Best Practices for Communication Between IND Sponsors and FDA During Drug Development

Guidance for Industry and Review Staff

Good Review Practice

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Rachel Hartford at 301-796-0319 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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

December 2015
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Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff[1]

Good Review Practice

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

The purpose of this guidance is to describe best practices and procedures for timely, transparent, and effective communications between investigational new drug application (IND) sponsors[2] and FDA at critical junctures in drug[3] development, which may facilitate earlier availability of safe and effective drugs to the American public. This guidance describes:

- FDA's philosophy regarding timely interactive communication with IND sponsors as a core activity
- The scope of appropriate interactions between the review team and the sponsor
- The types of advice appropriate for sponsors to seek from FDA in pursuing their drug development program
- 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 21 CFR 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 CBER and CDER, unless otherwise specified.

- Best practices and communication methods to facilitate interactions between the FDA review team and the IND sponsor 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 a quality improvement process is dynamic and will continue to evolve over time with further feedback from sponsors and review staff. Thus, 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 FDA'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 FDA 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 of 2012, 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, CDER and CBER agreed to develop a dedicated drug development communication and training staff within CDER and augment the manufacturers assistance staff in CBER, focused on enhancing communication between FDA and sponsors during drug development. CDER's Enhanced Communication Team (ECT) liaison staff and CBER's Ombudsman serve as a secondary point of communication within FDA for sponsors who are encountering challenges communicating with the review team.[5]

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

[4] http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

[5] See the Enhanced Communication Web page at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327281.htm.

(i.e., those who responded to a notice published in the *Federal Register*[6] or who provided input directly to CDER's ECT) to inform the writing 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 meeting request or an original IND) to the submission of a marketing application. The 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 work-up of compounds before IND submission and may include clinical trials conducted in other countries outside a U.S. IND.[7]

Each year, sponsors and FDA engage in thousands of formal and informal 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, 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 IND SPONSORS

Ideally, IND 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, IND sponsors and FDA have distinct roles and primary areas of responsibility.

- Sponsors' primary responsibilities are managing the overall development of their drug (i.e., supporting well-designed and well-conducted nonclinical and clinical trials for approval while ensuring patient safety), determining the nature and timing of regulatory submissions to the IND, soliciting input and guidance from FDA during the course of their development program, 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 an 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 drugs is adequate to permit

[6] 79 FR 64397; October 29, 2014

[7] 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 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

an evaluation of the drug's effectiveness and safety.[8] 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 an active role 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 participating in public workshops and public/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 giving 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.[9] Because the complexity and importance of material submitted to an IND will vary by therapeutic indication and 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.[10]

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,[11] 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 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

[8] 21 CFR 312.22

[9] 21 CFR 312.41(b)

[10] See CDER MAPP 6025.6 *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics* (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm).

[11] See the guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants* and *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*. See also the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (when final, this guidance will represent the FDA's current thinking on this topic).

for requesting and conducting effective meetings between IND 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), as resources allow. CDER has documented its good review practices and principles during the IND phase of drug development in a MAPP.[12] 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 IND sponsors and FDA during drug development. The MAPP lists timelines for 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.[13]

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

The review division regulatory project manager (RPM) is the *primary* point of contact for communications between IND sponsors 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. The RPM is also the primary contact for facilitating the timely resolution of technical, scientific, and regulatory questions, conflicts, or communication challenges between the sponsor and the review team**.**

During drug development there are circumstances under which it is appropriate for sponsors to directly contact FDA project managers other than the review division RPM in CDER. These other project managers include the following.

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

[13] 21 CFR 312.41(c)

- CDER's Office of Pharmaceutical Quality regulatory business project managers 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 regulatory project managers manage sponsor requests for proprietary name review.

