include pre-IND, end-of-phase 1 (EOP1), end-of-phase 2 (EOP2), and pre-NDA/BLA meetings.

- Pre-IND meetings are valuable for understanding the mechanism of actions of the drug and possible study designs and initiating dialogue regarding drug development in its early stages. They can prevent clinical hold issues from arising and aid sponsors in developing a complete IND. FDA encourages sponsors to request a pre-IND meeting for the following: a drug not previously approved or licensed; a new molecular entity (NME), especially one with a novel pharmacologic mechanism; a planned marketing application intended to be submitted under the 505(b)(2) regulatory pathway; drugs for which it is critical to public health to have an effective and efficient drug development plan (e.g., drugs for counter-terrorism, drugs to treat life-threatening or severely debilitating illnesses); drugs with substantial early development outside the United States; a planned human factors development program; and drugs with adequate and well-controlled trials to support a new indication. However, a sponsor of any IND can request a pre-IND meeting.
- EOP1 meetings are useful to review and reach agreement on the design of phase 2 controlled clinical trials and to discuss issues related to the proposed drug development program, including pediatric study plans, as appropriate. Because of limited resources, FDA has traditionally encouraged sponsors to request an EOP1 meeting only for drugs

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intended to treat life-threatening and severely debilitating illnesses, particularly situations where approval based on phase 2 trials or accelerated approval may be appropriate.¹⁹

- EOP2 meetings are of considerable importance in determining the safety of, and sufficiency of data (e.g., on dose selection) for, proceeding to phase 3, and for planning a complete and well-designed phase 3 development program. EOP2 meetings serve to evaluate the phase 3 plan and protocols, the adequacy of current studies and plans to assess pediatric safety and effectiveness, evaluate the human factors validation plan, and identify any additional information necessary to support a marketing application for the uses under investigation. FDA encourages sponsors to request an EOP2 meeting for NMEs or major new uses of marketed drugs. However, a sponsor of any IND can request an EOP2 meeting.
- Pre-NDA/BLA meetings are helpful in acquainting FDA reviewers with the format and content of the planned marketing application, including labeling and risk management activities (if applicable), presentation and organization of data, dataset structure, acceptability of data for submission, as well as the projected submission date of the marketing application. They are also intended to uncover major issues, identify studies intended to establish the drug's safety and effectiveness, discuss the status of pediatric studies, and discuss statistical analysis methods, or the results of analyses. FDA encourages sponsors to request pre-NDA/BLA meetings for all planned marketing applications, particularly applications to be reviewed under the Program.

Meetings under BsUFA include BIA and BPD Type 1 through Type 4 meetings. These meetings are intended to support an iterative process of interactions during the biosimilar development phase. They are based on the stage of development of the biosimilar product and on the amount and type of data and information provided to support the meeting.

- A BIA meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the Public Health Service Act (PHS Act) may be feasible for a particular product, and, if so, general advice on the expected content of the development program. This meeting type does not include any meeting that involves substantive review of summary data or full study reports.
- A BPD Type 1 meeting is a meeting that is necessary for an otherwise stalled drug development program to proceed (e.g., meeting to discuss clinical holds, dispute resolution meeting, a special protocol assessment meeting, or a meeting to address an important safety issue).
- A BPD Type 2 meeting is a meeting to discuss a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing BPD program. This meeting type can include substantive review of summary data, but does not include review of full study reports.

¹⁹ 21 CFR part 312, subpart E

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- A BPD Type 3 meeting is an in-depth data review and advice meeting regarding an ongoing BPD program. This meeting type includes substantive review of full study reports, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding additional studies, including design and analysis.
- A BPD Type 4 meeting is a presubmission meeting to discuss the format and content of a complete application for an original biosimilar biological product application under the Program or supplement submitted under 351(k) of the PHS Act. The purpose of this meeting is to discuss the format, content, and presentation of the planned submission and other items, including identification of those studies that the sponsor is relying on to support a demonstration of biosimilarity or interchangeability, discussion of any potential review issues, identification of the status of ongoing or needed studies to adequately address the Pediatric Research Equity Act, and acquainting FDA reviewers with the general information to be submitted in the marketing application (including technical information).

Feedback to sponsors via the formal meeting process is provided in three main formats: face-to-face meetings, teleconferences/videoconferences, and WRO responses. Detailed information about meeting requests, packages, scheduling, preparation, conduct, and documentation (meeting minutes) are described in other guidances.²⁰ The timelines are described in the PDUFA and BsUFA agreements.

The following represent meeting-related best practices for the various meeting formats.