- CDER's Formal Dispute Resolution Project Manager manages sponsor requests for resolving scientific and/or medical disputes that cannot be resolved at the division level.[14]

There are also limited circumstances where sponsors may need to 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 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 IND to expedite the exchange of information and to facilitate timely progress in their drug development program. Such communications are strongly discouraged and sponsors should not directly contact FDA reviewers. It is critical that sponsor inquiries be directed to the review division 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 team's current thinking on the issue, and this is best accomplished by adhering to the communication procedures described above. Direct contact by sponsors with review team members may interrupt their work on other critical public health assignments and may lead to responses that have not been vetted by the appropriate members of the review team and supervisors, resulting in the possibility that the feedback and advice provided are not accurate and complete and are not properly documented in the IND file. Sponsors are advised that such informal responses may not accurately or comprehensively capture FDA's thinking.

In rare cases, however, and with supervisory approval, it may be appropriate for FDA review team members to communicate directly with sponsors regarding minor issues related to their drug development program. In all such cases, the FDA review team member will document the conversation in a memorandum to the IND file and to provide a copy of that record to the RPM for sharing with the rest of the FDA review team. Decisions to allow such limited direct contact between IND sponsors and FDA reviewers will be made on a case-by-case basis by FDA management, not the IND sponsor, and represent an exception to usual best practices, not the norm.

Independent consultants in the pharmaceutical field, whether working on behalf of a specific IND sponsor or on their own behalf, who have basic drug development questions should use

[14] 21 CFR 10.75

existing FDA resources (e.g., Web pages, guidances, MAPPs, SOPPs, interactive media, presentations) and/or the contacts listed in section VIII., Additional Contacts, if needed. Independent consultants working on behalf of a specific sponsor who seek advice regarding the sponsor's drug development program should be authorized by the sponsor before initiating contact with FDA staff on behalf of the sponsor and should follow the procedures outlined above (i.e., direct requests to the review division RPM).[15]

If sponsors encounter challenges in obtaining timely feedback to inquiries to the review division RPM, they should contact the RPM's next level supervisor (e.g., the review division's chief of the project management staff (CPMS) in CDER, review division's branch chief in CBER). This generally results in timely resolution of the issue. In some cases, sponsors may wish to communicate with review team supervisors or division or office management officials when sponsors continue to encounter challenges in obtaining timely feedback. Such requests generally should be directed to the review division 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 phone. It is helpful if the sponsor provides the 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 conduct any preparations needed in advance of the call to make most efficient use of the allotted time. All such communications will be documented by either the CPMS/branch chief or the designated FDA official to the IND file and shared, as appropriate, with other review team members.

To streamline communications and have a mutual understanding of the preferences and expectations for IND sponsor/FDA communications during drug development, it is recommended that sponsors and FDA project managers, particularly the review division RPM responsible for managing their application, establish a mutually agreeable communication strategy. The informal 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 contacts. 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 back-ups (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).

For breakthrough therapy-designated drugs, a formal communication plan is established at the initial comprehensive multidisciplinary meeting between FDA and the sponsor. 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

[15] 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.

contact for communications between FDA and sponsors for drugs developed under the breakthrough therapy program and other expedited programs.[16]

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 development, sponsors often solicit advice at critical junctures in their development program. 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, validity of outcomes and endpoints, trial size, enrichment designs)

- Safety (e.g., safety issues identified in nonclinical studies and early clinical trials, size of the overall safety database, concerns related to particular populations, postapproval pharmacovigilance plans, risk evaluation and mitigation strategies, plans for human factors studies, issues related to evaluation of abuse potential)

- Clinical pharmacology and pharmacokinetics (e.g., dose selection, 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., proposed shelf life and stability studies, delivery systems, characterization of drug substance/product, facility compliance 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. In doing so, this allows both sponsors and FDA to conserve their respective resources to address the more complex and challenging drug development issues.

[16] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

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/technical drug development questions should be directed to the FDA project manager, 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 project manager, to the designated enhanced communication staff within each FDA center, or to CDER's Division of Drug Information, (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 with sponsors 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. As such, FDA staff strive to respond to sponsor questions promptly while balancing FDA public health priorities and their other workload responsibilities, noting 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 being simple or clarifying questions with the expectation that only minimal time will be needed for an FDA response. However, what appear to the sponsor to be simple or clarifying questions are often more complex and necessitate significant review and communication among review team members, including conducting an internal meeting(s), before an answer can be provided. For example, questions that involve interpretation of regulations and statutes, or application of existing FDA policy to novel circumstances, are often complex (*not simple*) and therefore demand additional vetting and response time. Similarly, questions involving combination products usually demand significant time to solicit and consider feedback from multiple FDA centers. In all cases, FDA takes a thoughtful and measured approach to answering sponsor questions efficiently and comprehensively, particularly those questions that are likely to have an important impact on critical decision points 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 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 sending feedback to sponsors via the formal meeting process are described in Prescription Drug User Fee Act (PDUFA) and Biosimilar User Fee Act (BsUFA) agreements[17] and in FDA's formal meetings guidances.[18] 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 hold[19]) 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, received via telephone, email, or in a submission (i.e., a submission without a review timeline described in a MAPP), that include specific questions for which sponsors are seeking FDA feedback, FDA project managers will strive to *acknowledge* such communications via telephone or email within 3 business days of receipt by the FDA project manager. FDA's acknowledgment will:

- 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 are involved) and therefore an estimated response time frame will be forthcoming;

[17] See http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm or http://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm.

[18] See the guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants* and *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*. See also the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

[19] See 21 CFR 312.42(e).

- 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 project manager 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 strives 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 an IND submission, FDA will provide an answer when it is fully formed, rather than adhering to a timeline when doing so may not provide useful 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 project manager will try to keep sponsors apprised of changes to the estimated response timeline. When sponsors encounter delays in obtaining FDA response to questions for which they have solicited feedback, the following approach should be taken sequentially:

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

  Or

  Contact the appropriate FDA project manager, 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 project manager's next level supervisor for assistance in eliciting a response from the project manager

- Contact the appropriate division or office management officials for assistance in eliciting a response from the project manager

- Contact CDER's ECT or CBER's Ombudsman for assistance in eliciting a response from the project manager

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 orally 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.

- As a best practice, FDA staff will use the following words to communicate advice (e.g., on trial design), comments, or current thinking often include the following terminology: *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 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 staff recognize that new data will become available and that scientific 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 drug, sponsors should closely 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 program. Although FDA reviewers consider new information and revise recommendations as needed, they try to support and adhere to their prior critical recommendations where 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 project manager should inform sponsors in writing of these changes and the rationale behind the changes.

Both FDA and sponsors use various communication methods for focusing 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 project manager may be more effective than email for time-sensitive matters. A best practice would be to follow up after the phone 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 contact.

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 sponsors' questions. They were developed by gathering the experiences of CDER and CBER staff and by incorporating input from interested parties. Communication via any of these

methods (except meetings where numerous attendees participate) should be conducted via the FDA project manager, 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. 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 define adequate evidence of effectiveness, safety, and product quality. It is critical to efficient drug development for sponsors to ascertain FDA's views on the applicable statutory and evidentiary requirements well in advance of submission of an application.

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 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 proof of concept and initiating dialogue for drug development in its early stages. They can prevent clinical hold issues from arising and aid sponsors in developing a complete IND submission. FDA encourages sponsors to request a pre-IND meeting for the following: a drug not previously approved/licensed, a new molecular entity (NME), 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., counter-terrorism), 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. Because of limitations of FDA resources, it is common for review divisions to use the WRO meeting procedures for pre-IND meetings; however, in selected circumstances a face-to-face meeting or teleconference may be granted.