- **Meeting Requests**
 - Before requesting a meeting with FDA, sponsors should use the extensive sources of drug development information that are publically available. See section VII.I., Resources for Sponsors.
 - Sponsors are encouraged to request feedback via formal meetings with FDA at the major drug development milestones under PDUFA or at the appropriate stage of a biosimilar development program under BsUFA as described above. FDA typically grants meeting requests at these major milestones or at the appropriate stage of development of a biosimilar product.
 - Sponsors should only submit milestone meeting requests or biosimilar-related meeting requests when drug development has progressed to the point where a full discussion of issues germane to that development stage is possible. Premature meeting requests are often denied by FDA or are re-categorized by FDA as a different meeting type.

²⁰ See the guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* and *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

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- In lieu of a traditional meeting with FDA (i.e., face to face or teleconference), sponsors also can seek feedback through WRO requests for any type of PDUFA meeting (e.g., Types A, B, B (EOP), or C) or for BIA and BPD Type 2 BsUFA meetings.²¹ FDA may also exercise discretion in converting a traditional meeting request for a pre-IND or Type C meeting to WRO responses under PDUFA. The number of questions posed in a WRO request should be no more than what would be reasonably expected to be addressed in a traditional meeting's allotted duration.
- Sponsors must outline the purpose of the meeting in the meeting request.²²
- Sponsors' meeting requests should include their preferred dates and must include the requested FDA attendees.²³ The FDA RPMs should take these preferences into consideration when scheduling meetings.
- Sponsors should try to anticipate future needs and, to the extent practical, combine discussion of drug development issues into the fewest possible meetings.
- **Meeting Packages.** Premeeting preparation is critical for achieving a successful meeting with productive discussion and exchange of information.
 - Sponsors should submit meeting packages for all meeting formats, including WRO, within the timelines described in the PDUFA and BsUFA agreements. FDA grants and schedules meetings expecting that appropriate information to support the discussion will be submitted with sufficient time for review and preparatory discussion. Thus, the meeting or WRO may be canceled or denied if the meeting package is inadequate or not received within the specified timelines.
 - Sponsors should submit a limited number of clearly worded and targeted questions that directly address concerns about the drug development programs. The number of questions in a meeting package should not exceed what can be reasonably discussed within the duration of the allotted meeting time. The information and data provided by a sponsor in the meeting package should facilitate FDA responses to the questions asked.
 - Sponsors' meeting packages should be well organized and tabbed or bookmarked to enhance the reviewers' navigation within the packages both in preparation for and during the meetings.
 - The FDA RPM should send preliminary responses to sponsor questions before the meeting so that the meeting time can be dedicated to unresolved issues for which

²¹ Ibid.

²² See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022 (PDUFA VI) available at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>.

²³ Ibid.

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more discussion is needed. The timelines for preliminary responses are described in the PDUFA and BsUFA agreements and in FDA's formal meetings guidances. In the preliminary responses, FDA should provide high-level recommendations for important issues identified during the review of the meeting package, even if questions concerning those issues were not explicitly posed by the sponsor.

- **Meeting Conduct**

- Sponsor presentations generally are not needed because the information necessary for review and discussion should have been included in the meeting package. Instead, valuable meeting time should be reserved for a focused discussion of issues identified in the meeting package, particularly those that remain unresolved after FDA's preliminary responses have been sent to the sponsor or issues that have been raised in FDA's responses.
- The meeting facilitator should take into account the total meeting time available and keep the discussion focused on the questions posed by the sponsor in the meeting package, as well as relevant FDA preliminary responses. During the course of the meeting, the sponsor generally should not ask substantive questions that were not included in the meeting package, or present new data or information that was not previously provided to FDA or requested by FDA in its preliminary comments. Such questions and presentation of new data generally are best addressed in a subsequent communication or meeting request to FDA.
- Pre-IND, pre-NDA/BLA, BIA, and BPD Type 4 meetings should include a discussion of what constitutes a complete application to ensure there is mutual understanding and agreement on the contents of a complete application.
- Pre-NDA/BLA meetings for applications reviewed in the Program under PDUFA should include preliminary discussions of REMS or other risk management actions, the development of formal communication plans, and where applicable, timelines for review activities associated with a scheduling recommendation under the Controlled Substances Act for drugs with abuse potential. They should be held sufficiently in advance of the planned submission of the application to allow for meaningful consideration of FDA feedback and generally should not occur sooner than 2 months before the planned submission of the application.
- BPD Type 4 (pre-351(k) BLA) meetings for applications reviewed under BsUFA should include preliminary discussions of REMS, where applicable, patient labeling (e.g., Medication Guide and Instructions for Use), and, where applicable, the development of formal communication plans. They should be held in sufficient advance of the planned submission of the application to allow for meaningful consideration of FDA feedback, and generally should not occur sooner than 2 months before the planned submission of the application.