- 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 intended to treat life-threating and severely debilitating illnesses, particularly situations where approval based on phase 2 trials or accelerated approval may be appropriate.[20]

- EOP2 meetings are of considerable importance in planning later studies and in determining the safety of proceeding to phase 3. EOP2 meetings evaluate the phase 3 plan and protocols, the adequacy of current studies and plans to assess pediatric safety

[20] See 21 CFR part 312, subpart E.

and effectiveness, 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 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 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 appropriate statistical analysis methods, or results of analyses. FDA encourages sponsors to request pre-NDA/BLA meetings for all planned marketing applications, particularly applications to be reviewed under the PDUFA V Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs.[21]

Feedback to sponsors via the formal meeting process is provided in three main formats: face-to-face meetings, teleconferences, and WRO responses. Detailed information about meeting requests, packages, scheduling, preparation, conduct, and documentation (meeting minutes) are described in other guidances.[22] The timelines are described in 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 expansive 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 described above. FDA typically grants meeting requests at these major milestones.

  – Sponsors should only submit milestone 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.

[21] As part of its commitments in PDUFA V, FDA established a new review program to promote greater transparency and increased communication between the FDA review team and the applicant on the most innovative drugs reviewed by FDA. This new review program applies to all NME NDAs/original BLAs that are received from October 1, 2012, through September 30, 2017. See http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327030.htm.

[22] See the guidances for industry *Formal Meetings Between the FDA and Sponsors or Applicants* and *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*. See also the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

- In lieu of a traditional meeting with FDA (i.e., face-to-face or teleconference), sponsors also can seek feedback through WRO requests, specifically for pre-IND feedback and feedback that would otherwise have been requested in a Type C meeting request.[23] To conserve resources, FDA may also exercise discretion in converting a traditional meeting request for a pre-IND or Type C meeting to WRO responses. 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 should outline the purpose of the meeting in the meeting request.

- Sponsor's meeting requests should include their preferred dates and requested FDA attendees. FDA project managers 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 PDFUA 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 cancelled if the meeting packages are 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 and development program. The number of questions in a meeting package should not exceed what can be reasonably discussed within the duration of allotted meeting time.

  - Sponsors should provide sufficient data to support the questions being asked. If the meeting package is determined to be inadequate or too voluminous, the meeting may be rescheduled.

  - Sponsors' meeting packages should be well-organized and tabbed to enhance the readability of the background information both before and during the meeting.

  - FDA project managers should send preliminary responses to sponsor questions before the meeting so that the meeting time can be dedicated to unresolved issues for which more discussion is needed. In the preliminary responses, FDA should provide high-

[23] Ibid.

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 preserved for a focused discussion of issues identified in the meeting package, particularly those that are still unresolved after FDA's preliminary responses have been sent to the sponsor or that have been raised in FDA's responses.

  – Meeting facilitators should keep the discussion focused on the questions posed by the sponsor in the meeting package, as well as relevant FDA preliminary responses, taking into account the total time available for discussion of the questions. During the course of the meeting, sponsors should generally 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 their preliminary comments. Such questions and presentation of new data generally are best addressed in a subsequent communication or meeting request to FDA.

  – Pre-IND and pre-NDA/BLA 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.

  – Sponsors and/or FDA attendees should summarize important discussion points, agreements, clarifications, and actions 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 IND sponsors are not intended to represent a transcript of the meeting but rather are intended to summarize the important elements of the discussion while also identifying any agreements, disagreements, and action items that were identified during the meeting.

  – FDA project managers will use established meeting minutes templates to ensure that all important meeting information is captured.

- FDA project managers will issue meeting minutes, or provide responses to WRO requests, according to the timelines described in PDUFA and BsUFA agreements.

- If there is a significant difference in the sponsor's 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 project managers will use established letter templates to ensure consistency and accuracy in regulatory communications. Project managers should send a courtesy copy of written FDA correspondence to sponsors via secure email when such communications are time-sensitive or communicate actions (e.g., clinical hold). Project managers 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,[24] describe types of submissions that are required to be submitted by sponsors during the IND phase of drug development. 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 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

[24] See, for example, 21 CFR 312.23, 312.30, 312.31, 312.32, 312.33, and 312.42.