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- Sponsors and/or FDA attendees should summarize important discussion points, agreements, clarifications, and action items either at the end of the meeting or after the discussion of each question. It is helpful for the sponsor to provide an overall summary of the discussion at the end of the meeting to ensure that there is mutual understanding of meeting outcomes and action items.
- **Meeting Minutes.** FDA’s documentation of meeting outcomes, agreements, disagreements, and action items is critical to ensuring that this information is preserved for meeting attendees and future reference, because the FDA minutes are the official record of the meeting.
 - FDA minutes of meetings with sponsors are summaries of the important elements of the discussion and document the identified agreements, disagreements, and action items raised during the meeting. Meeting minutes are not intended to represent transcripts of the meetings. The summarized elements need not be described in exhaustive detail.
 - FDA RPMs will use established meeting minute templates to ensure that all important meeting information is captured.
 - FDA RPMs will issue meeting minutes, or provide responses to WRO requests, according to the timelines described in the PDUFA and BsUFA agreements.
 - If there is a significant difference in the sponsors’ and FDA’s understanding of the content of the meeting minutes, sponsors should seek resolution by notifying FDA of their understanding of the discrepancy.

B. Written Correspondence From FDA

FDA RPMs will use established letter templates to ensure consistency and accuracy in regulatory communications. FDA RPMs should send courtesy copies of written FDA correspondence to sponsors via secure email when the correspondence communicate regulatory actions (e.g., clinical hold) or are time-sensitive. The FDA RPM should send the courtesy copy via fax if secure email has not been established by the sponsor.

C. Submissions From Sponsors

During the life cycle of IND drug development, sponsors submit an array of regulatory submissions to FDA that require varying degrees of review, response, and/or feedback. The regulations under 21 CFR part 312, subparts B and C, describe types of submissions that are required during the IND phase of drug development.²⁴ Some are administrative in nature (e.g., investigator information, meeting request, request for inactivation, annual reports), others focus on patient safety (e.g., IND safety reports, response to clinical hold deficiencies), and others describe clinical and nonclinical trial plans (e.g., protocols and protocol amendments, pediatric study plans, information amendments including drug quality amendments) for which sponsors

²⁴ For example, 21 CFR 312.23, 312.30, 312.31, 312.32, 312.33, and 312.42.

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may seek FDA comment and advice. Detailed information about the review of IND submissions, including FDA-established or regulatory-mandated review timelines, is described in a CDER MAPP.²⁵

Sponsors must adhere to required timelines for their submissions (e.g., IND safety reports, annual reports).²⁶ In addition, FDA regulations describe the timing requirements for submitting a new protocol as an amendment to an IND that is already in effect or for when a new investigator is added to carry out a previously submitted protocol.²⁷ When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.²⁸ Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more often than every 30 days.²⁹

FDA regulations describe general principles of, as well as content and format requirements for, INDs.³⁰ Complete and well-organized sponsor submissions, in a format appropriate for scientific review, can increase the efficiency of FDA review. Form FDA 1571 is an administrative form that should accompany most IND submissions to indicate the content and purpose.³¹ All IND submissions should include overall summaries sufficient to allow FDA staff to understand the regulatory and developmental context of the submissions. The summary should list the objectives of the submission, and include any questions the sponsor would like addressed in writing. Questions to FDA should be framed within the regulatory context to allow reviewers to understand why the issue is important.

FDA encourages sponsors to identify issues or areas of concern in their submissions by describing them fully and soliciting feedback on specific areas of concern where further progression in drug development depends largely on receiving FDA feedback. Sponsors run the risk of not receiving timely FDA feedback, and therefore conducting inefficient or inadequate development programs, if they omit important information, do not identify the regulatory intent of the submissions, or provide insufficient detail.

²⁵ CDER MAPP 6030.9 *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*.

²⁶ 21 CFR part 312

²⁷ 21 CFR 312.30(b)

²⁸ 21 CFR 312.30(e)

²⁹ 21 CFR 312.31(c)

³⁰ 21 CFR 312.22 and 312.23

³¹ 21 CFR 312.23(a)(1)

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D. Acknowledging Receipt of Communications

FDA RPMs will send written acknowledgments of receipt of certain submissions that have review timelines (e.g., charging request, request for fast track designation). They will also strive to acknowledge receipt of questions received from sponsors via telephone calls, emails, and other submissions within 3 business days of receipt. The acknowledgment may include the response itself, an estimated response time frame, notification that the question(s) have been consulted to other offices or centers with an undetermined response time frame, a recommendation to submit the questions via a formal meeting request, or redirection to another specialized functional area in FDA (e.g., import/export).

Sponsors should likewise acknowledge receipt of FDA information requests and provide an estimated response time.

E. Email Between FDA and Sponsors

Use of secure email allows transparent and complete communication between FDA and sponsors although it is not a substitute for formal submissions (e.g., new INDs and amendments); formal submissions should be submitted to the respective center's document room (paper submissions) or via the electronic gateway, as applicable. FDA communication via unsecure email cannot include confidential commercial information (e.g., trade secrets, manufacturing, or patient information). Therefore, sponsors should establish secure email with FDA to allow for communications that may include confidential commercial information.³²

Sponsors should contact the Office of Information Management and Technology (OIMT) to request secure email.³³ OIMT provides requestors with general industry standard practices and instructions on how to obtain FDA digital certificates but does not otherwise provide outside support. If a digital certificate has expired, sponsors should send a signed message with the current digital signature to the email address provided on the Electronic Regulatory Submission and Review web page.

F. General Telephone Calls Between FDA and Sponsors

General or administrative questions are suitable for communications between sponsors and FDA RPMs via telephone. However, when complex, regulatory, or technical issues are discussed during the course of a telephone conversation between the sponsor and the FDA RPM, the caller should follow up with a written communication (e.g., email, sponsor submission, FDA correspondence) to document the discussion and/or respond to information requested during the conversation. Telephone calls, even when documented in the administrative record, are not a substitute for formal submissions such as a formal meeting request, IND amendment, or a

³² Sponsors that are unable to establish secure email should contact the appropriate review division to discuss acceptable alternative arrangements for communication.

³³ See the Electronic Regulatory Submission and Review web page for contact information (<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm2007043.htm>).

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request for a special protocol assessment. Depending on the nature of the questions presented during the conversation, the sponsor may be referred to the formal meeting process for a fuller discussion of the issue(s) with additional review staff and management.

Both FDA RPMs and sponsors should exchange contact information for communicating time-sensitive issues (e.g., notification of clinical hold). This contact information should be included in out-of-office messages, whenever appropriate. This is particularly important during the 30-day period after submission of an original IND.

G. Faxes Between FDA and Sponsors

Faxes can be used when secure email has not been established between FDA and sponsors although they are not substitutes for formal submissions (e.g., new INDs and amendments); formal submissions should be submitted to the respective center's document room (paper submissions) or via the electronic gateway, as applicable. Before transmitting faxes, sponsors and FDA RPMs should contact their respective counterparts to arrange for confirmation of receipt. Given the volume of communications received by FDA and sponsors, this reduces the possibility that faxes will be overlooked. To facilitate accurate and timely routing, coversheets should be included with faxes.

H. Use of Out-of-Office Messages by FDA and Sponsors

Sponsors and FDA staff should alert others to their unavailability by using email or voicemail out-of-office messages, or by communicating a planned absence in advance by email or telephone. The messages should include an expected return time and contact information for other staff that may be able to assist in the interim, particularly for time-sensitive communications (e.g., notification of clinical hold). FDA RPMs should also include contact information for their divisions' CPMS in CDER or the alternative project management staff in CBER.

I. Resources for Sponsors

To disseminate a broad range of information in a manner that can be easily and rapidly accessed by interested parties, FDA develops and maintains web pages, portals, and databases, and participates in interactive media as a means of providing self-service tools for its stakeholders, including sponsors. Sponsor use of these tools allows FDA to focus its limited resources on providing advice regarding scientific and regulatory issues that fall outside of established guidance, policy, and procedures.

1. FDA Guidances

FDA uses guidance documents to explain its current thinking on policy, scientific, and/or regulatory issues.³⁴ FDA guidances are useful for industry, FDA staff, and other stakeholders who may refer to them to address such matters as the design, manufacturing, and testing of regulated products; scientific issues; format and content of marketing applications; and

³⁴ 21 CFR 10.115

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inspection and enforcement policies. In general, FDA guidances do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. Stakeholders can use an alternative approach if the approach satisfies the requirements of applicable laws and regulations. For available guidances, see the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

2. FDA Policy and Procedures

CDER's MAPPs document CDER internal policies and procedures, while CBER's SOPPs document CBER internal policies and procedures. Both MAPPs and SOPPs are made available to the public for purposes of transparency regarding FDA processes.

- A listing of CDER MAPPs can be found at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>
- A listing of CBER's SOPPs can be found at <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm>

3. FDA Basics for Industry

The FDA website contains two web pages that provide basic information for industry.

The FDA Basics for Industry web page provides basic information about the regulatory process in addition to resources to better understand how to work with FDA. It is intended to improve communication between FDA and industry. The FDA Basics for Industry web page can be found at <https://www.fda.gov/forindustry/fdabasicsforindustry/default.htm>.

The Investigator-Initiated Investigational New Drug (IND) Applications web page includes links to information for investigators about submitting INDs to FDA and can be found at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm>.

4. FDA Interactive Media

FDA uses interactive media to communicate information about emerging science, new policies, procedures, guidances, MAPPs, SOPPs, and public advisory committee meetings or workshops that affect or can inform drug development. To stay informed, sponsors and review staff should subscribe to interactive media. A listing of interactive media resources can be found at <https://www.fda.gov/NewsEvents/InteractiveMedia/default.htm>.

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5. FDA Presentations

CDER's Presentation Library provides access to information about FDA policies and procedures presented to external audiences at meetings, conferences, and workshops sponsored or co-sponsored by FDA. The information covers a range of topics, including, for example, user fees, drug advertising and marketing, genomics, drug quality, and nonprescription drugs. Materials and overviews from some of these meetings are listed in the Presentations Library at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm074833.htm>.

CDER's web-based outreach program provides presentations about the work performed by the CDER offices. A listing of available presentations can be found at <https://www.fda.gov/BiologicsBloodVaccines/InternationalActivities/ucm273267.htm>.

6. FDA Labeling and Approvals

CDER's Drugs@FDA database contains information about FDA-approved brand name and generic prescription and nonprescription human drugs and the biological therapeutic products regulated by CDER. It includes most of the approvals since 1939 and the majority of patient information, labels, approval letters, reviews, and other information for drug products approved since 1998. The database can be used to view approval history and find all drugs with a specific active ingredient, consumer information, therapeutically equivalent drugs for an innovator or generic, generic drugs for an innovator, and labels for approved drugs. The database can be found at <https://www.accessdata.fda.gov/scripts/cder/daf>.

CDER's Biologics Products & Establishments web page contains searchable information and supporting documents for approved NDAs regulated by CDER, licensed biological products (except for therapeutic biological products regulated by CDER), premarket approvals, humanitarian device exemptions, and cleared 510(k) submissions. The web page also contains information regarding 510(k) blood establishment computer software, donor screening assays for infectious agents and HIV diagnostic assays, a complete list of vaccines licensed for immunization and distribution in the United States, and reports including the User Fee Billable Biologic Products and Potencies Approved Under Section 351 of the PHS Act report. This web page can be found at <https://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm>.

The FDA Online Label Repository is a searchable list of licensed products and establishments; it contains the most recent drug listing information companies have submitted to FDA. The repository can be found at <https://labels.fda.gov/>.

The FDA New Pediatric Labeling Information Database is a searchable list that highlights key pediatric information from the studies submitted in response to pediatric legislative initiatives. For information on new pediatric information that has been added to product labeling since September 9, 2007, see <https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>.

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7. *FDA Rules and Regulations*

FDA publishes regulations and other notices in the *Federal Register*, the Federal Government's official publication for notifying the public of many kinds of agency actions. The FDA Rules and Regulations web page contains information about the notice and comment rulemaking process, the review of proposed and final rules, and related resources. See <https://www.fda.gov/RegulatoryInformation/RulesRegulations/default.htm>.

8. *FDA-Funded Scientific Research Results*

FDA publishes the results of FDA-funded scientific research. The broad availability of scientific information and underlying data allow for the critical review, replication, and verification of findings that are central to the scientific method. Making research findings and the digital data supporting those findings accessible and analyzable promotes robust and open communication with the scientific community thereby bolstering the credibility of scientific findings and the regulatory decision-making based upon those findings. See <https://www.fda.gov/ScienceResearch/AboutScienceResearchatFDA/ucm433459.htm>.

9. *Code of Federal Regulations*

The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the *Federal Register* by the departments and agencies of the Federal government. Final rules are integrated into the CFR by the Office of the Federal Register and Government Publishing Office staff. Regulations under 21 CFR part 312 contain the procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, FDA of INDs.³⁵ These are done on a yearly basis. See <https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR>.

The Electronic Code of Federal Regulations (e-CFR) is an unofficial editorial compilation of CFR material and *Federal Register* amendments. It is not an official legal edition of the CFR. The Office of the Federal Register updates the material in the e-CFR on a daily basis. Generally, the e-CFR is current within 2 business days. See <http://www.ecfr.gov>.

VIII. ADDITIONAL CONTACTS

As stated in section IV., Scope of Interactions Between the Sponsor and the Review Team, the review division RPM is the primary point of contact between sponsors and FDA during drug development. Reviewers, team leaders, and senior management generally should not be contacted directly. However, in certain limited circumstances, sponsors can directly contact other FDA RPMs (see examples in section IV) or FDA staff who:

- Serve as resources in specific functional areas (e.g., product quality, pediatrics, orphan drugs or rare diseases, combination products, GCP, import/export, product jurisdiction,

³⁵ 21 CFR 312.1

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biosimilar development) for the purposes of obtaining direct answers to simple regulatory, procedural, or administrative questions related to those functional areas

- Serve as an alternative means to obtain general information (e.g., CDER's DDI, Small Business and Industry Assistance (SBIA), and ECT; CBER's MATTB; CDER or CBER Ombudsman)
- Address issues that arise in the context of the regulatory process (e.g., ombudsmen)

Inquiries sent to any of the specific functional areas or general contacts identified herein should not include questions that are integral to an existing or planned drug development plan (e.g., questions concerning clinical trial design, amount of data needed to support future phases of development or approval, nonclinical study requirements). Those types of questions should always be directed to the appropriate FDA RPM, typically the review division RPM, because those questions are best answered by review staff who have properly considered the question within the context of the sponsor's overall development plan, as well as having vetted their advice with appropriate review team members and documented the advice or decisions rendered to the sponsor. By using these additional contacts and resources appropriately, sponsors may receive timely and comprehensive responses to basic or procedural questions in these functional areas that they can apply in parallel with the scientific, technical, and regulatory advice they receive directly from the review division RPMs during the course of their drug development programs. Basic or procedural drug development questions not tied to an existing or planned development program (e.g., IND exemptions, expanded access, adverse event reporting, FDA forms) can be directed to DDI/MATTB if not identified separately here.

When a sponsor chooses to contact one of these resources via email, the review division RPM should be copied on the email when the questions and subsequent responses may have bearing on review division activities or communications related to the question(s) at hand. Similarly, when one of the FDA resources is responding directly to a sponsor question, the appropriate FDA RPM, when known and when appropriate, should be copied. This ensures that the FDA RPM, and therefore review team members, are aware of pertinent information or advice conveyed to sponsors. When contacting an ombudsman, the sponsor can request that the ombudsman consider its communications confidential; therefore, the FDA RPM may or may not be copied on inquiries and responses between these two parties.

A. CDER

1. Biomarker Qualification Program

The Biomarker Qualification Program encourages biomarker development by providing a framework for development and regulatory acceptance.

Contact information can be found on the Biomarker Qualification Program web page at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm20086360.htm>.

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2. Controlled Substance Staff

The Controlled Substance Staff (CSS) promotes the public health through the medical science-based assessment of the abuse potential of investigative and marketed drugs. CSS accomplishes this by providing consultation services to CDER review divisions as FDA's experts in the area of drug abuse and dependence and also serving as liaisons to the Drug Enforcement Administration for FDA's role in the drug scheduling process under the Controlled Substances Act. CSS responds to inquiries about the drug scheduling process and the study of abuse potential in animal and human studies.

See the Controlled Substance Staff web page at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180753.htm>.

3. Division of Drug Information

The DDI responds to a broad variety of public inquiries. It is staffed with a team of pharmacists and other health professionals who provide expert advice and guidance regarding all aspects of CDER activities to U.S. and international consumers, health care professionals, insurance companies, regulated industry, academia, law enforcement, FDA, and other government agencies.

The DDI can be contacted for responses to questions not related to a specific development program in a functional area that is not already listed within this section (e.g., FDA forms, adverse event reporting, IND exemptions).

Contact information can be found on the CDER Division of Drug Information web page at <https://www.fda.gov/aboutDDI>.

4. Division of Pediatric and Maternal Health

The Division of Pediatric and Maternal Health (DPMH) oversees quality initiatives that promote and necessitate the study of drug and biological products in the pediatric population, and improve pregnancy- and lactation-related information in product labeling. DPMH collaborates with stakeholders both inside and outside FDA to facilitate the collection of clinically relevant, evidence-based information that advances the informed use of medicines in children and women of childbearing potential.

Pediatric email: pedsdrugs@fda.hhs.gov

Maternal health email: cder.pmhs@fda.hhs.gov

5. Emerging Technology Team

The Emerging Technology Team (ETT), located in OPQ, is a centralized group for external inquiries on novel product design and manufacturing technologies likely to improve product safety, identity, strength, quality, and purity. It supports innovation by providing a forum for

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sponsors to engage FDA early in development and ensures consistency, continuity, and predictability in review and inspection. ETT also evaluates existing guidance, policy, and practice and helps sponsors identify and develop strategies to address potential challenges with respect to developing and implementing novel technologies.

Contact information can be found on the Emerging Technology Program web page at <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm523228.htm>.

6. Enhanced Communication Team

The ECT is composed of individuals in the Office of New Drugs (OND) who are experienced and knowledgeable about the drug review process, interact regularly with review division staff, and are skilled in facilitating communications between sponsors and FDA staff. ECT is a point of contact for general questions about the drug development process or for clarification on which OND review division to contact with questions. ECT is also a secondary point of communication for sponsors who are encountering challenges in communicating with the review teams for their INDs. When sponsors encounter such challenges, ECT facilitates eliciting review division responses to sponsor questions as described in section VI., General Expectations for Timing of Communications.

In addition to the tasks described above, ECT is responsible for identifying and disseminating best practices for enhanced communication to CDER staff involved in the review of INDs. Also, in collaboration with CDER's training staff, ECT develops and provides training programs for both CDER staff and sponsors on best practices for communication.

Contact information can be found on the Enhanced Communication web page at <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327281.htm>.

7. Import/Export

The Import Export Compliance Branch serves as the coordinator for human drug import and export compliance issues.

Contact information for general import compliance questions and export certificate and compliance questions can be found on the Import Export Compliance Branch (IECB) web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ImportsandExportsCompliance/default.htm>.

8. Office of Pharmaceutical Quality

OPQ is dedicated to ensuring product quality. OPQ's work provides a uniform drug quality program with oversight across all manufacturing sites, whether domestic or foreign, and across all drug product areas — new drugs, biologics, biosimilars, generic drugs, and nonprescription drugs.

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OPQ's RBPMs are located in the Office of Program and Regulatory Operations. RBPMs are the central point of contact for inquiries related to product quality. Application-specific inquiries related to product quality should be directed to the responsible RBPM; if not known, sponsors should contact CDER-OPQ-Inquiries@fda.hhs.gov.

Additional information can be found on the Office of Pharmaceutical Quality web page at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm418347.htm>.

9. Ombudsman

The CDER Ombudsman serves as a point of contact for informal advice or referrals and also provides an alternative means to address issues that arise in the context of the regulatory process. The Ombudsman receives questions and investigates complaints from regulated industry, law firms, and consultants, and informally resolves disputes between those entities and CDER. These disputes can be of a regulatory, scientific, or administrative nature.

In addition, the Ombudsman can assist with resolution of scientific differences of opinion among staff. The Ombudsman performs these duties while adhering to the ombudsman principles of confidentiality, neutrality, and informality. Every effort is made to respond to all complaints in a timely and effective manner. Upon request, communication with the Ombudsman will be considered confidential.

Contact information can be found on the CDER Ombudsman web page at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ContactCDER/CDEROmbudsman/default.htm>.

10. Rare Diseases Program

The Rare Diseases Program (RDP) facilitates, supports, and accelerates the development of CDER-regulated drug and biological products for the benefit of patients and families affected by rare disorders. The RDP coordinates development of CDER policy, procedures, and training related to rare disease drug development to promote consistency and innovation in review. Through collaborative work with external and internal rare disease stakeholders, RDP promotes evidence-based science as the basis for rare disease drug development. RDP is CDER's focal point to the rare disease drug development community for effective interactions with CDER.

Contact information can be found on the Rare Diseases Program web page at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm221248.htm>.

11. Small Business and Industry Assistance Program

The SBIA Program promotes productive interaction with regulated industry by providing timely and accurate information relating to development and regulation of human drug products

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primarily to domestic and international small businesses; however, such assistance is available to everyone.

Contact information can be found on the CDER Small Business & Industry Assistance (SBIA) web page at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/default.htm>.

12. Therapeutic Biologics and Biosimilars Staff

The Therapeutic Biologics and Biosimilars Staff (TBBS) is responsible for ensuring consistency in the scientific and regulatory approach and advice to sponsors regarding development programs for proposed biosimilar products and related issues regarding development programs for therapeutic biologics.

Contact information can be found through the Industry Information and Guidance link on the Biosimilars web page at <https://www.fda.gov/biosimilars>.

B. CBER

1. Manufacturers Assistance and Technical Training Branch

The MATTB provides assistance and training to industry, including large and small manufacturers and trade associations, and responds to general information requests for information received via email and telephone regarding CBER policies and procedures.

Assistance is available in numerous areas including clinical investigator information, adverse event reporting procedures, electronic submissions guidance and requirements, and information on how to submit an IND to administer an investigational product to humans.

Contact information can be found on the Manufacturers Assistance (CBER) web page at <https://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/manufacturingquestions/default.htm>.

2. Ombudsman

The CBER Ombudsman provides an alternative means to obtain information or address issues that arise in the context of the regulatory process. The Ombudsman receives questions and investigates complaints from regulated industry, law firms, and consultants, and works informally to resolve disputes between those entities and CBER. The Ombudsman may be engaged by the regulated industry to address issues of a regulatory, scientific, or administrative nature. In addition, the Ombudsman can assist with resolution of scientific differences of opinion among staff within FDA. The Ombudsman performs these duties while adhering to the ombudsman principles of confidentiality, neutrality, and informality. Every effort is made to respond to all complaints in a timely and effective manner. Upon request, communication with the Ombudsman will be considered confidential.

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The CBER Ombudsman serves as a point of contact for informal advice or referrals, including product jurisdiction information, and also manages the administrative process for formal dispute resolution requests.

Contact information can be found on the CBER Ombudsman web page at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122881.htm>.

C. Office of Special Medical Programs

The Office of Special Medical Programs (OSMP) serves as the FDA focal point for special programs and initiatives that are cross-cutting and clinical, scientific, and/or regulatory in nature. OSMP oversees and provides executive leadership to five program area offices and is comprised of the following: (1) Advisory Committee Oversight and Management Staff; (2) Office of Combination Products; (3) Office of Good Clinical Practice; (4) Office of Orphan Products Development; and (5) Office of Pediatric Therapeutics.

Contact information can be found on the Office of Special Medical Programs web page at <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/officeofscienceandhealthcoordination/default.htm>.

The following sections describe the five OSMP offices in further detail.

1. Advisory Committee Oversight and Management Staff

The Advisory Committee Oversight and Management Staff (ACOMS) works in close collaboration with all FDA centers to provide consistent operations and seek continuous improvements in the FDA advisory committee program. ACOMS ensures that all FDA committee management activities are consistent with the provisions of the Federal Advisory Committee Act, departmental policies, and related regulations and statutes. ACOMS provides guidance and assistance on the establishment, staffing, and management of public advisory committees to obtain the best possible expert scientific advice to assist FDA in meeting its public health mission.

Contact information can be found on the Advisory Committees web page at <https://www.fda.gov/AdvisoryCommittees/default.htm>.

2. Office of Combination Products

The Office of Combination Products (OCP) oversees the regulatory life cycle of combination products and serves as the focal point for resolving combination product issues. A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product.³⁶ OCP ensures the prompt assignment of combination products to FDA centers, the timely and effective premarketing review of such applications, and consistent and appropriate postmarketing

³⁶ 21 CFR 3.2(e)

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regulation of these products. When a product's classification and/or assignment is unclear or in dispute, OCP is also responsible for classifying the product as a drug, medical device, biological product, or combination product. OCP assigns the product to the appropriate FDA center or, in the case of a combination product, assigns it to the FDA center that will have primary responsibility for its regulation. In addition, OCP develops guidances and regulations to foster greater clarity, efficiency, and effectiveness of the regulatory process for combination products. OCP routinely provides responses to requests for assistance from regulated industry and FDA staff relating to premarketing review and postmarketing regulation of combination products.

Contact information can be found on the Office of Combination Products web page at <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/officeofscienceandhealthcoordination/ucm2018184.htm>.

3. Office of Good Clinical Practice

The Office of Good Clinical Practice (OGCP) is the focal point within FDA for HSP and GCP issues arising in clinical trials regulated by FDA. OGCP develops FDA-wide HSP and GCP policy for informed consent, institutional review boards, and clinical trial conduct; advises FDA staff and the research community on HSP and GCP issues; and coordinates FDA's Bioresearch Monitoring program, working with FDA's product centers and the Office of Regulatory Affairs. OGCP develops and conducts training and outreach programs, both internally and externally.

Contact information can be found on the Office of Good Clinical Practice web page at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018191.htm>.

4. Office of Orphan Products Development

The Office of Orphan Products Development (OOPD) advances the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions that affect fewer than 200,000 people in the United States, or that affect more than 200,000 people when the sponsor is not expected to recover the costs of developing and marketing a new drug. OOPD administers the orphan drug program that provides incentives for sponsors to develop products for rare diseases. It works on rare disease issues with the medical and research communities, professional organizations, academia, governmental agencies, industry, and rare disease patient groups. OOPD regularly participates in meetings with these stakeholders who seek input on orphan drug designation requests, humanitarian use device designation requests, rare pediatric disease designation requests, funding opportunities through the Orphan Products Grants Program and the Pediatric Device Consortium Grants Program, and other orphan product patient-related issues.

Contact information can be found on the Developing Products for Rare Diseases & Conditions web page at <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>.

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5. Office of Pediatric Therapeutics

The Office of Pediatric Therapeutics works to ensure timely access to medical products proven to be safe and effective for children. It is comprised of four distinct yet interrelated programs: scientific activities, ethics, safety, and international activities. The Office of Pediatric Therapeutics provides consultative services in ethics and neonatology, coordinates the monthly international Pediatric Cluster, administers the congressionally mandated postmarketing safety reviews for pediatric products, and provides scientific data and reports on pediatric product development activities.

Contact information can be found on the Pediatrics web page at <https://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm>.

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REFERENCES

Related Guidances³⁷

Draft guidance for industry *Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators*³⁸

Guidance for industry *Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization*

Guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*

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

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

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

Guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

Guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act*

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

Related CDER MAPPs³⁹

MAPP 4515.1 *Email Best Practices*

MAPP 6025.1 *Good Review Practices*

³⁷ Guidances can be found on the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

³⁸ When final, this guidance will represent the FDA's current thinking on this topic.

³⁹ MAPPs can be found on the Manual of Policies and Procedures web page at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

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MAPP 6025.6 Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics

MAPP 6030.9 Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review

Related CBER SOPPs⁴⁰

SOPP 8101.1 Regulatory Meetings With Sponsors and Applicants for Drugs and Biological Products

SOPP 8104 Documentation of Telephone Contacts With Regulated Industry

SOPP 8113 Handling of Regulatory Faxes in CBER

SOPP 8119 Use of Email for Regulatory Communications

SOPP 8212 Management of Breakthrough Therapy-Designated Products: Sponsor Interactions and Status Assessment Including Rescinding

⁴⁰ SOPPS can be found on the Biologics Procedures (SOPPs) web page at <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm>.