[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)

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. FDA Form 1571 is an administrative form that should accompany most IND submissions to indicate the content and purpose.[31] All IND submissions should include an overall summary sufficient to allow FDA staff to understand the regulatory and developmental context of the submission. The summary, which usually comprises the first page of the submission, should list the objectives of the submission, 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 an inefficient or inadequate development program that may increase the length of time to approval, if they omit important information, do not identify the regulatory intent of the submission, or provide insufficient detail.

D. Acknowledging Receipt of Communications

FDA project managers will send written acknowledgment 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 by the project manager. The acknowledgment may include: the response itself, an estimated response time frame, notification that the question(s) have been consulted to other offices/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

[29] 21 CFR 312.31(c)

[30] 21 CFR 312.22, 312.23

[31] See 21 CFR 312.23(a)(1).

include commercial confidential information (e.g., trade secrets, manufacturing, or patient information). Therefore, sponsors should establish secure email with FDA to allow for informal communications that may include commercial confidential information.[32]

Sponsors should contact the Office of Information Management (OIM) to request secure email.[33] OIM 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 informal communications between sponsors and FDA project managers via telephone. However, when complex, regulatory, or technical issues are discussed during the course of a telephone conversation between the sponsor and the FDA project manager, 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 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 project managers and sponsors should provide mutual names and telephone numbers for communicating time-sensitive issues (e.g., notification of clinical hold). This contact information should be included in out-of-office messages, whenever appropriate.

G. Faxes Between FDA and Sponsors

A fax can be used when secure email has not been established 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. Before transmitting the fax, sponsors and FDA project managers should contact their respective counterparts to arrange for confirmation of receipt. Given the volume of communications received by FDA, this reduces the possibility that faxes will be overlooked. To facilitate accurate and timely routing, a coversheet should be included with the fax. Faxes should be sent to FDA during official business hours (8:00 a.m. to 4:30 p.m. EST/EDT) Monday through Friday (except Federal government holidays).

[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 (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm2007043.htm).

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

IND sponsors and FDA staff should alert others to their unavailability by using email and voicemail out-of-office messages. 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 project managers should also include contact information for their division's 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 IND sponsors. Sponsor use of these tools allows for more effective utilization of limited FDA resources in providing advice on 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 and other stakeholders and FDA staff that may refer to them to address such matters as the design, manufacturing, and testing of regulated products; scientific issues; content and evaluation of applications for product approvals; and 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. However, 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 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

2. FDA Policy and Procedures

CDER's MAPPs document CDER internal policies and procedures. MAPPs are made available to the public to make CDER a more transparent organization. A listing of CDER MAPPs can be found at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

CBER's SOPPs document CBER internal policies and procedures. SOPPs are made available to the public to make CBER a more transparent organization. CBER's SOPPs are organized by area of activity. A listing of CBER SOPPs can be found at

[34] See 21 CFR 10.115.

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm.

3. FDA Basics for Industry

The FDA Web site contains two Web pages that provide basic information for industry.

The FDA Basics for Industry Web page is a portal to information frequently requested by industry about the regulatory process and to resources on understanding how to work with the FDA. It is intended to improve communication between FDA and industry by providing basic information about the regulatory process in a user-friendly format. The FDA Basics for Industry Web page can be found at http://www.fda.gov/FDABasicsforIndustry.

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 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm.

4. FDA Interactive Media

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

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 http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm074833.htm.

CBER's Web-based outreach program provides presentations about the work each of the CBER offices performs. A listing of available presentations can be found at http://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 http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

CBER's Biologics Products & Establishments Web page contains searchable information and supporting documents for approved NDAs regulated by CBER, licensed biological products (except for therapeutic biological products regulated by CDER), premarket approvals, humanitarian device exemptions, and cleared 510(k) submissions. It includes a complete list of licensed products and establishments and an FDA Online Label Repository. 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 http://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm.

The FDA 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 http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase.

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. FDA's Rules & Regulations Web page contains information about the notice and comment rulemaking process, the review of proposed and final rules, and related resources. See http://www.fda.gov/RegulatoryInformation/RulesRegulations/default.htm.

8. 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] See http://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR.

[35] 21 CFR 312.1

The Electronic Code of Federal Regulations (e-CFR) is a current, daily updated version of the CFR.[36] It is not an official legal edition of the CFR. The e-CFR is an unofficial editorial compilation of CFR material and *Federal Register* amendments. 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/cgi-bin/ECFR?page=browse.

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, and reviewers, team leaders, and senior management generally should not be contacted directly. However, in certain limited circumstances, sponsors can directly contact other FDA project managers (see examples in section IV) or FDA staff who: (1) serve as resources in specific functional areas (e.g., product quality, pediatrics, orphan drugs or rare diseases, combination products, GCP, import/export, product jurisdiction) for the purposes of obtaining direct answers to simple regulatory, procedural, or administrative questions related to those functional areas; (2) serve as an alternative means to obtain general information (e.g., CDER's Division of Drug Information (DDI), Small Business and Industry Assistance (SBIA), and ECT; CBER's Manufacturers Assistance and Technical Training Branch (MATTB); CDER or CBER Ombudsmen); or (3) 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 listed 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 project manager, 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 RPM during the course of their drug development program. Responses to other 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 listed separately here.

When sponsors do choose 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 review division

[36] See the Electronic Code of Federal Regulations Web page at http://www.ecfr.gov/cgi-bin/ECFR?page=userinfo.

RPM and/or respective FDA project manager, when known and when appropriate, should be copied. This ensures that the project manager, 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 project manager(s) may or may not be copied on inquiries and responses between these two parties.

A. CDER

1. 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 liaison 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 http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180753.htm.

2. 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 Division of Drug Information (DDI) Web page at http://www.fda.gov/aboutDDI.

3. 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 develop clinically relevant, evidence-based labeling and other communications that facilitate 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

4. 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 the staff in review divisions, 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 team for their IND. 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 IND sponsors on best practices for communication.

Contact information can be found on the Enhanced Communication Web page at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327281.htm.

5. Import/Export

The Import Operations Branch is the focal point for human drug import and export compliance issues.

Contact information for general imports compliance questions and export certificate and compliance questions can be found on the Import Operations Branch Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ImportsandExportsCompliance/default.htm.

6. 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 http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ContactCDER/CDEROmbudsman/default.htm.

7. Rare Diseases Program

The Rare Diseases Program (RDP) facilitates, supports, and accelerates the development of CDER-regulated drug and biologic 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 http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm221248.htm.

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

Contact information can be found on the CDER Small Business and Industry Assistance (CDER SBIA) Web page at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/default.htm.

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 http://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.

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 http://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 http://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 http://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.[37] OCP ensures the prompt assignment of combination products to FDA centers, the timely and effective premarket review of such applications, and consistent and appropriate postmarketing 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, and assigning the product to the appropriate FDA center; or in the case of a combination product, assigning 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 http://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/GCP policy for informed consent, institutional review boards, and clinical trial conduct, advises FDA staff and the research community on HSP/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 http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018191.htm.

[37] See 21 CFR 3.2(e).

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 persons but are not expected to recover the costs of developing and marketing a treatment drug. OOPD provides incentives for sponsors to develop products for rare diseases. They work 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 http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm.

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 http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm.

REFERENCES

Related Guidances[38]

Draft guidance for industry *Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators*[39]

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*

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

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

Related CDER MAPPs[40]

MAPP 4515.1 *Email Best Practices*

MAPP 6025.1 *Good Review Practices*

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*

[38] Guidances can be found on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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

[40] MAPPs can be found on the Manual of Policies and Procedures Web page at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

1235 **Related CBER SOPPs**[41]

1236

1237 SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and*
1238 *Applicants*

1239

1240 SOPP 8104 *Documentation of Telephone Contacts with Regulated Industry*

1241

1242 SOPP 8113 *Handling of Regulatory Faxes in CBER*

1243

1244 SOPP 8119 *Use of Email for Regulatory Communications*

1245

[41] SOPPS can be found on the Biologics Procedures (SOPPs) Web page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm.