PDUFA VI IND Communications Assessment

Final Report

PREPARED BY:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02420

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Executive Summary

Development of new drugs and biologics occurs in several stages: discovery, preclinical studies, clinical studies, Food and Drug Administration (FDA) review, and marketing and surveillance. To begin clinical studies for their new drugs and biologics, sponsors prepare Investigational New Drug (IND) submissions for FDA review. During the years of clinical studies (also known as the IND stage of drug/biologic development), sponsors and FDA communicate to discuss various aspects of drug development i.e. clinical trial design, endpoints, data, milestones, and next steps. Under the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI)—the current authorizing legislation for FDA review of new drugs and biologics—FDA committed to contracting with an independent third party to assess FDA-sponsor communication practices during the IND stage of new drug/biologic development. FDA enlisted Eastern Research Group, Inc. (ERG) to conduct the assessment.

To conduct the assessment, ERG developed a set of evaluation questions and metrics, data collection protocols and instruments, and a representative sample of 147 commercial INDs with communication activity between July 31, 2018 and July 31, 2019 (Table ES-1, Table ES-2). ERG then collected data about the INDs from FDA databases, observed FDA-sponsor meetings that occurred during this assessment period, collected data about other FDA-sponsor communications, and conducted separate surveys and interviews with sponsors and FDA reviewers for INDs in the sample. Based on quantitative and qualitative analyses of the data collected, ERG developed integrated answers to the evaluation questions along with a set of findings and recommendations.

Table ES-1. Sample of Commercial INDs Used in Assessment of Sponsor-FDA Communication Practices (n=147)

IND Trait	Categories		Representation in Sample
Sponsor size	Small		59 (40%)
	Medium		18 (12%)
	Large		37 (25%)
	Private		33 (23%)
BTD	With BTD		13 (9%)
RMAT	With RMAT		6 (4%)
FDA review office*	*CDER*	OAP	17 (12%)
		ODEI	24 (16%)
		ODEII	25 (17%)
		ODEIII	19 (13%)
		ODEIV	8 (5%)
		OHOP	26 (18%)
	CBER	OBRR	6 (4%)
		OCBQ	0 (0%)
		OVRR	6 (4%)
		OTAT	16 (11%)

IND Trait	Categories	Representation in Sample
Meeting type requested**	Type A	7 (3%)
	Type B	74 (30%)
	Type B (EOP)	51 (21%)
	Type C	115 (46%)
IND phase***	Phase 1	16 (11%)
	Phase 2	31 (21%)
	Phase 3	61 (41%)
	Multiple Phases	35 (24%)
	Other	4 (3%)

*These offices represented the organizational structure of the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) at the time of data collection. CDER's drug/biologic review offices and divisions have since been reorganized (see FDA's *website*).

**Meeting requests sum to 249; two meeting requests did not specify a meeting type, so the values for meeting types requested sum to 247.

***For IND phase, ERG used the most recent phase(s) that sponsors included in documents submitted to FDA.

BTD = Breakthrough Therapy Designation. RMAT = Regenerative Medicine Advanced Therapy. **CDER Offices:** OAP = Office of Antimicrobial Products. ODEI = Office of Drug Evaluation I. DCRP = Division of Cardiovascular and Renal Products. ODEII = Office of Drug Evaluation II. ODEII = Office of Drug Evaluation III. OHOP = Office of Hematology and Oncology Products. **CBER Offices:** OBRR = Office of Blood Research and Review. OCBQ = Office of Compliance and Biologics Quality. OVRR = Office of Vaccines Research and Review. OTAT = Office of Tissues and Advanced Therapies. EOP = End Of Phase.

Table ES-2. Communications Activity in Sample of Commercial INDs (n=147) During Assessment Period (July 31, 2018 to July 31, 2019)

Category	Communication Type	Number in Sample
Meeting-Related Communication	Meeting Requests	249
	Meeting Request Responses	237
	Meeting Packages	216
	Preliminary Comments	154
	Meetings Held (Including Written Responses Only, or WROs)*	161
	Meeting Minutes (Including WROs)*	152
Other	FDA IRs	647
	Sponsor Amendments	2,137
	Sponsor Questions and FDA Answers	369

*FDA considers WROs to be meetings and the final written communications (minutes) for these meetings. Therefore, ERG counted WROs as meetings held and as meeting minutes. For this assessment, ERG examined WROs differently for these two purposes; that is, ERG examined WROs against meeting metrics in the analysis of meetings and against meeting minute metrics in the analysis of meeting minutes.

Study limitations included the following: (1) sample sizes were too small to determine whether differences seen with less prevalent traits of interest (e.g., RMAT designation) were statistically significant, and (2) qualitative information from interviews and surveys was valuable in understanding good communication practices, challenges, and opportunities for improvement, but could not be used for quantification or statistical analysis.

Answers to Evaluation Questions

Using data collected from this assessment of current IND communication practices, ERG answered a set of evaluation questions for this final report. These questions and answers appear below.

1a. What are current FDA review staff and sponsor IND communication practices?

For the 147 INDs in the sample for this assessment, FDA review staff and sponsors communicated about INDs through:

- ***Formal meeting process,*** including sponsor meeting request, FDA response, sponsor meeting package, FDA preliminary comments, meeting, and meeting minutes. Sponsors and FDA reviewers stated that this process was an effective way of addressing substantive questions and issues that arise during the IND stage of development. Most meetings held were Type C (53%) or Type B (30%) and were held to address mainly clinical topics. During the one-year assessment period, the mean number of meetings per IND was 1.1; this number was statistically significantly higher for INDs with Breakthrough Therapy Designation (BTD). FDA staff nearly always used Agency templates for preliminary comments and meeting minutes. They often included regulatory/statutory and advisory language to distinguish between requirements and recommendations, as well as references to FDA guidance to help answer sponsor questions.

- ***Information Requests (IRs) and amendments.*** FDA reviewers sent IRs to sponsors to request clarification of data already submitted for the IND or more data; in about a quarter of cases, FDA included a due date for response (mean 7 days). Sponsors responded with amendments containing answers and additional data; they also submitted unsolicited amendments to provide additional information that FDA did not request, such as updates and additional protocols. Most IRs and amendments pertained to clinical topics. During the one-year assessment period, the mean number of IRs per IND was 4.4, and the mean number of amendments per IND was 14.3; these numbers were statistically significantly higher for INDs with BTD and for INDs in Phase 1. Sponsors also submitted questions and requests for comments on submissions to FDA, which Agency reviewers answered (mean 2.5 per IND during the one-year assessment period).

- ***Telephone and email communications.*** Outside of the meeting and IR/amendment process, communications consisted primarily of emails and telephone calls between FDA's Regulatory Project Manager (RPM) and the IND sponsor's authorized representative. Many RPMs preferred to communicate via email, which provides documentation of the interaction for reference; many IND sponsors asked about the RPMs' communication preferences early in the relationship. RPMs and sponsors agreed that email and telephone communication was an effective way of addressing logistical and relatively straightforward questions and issues, and that these communications were most frequent around the time of major development milestones and before major sponsor submissions to FDA. RPMs occasionally facilitated teleconferences that

included other reviewers during those periods. RPMs and sponsors also stated that the OND Meeting Support Team was helpful in assisting with meeting scheduling and logistics.

1b. To what extent do current IND communications incorporate recommended practices, guidances, and standard operating procedures?

FDA has recommended practices, guidances, and standard operating procedures[1] to help ensure that communications are efficient and effective. For the 147 INDs in the sample, FDA-sponsor communications generally conformed to these guidelines during the one-year assessment period:

- ***Timelines.*** FDA reviewers and IND sponsors sent most materials within the timelines outlined in the guidances. About half of sponsors' suggested meeting dates fell outside of recommended timelines (mean 9-21 days later, depending on the type of meeting requested).
- ***Content.*** About one-third of meeting requests contained all recommended items and about half contained all required items. The recommended item most often missing was proposed regulatory pathway. FDA guidance includes recommendations (not requirements) for meeting packages; about one-third of meeting packages included all recommended items.
- ***Point of contact.*** Per FDA guidance, sponsors almost always communicated with FDA via the RPM as the single point of contact. In rare instances, sponsor representatives with a lengthy history with FDA reviewers contacted those staff directly rather than through the RPM.
- ***Templates and language.*** Nearly all FDA reviewers used established templates for preliminary comments and meeting minutes. They typically used regulatory/statutory and advisory language to distinguish between what was required and what was recommended. In about half of cases, they included references to published FDA public guidances to help answer sponsor questions.

2. How do communication practices vary by IND characteristics such as sponsor size, special designations, review division, meeting type, and IND phase?

For the 147 INDs in the sample, during the one-year assessment period communication practices were generally consistent across sponsor sizes, FDA review offices and divisions, and meeting types. Communication practices were similar, but more frequent, for INDs with BTD and for INDs in Phase 1 trials. This finding is consistent with expectations given that BTD explicitly provides for more frequent communications, and more frequent communications are often needed during the early stages of drug/biologic development.

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[1] Guidances and Standard Operating Procedures include:

U. S. Food and Drug Administration. (2017). Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff

U. S. Food and Drug Administration. (2019). Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

U. S. Food and Drug Administration. (2017). Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA. Products Guidance for Industry

U. S. Food and Drug Administration. (2015). Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators Guidance for Industry.

U. S. Food and Drug Administration. Center for Biologics Evaluation Research (2019). SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products

3. How do FDA review staff and sponsors characterize IND communications during drug development?

For the 147 INDs in the sample, most FDA review staff and sponsor representatives surveyed and interviewed for this assessment characterized their communications as clear, effective, efficient, collaborative, and timely. They also stated that the timelines outlined in FDA guidances for meetings are reasonable and appropriate. In a few instances, interviewees noted that FDA reviewers or sponsor representatives were less responsive than typical, or that more meeting time was needed due to the novel or complex nature of the development program.

Most sponsors interviewed for this assessment characterized communications with FDA as very important in enabling them to improve or make decisions about their development programs—in order to make progress as efficiently and confidently as possible.

4. What practices help optimize IND communications, what challenges hinder optimum communications, and what steps can FDA take to improve communications moving forward?

Good practices for fostering transparency and predictability for FDA reviewers and sponsors included:

- ***Proactive and courtesy communications,*** such as sponsors providing courtesy copies of submissions and amendments, sponsors notifying the RPM of upcoming large submissions to the IND, FDA RPMs providing estimates for when they will respond to sponsor questions, and FDA RPMs providing due dates for sponsor responses to IRs. These practices helped FDA reviewers and sponsors plan their time effectively.

- ***Early submission*** of meeting packages and preliminary comments. Doing this made it easier for FDA reviewers and sponsors to review and respond to the materials in a timely manner.

- ***Use of templates and conformance with guidances*** to maintain consistency in written materials, making it as easy as possible to scan for, locate, and consider pieces of information.

IND sponsors and FDA reviewers interviewed for this assessment reported some challenges:

- ***Short time between FDA preliminary comments and sponsor responses and meetings.*** For some sponsors, receiving preliminary comments 48 hours before a meeting made it difficult to respond to comments and plan travel to FDA. For FDA reviewers, receiving additional data or questions from the sponsor within 48 hours of a meeting did not provide enough time to review materials, especially when the meeting package contained numerous or complex questions. Most sponsors and FDA staff agreed that moving timelines earlier could make it difficult to meet deadlines, however.

- ***Balancing sponsors' desire for early feedback and FDA's need for adequate data as a basis for scientifically sound advice.*** For sponsors, early feedback from FDA is extremely useful in shaping development programs in ways that optimize the likelihood of forward progress. During the assessment period, frustration sometimes ensued when sponsors hoped to receive early feedback and FDA reviewers instead directed sponsors to guidance because existing data were an insufficient basis for advice. There was no easy solution to this dilemma.

- ***Technical problems*** with the teleconference system in meetings. These problems sometimes disrupted meetings and prevented attendees from hearing each other, especially when one or more attendees participated via external cell phones.
- ***Uncertainty about when FDA would provide feedback*** about sponsor questions or submissions (occasional).
- ***Lack of responsiveness on the part of the RPM or the sponsor representative*** (uncommon).

Although they generally characterized their communications very favorably, IND sponsors and FDA reviewers interviewed for this assessment offered some suggestions for further enhancing these communications:

- ***Provide guidelines for how quickly FDA should respond*** to questions and submissions from sponsors submitted via email or telephone correspondence.
- ***Recommend that sponsors prepare the meeting package (to the point of near completeness) early,*** before submitting a meeting request.
- ***Provide guidelines to sponsors on the appropriate number and scope/complexity of questions*** for meetings to ensure that it is feasible to fully address the questions during the meeting.
- ***Continue FDA's focus on hiring and retaining talented review staff*** and rebalancing workloads and resources as necessary.

Findings and Recommendations

Based on the results of this assessment of current IND communication practices, ERG developed a set of findings and recommendations (Table ES-3) organized in two categories: overarching (related to IND communications overall) and specific (related to particular aspects of communication or portions of the IND drug development process).

Table ES-3. Findings and Recommendations Related to FDA-Sponsor Communication Practices During the IND Stage of Development

Type	No.	Finding	Recommendation(s)
Overarching	O1	During the IND stage of drug/biologic development, communications between IND sponsors and FDA reviewers are typically clear, effective, efficient, collaborative, and timely.	No action needed.
	O2	RPMs are effective in their role as the point of contact who coordinates all other communication activities with and for IND sponsors.	No action needed.
	O3	FDA staff usually complete work for IND meetings within specified timelines, but heavy workloads and regular staff turnover can make this challenging.	Continue FDA's efforts to hire and retain talented and qualified reviewers. Continue to rebalance workloads judiciously to ensure efficient use of resources.
	O4	Technical problems with FDA's teleconference systems sometimes cause disruptions in meetings with sponsors (and internal meetings as well).	Consider (1) capacity and technical testing for the current teleconference system, including with the use of external cell phones; (2) providing more handheld microphones for main conference rooms; and (3) providing a brief quick-reference guide for troubleshooting the system during meetings.
	O5	Proactive and courtesy communications facilitate transparency and predictability (FDA).	Add recommendations for these types of communications to guidelines or guidance: courtesy copies of submissions or amendments (sponsors), notification of upcoming responses or submissions (sponsors), estimates of when FDA will respond to sponsor questions (FDA), and due dates for sponsor responses to IRs (FDA).
	O6	FDA advice to sponsors remains consistent and stable throughout the IND's lifetime, except when new data warrants changes in advice. This is true even when there is turnover in FDA's review team.	No action needed.

Type	No.	Finding	Recommendation(s)
Specific	S1	Submitting meeting packages (sponsors) and preliminary comments (FDA) as early as possible helps the parties prepare effectively for meetings.	No action needed. Both parties attempt to do so to the extent feasible.
	S2	Sponsor meeting requests and meeting packages vary widely in completeness. In some cases, this is due to the stage of drug/biologic development.	Draft and pilot templates for meeting requests and meeting packages to make it easy to include more items or to be explicit why the items are not included (e.g., not applicable, or not yet available).
	S3	IND sponsors occasionally submit more questions (or more complex questions) than can be fully addressed during a meeting. They occasionally ask questions that are premature for the drug or biologic's phase of development.	Add guidelines on (1) the number and scope of questions that are appropriate for a single meeting package, and (2) exceptional circumstances when the sponsor should consider two meeting requests or FDA should consider a longer meeting.
	S4	The OND Meeting Team is helpful in managing meeting logistics, offloading burden from RPMs and making it easier for sponsors to arrive at meeting rooms on time.	Consider expanding OND Meeting Team to cover OPQ-led CMC-specific IND meetings and pre-NDA and pre-BLA meetings requested under the NDA or BLA.

OND = Office of New Drugs. OPQ = Office of Pharmaceutical Quality. CMC = Chemistry, Manufacturing, and Controls. NDA = New Drug Application. BLA = Biologics License Application.

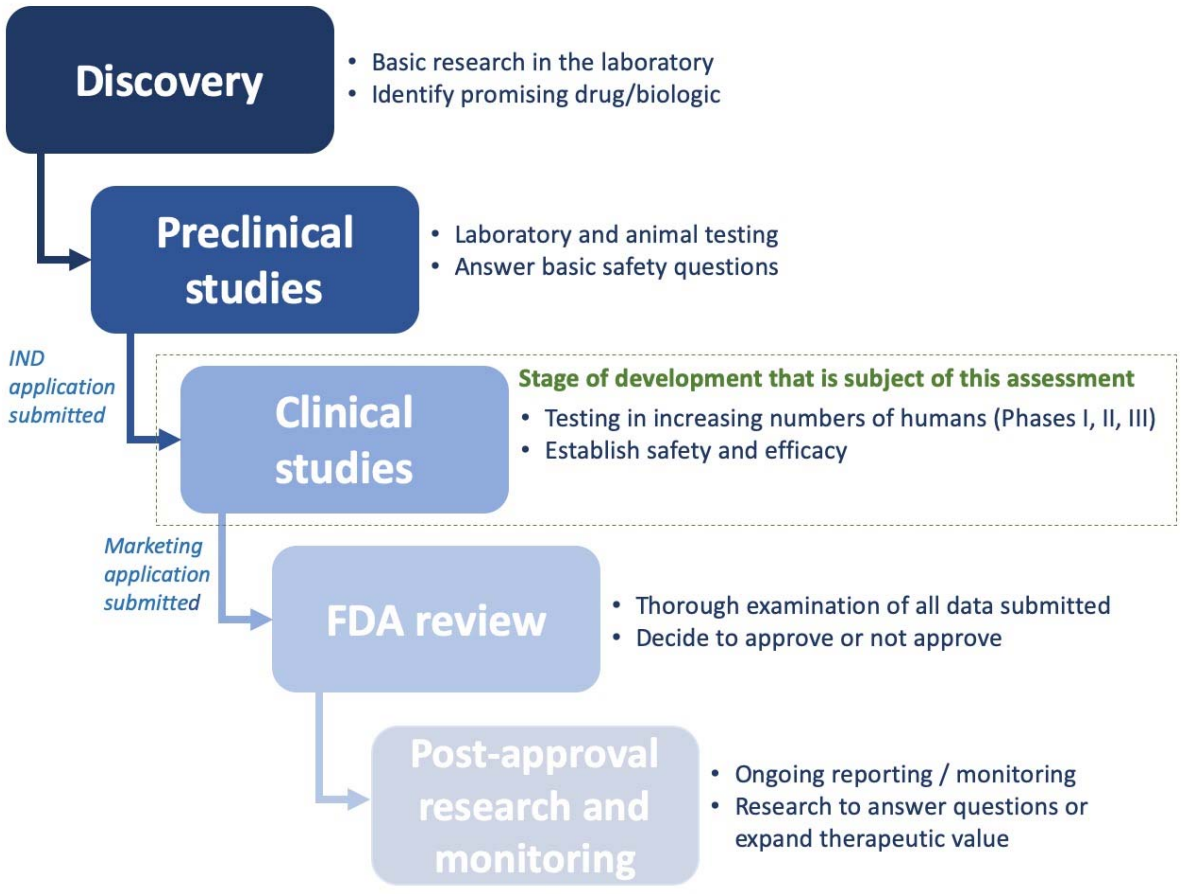
1. Introduction

1.1 PDUFA VI IND Communications

In the United States, development of drugs and biologics occurs in five main stages (Figure 1-1). Drug and biologic sponsors begin with basic research to discover promising substances, then conduct laboratory and animal studies to answer basic safety questions. In order to begin the next stage of development, clinical studies, sponsors must submit an IND application for review by FDA. FDA reviews animal study and toxicity data, manufacturing information, proposed clinical protocols, any prior human research data, and investigator information in order to determine whether clinical trials can be conducted safely.

If authorized, most INDs proceed through three major phases of clinical trials: Phase I trials with small numbers of healthy subjects, Phase II trials with small numbers of patients, and Phase III trials with large numbers of patients. Occasionally sponsors shorten or omit a phase—for example, if their IND has special designations such as Accelerated Approval, Breakthrough Therapy Designation (BTD), Fast Track, or Regenerative Medicine Advanced Therapy (RMAT) designation and results are strong enough that it would be unethical to delay treatment to a broader population. While sponsors have a wide degree of freedom in designing clinical trials, most request FDA advice and assistance to maximize the likelihood

Figure 1-1. Drug/Biologic Development Process



that their clinical trials and data will meet FDA standards. Effective communication during this stage of development is essential for generating enough data for a marketing application.

During the IND stage of development, sponsors and FDA reviewers communicate via:

- *Formal meetings*—Meetings between sponsor representatives and the FDA review team as requested by sponsors and granted by FDA (Figure 1-2).
- *Information Requests (IRs), amendments, and sponsor questions*—Requests from FDA reviewers for clarifications or additional data/analyses and submission of such information from sponsors, as well as questions from sponsors that FDA answers.
- *Email and telephone communication*—Email, telephone calls, and conference calls, usually to discuss straightforward questions or issues.

In Fiscal Year (FY) 2015, FDA created a draft guidance for review staff and industry detailing best practices for communication between FDA and sponsors during drug/biologic development, with the final guidance published in FY 2018. These guidances (Table 1-1) outline guidelines for timing of communications and set expections for good practices for communication between IND sponsors and FDA to ensure communciation efficiency, consistency, and clarity. Special designations, such as BTD and RMAT designation, also affect the timing and frequency of communication.

Figure 1-2. Formal Meetings During the IND Stage of Drug/Biologic Development

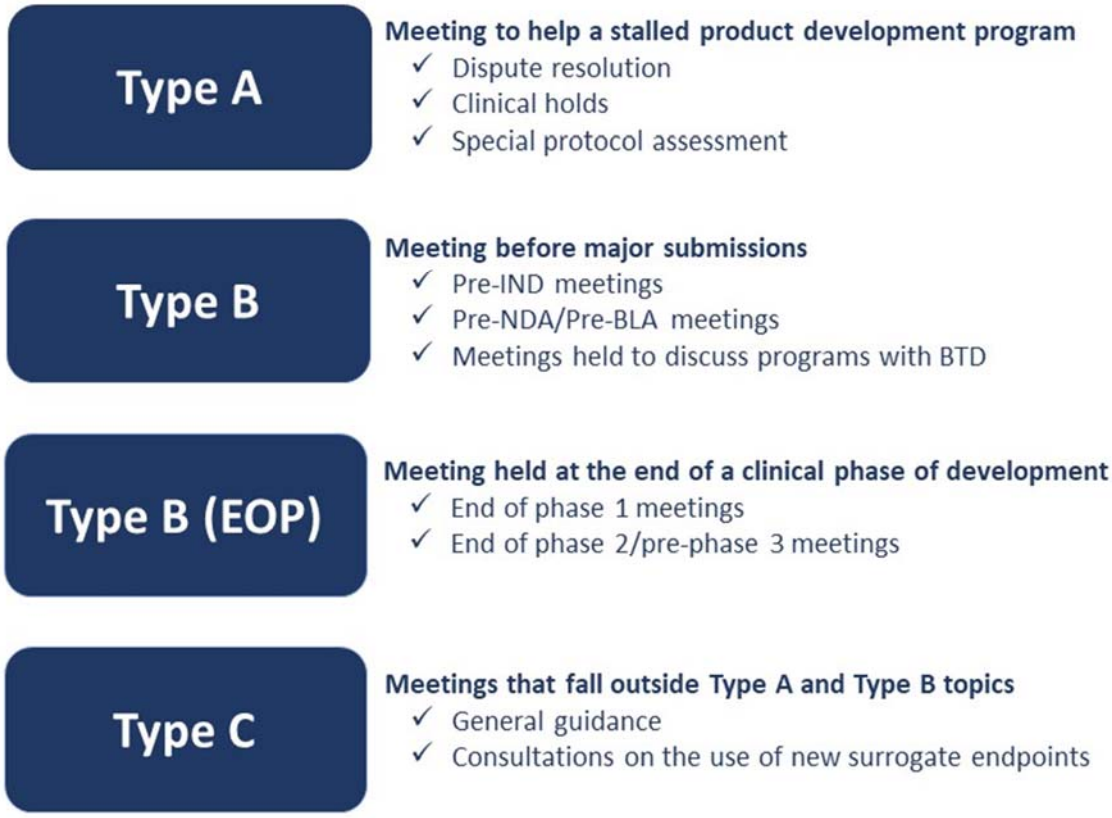


Table 1-1. Guidances Covering IND Communications in PDUFA VI

Guidance (with hyperlinks to document)	Communication or Program Type Covered
Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products: Guidance for Industry	Formal meetings
Best Practices for Communication Between IND Sponsors and FDA During Drug Development: Guidance for Industry and Review Staff	Communications between FDA and IND sponsors
Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators: Guidance for Industry	Preparation of IND submissions
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Guidance for Industry	BTD and RMAT
SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products *SOPP = Standard Operating Procedure and Policy.*	Formal meetings

1.2 The PDUFA VI IND Communications Assessment

Congress originally enacted the Prescription Drug User Fee Act (PDUFA) in 1992 to help ensure timely review of new drugs and biologics. Since then, Congress has reauthorized PDUFA every five years. In PDUFA V (FYs 2013-2017), FDA instituted a new review model called the "Program for enhanced communication and review transparency for New Molecular Entity (NME) New Drug Applications (NDAs) and Biologics License Applications (BLAs)", or "the Program" for short. Among other things, FDA established a drug/biologic development communication and training staff to act as a special liaison to sponsors and to internally promote good communication practices with sponsors. PDUFA VI (FYs 2018–2022) further promotes enhanced communication and gives greater specificity into the timing and content of meeting requests, meeting packages, and special meeting types.

As part of PDUFA VI, FDA committed to contracting with an independent third party to assess FDA-sponsor communication practices during the IND stage of drug/biologic development. Accordingly, FDA enlisted Eastern Research Group, Inc. (ERG) to conduct such an independent assessment. Specifically, FDA asked ERG to:

1. Assess the current state of FDA and sponsor IND communication practices using information from FDA's corporate databases as well as other databases (e.g., database or other tracking mechanisms developed by contractor).

2. Collect and analyze qualitative feedback from FDA review staff and sponsors, identifying current practices, best practices, and major pain points for sponsors and FDA in communicating during IND drug development.

ERG translated these tasks into a set of specific questions to be answered during the independent assessment (see text box).

Assessment Questions

1a. What are current FDA review staff and sponsor IND communication practices?

1b. To what extent do current IND communications incorporate recommended practices, guidances, and standard operating procedures?

2. How do communication practices vary by IND characteristics such as sponsor size, special designations, review division, meeting type, and IND phase?

3. How do FDA review staff and sponsors characterize IND communications during drug development?

4. What practices help optimize IND communications, what challenges hinder optimum communications, and what steps can FDA take to improve communications moving forward?

For this assessment of IND communication practices, ERG has analyzed and reported on results as follows:

- **Quarterly presentations to FDA**: Summaries of communication activities and preliminary results by the end of each quarter during the data collection period.
- **Written report:** For publication on FDA's public website (this document).
- **Public meeting:** Presentation to the public on report findings and recommendations (summer 2020).

FDA will consider the results, findings, and recommendations from this assessment to determine what, if any, refinements in IND stage communication practices are warranted.

1.3 This Report

This report describes ERG's assessment of current communication practices between sponsors and FDA reviewers during the IND stage of drug/biologic development. The remainder of this report includes:

- Section 2: Methods
- Section 3: Results
- Section 4: Assessment Questions and Answers
- Section 5: Findings and Recommendations
- Appendix A: Acronyms and Glossary
- Appendix B: Evaluation Metrics

2. Methods

ERG used a systematic process to identify, collect, and analyze comprehensive data for the PDUFA VI IND communications assessment. This process involved six key steps:

1. Develop evaluation metrics
2. Develop evaluation protocols and instruments
3. Develop sample of active commercial INDs
4. Collect data
5. Analyze data
6. Develop findings and recommendations

2.1 Evaluation Metrics

ERG began by establishing a set of measurable evaluation metrics that are directly related to FDA's goals for IND communications as outlined in PDUFA VI. ERG defined these metrics (and calculation methodologies) to measure conformity with FDA goals based on data fields available for INDs in the sample that ERG developed (Section 2.3). Please see Appendix B for a complete list of metrics.

The metrics fall into the following categories:

- Overview of composition of and activity in IND sample
- General feedback regarding IND communications under PDUFA VI
- Meeting requests
- Meeting request responses
- Meeting packages
- Preliminary FDA comments
- Meetings, including Written Responses Only (WROs)
- Meeting minutes, including (WROs)
- IRs and amendments
- Email and telephone communications
- Use of templates
- Use of regulatory and guidance language
- Changes in FDA advice
- FDA transitions in review team members

2.2 Protocols and Instruments

The evaluation metrics established a structure for data that needed to be collected to generate results. Accordingly, ERG prepared evaluation protocols and instruments for collecting the necessary data (Table 2-1). These protocols and instruments served as a guide for ERG in collecting data from FDA

databases (to obtain descriptive information about the INDs), observing FDA-sponsor interactions (to characterize communication practices and conformance with FDA guidances), collecting data about IRs and amendments (to determine frequency, topics, and conformance with FDA guidances), and conducting surveys and interviews with IND sponsors and FDA review teams (to elicit information about communication practices and opinions about good practices, challenges, and suggestions).

As noted, these evaluation protocols and instruments required ERG to collect information via surveys and interviews with both federal employees (FDA reviewers) and non-federal employees (sponsors). Collection of interview and survey information from sponsors necessitated clearance from the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA). The OMB control number for the information collection is 0910-0863. ERG sent surveys to selected FDA and sponsor attendees (those who played an active role in the meeting) within 48 hours of each observed sponsor meeting. ERG sent interview requests to sponsors and FDA review teams for INDs associated with some type of meeting activity (meeting request, response, package, preliminary comments, or meeting). Response rates for interviews were 100% for FDA and 81% for sponsors, and response rates for surveys were 68% for FDA and 37% for sponsors.

Table 2-1. Evaluation Protocols and Instruments for IND Communications Assessment

Category	Data Collection Protocol	Associated Data Collection Instruments	Sources	Purpose
Overview of Composition of Sample	IND Descriptive Data	Data Collection Instrument for Descriptive Data (product, IND start date, clinical trial phases, special designations, sponsor, sponsor size, sponsor experience, FDA review division, etc.)	DARRTS CBER EDR CDER EDR Annual reports	Collect data required to characterize INDs and analyze all other data by specified traits of interest
General Feedback About IND Communications in PDUFA VI	Interviews	Interview Script: FDA Interview Script: Sponsor	Interviews with FDA reviewers Interviews with sponsor representatives	Collect broader feedback about IND communications – use of different types of communications, good practices, challenges and pain points, lessons learned, suggestions, and other comments Also collect feedback on impacts (if any) of changes in review team, advice to sponsors, etc.
FDA-Sponsor Written Communications	Meeting-Related Communication	*Data Collection Instruments for:* Meeting Requests Meeting Request Responses Meeting Packages Preliminary Comments Meeting Minutes WROs	DARRTS EDR CBER EDR	Collect data on timing, use of templates, use of regulatory and guidance language, conformance with guidances / MAPPs / SOPPs, etc.

Category	Data Collection Protocol	Associated Data Collection Instruments	Sources	Purpose
	IRs and Amendments	*Data Collection Instruments for:* Sponsor Questions FDA Responses IRs Sponsor Submissions/Responses	DARRTS EDR CBER EDR	
Meetings	Observation of FDA-Sponsor Meetings	Meeting: Direct Observation Instrument	Direct observation	Collect observations on language use, conformance with guidances / MAPPs / SOPPs, meeting practices, etc.
	Post-Meeting Surveys	Type A Meeting Survey Type B Meeting Survey Type B (EOP) Meeting Survey Type C Meeting Survey	Surveys of active FDA and sponsor meeting participants, sent within 48 hours of meeting	Collect immediate feedback about meeting effectiveness, good practices, challenges, lessons learned, suggestions, and other comments
Review Team Changes	Data on FDA Review Team Changes	Review Team Changes: Data Collection Instrument	DARRTS CBER EDR	Collect data on the composition of the review team and any changes in team membership

CBER = Center for Biologics Evaluation and Research. CDER = Center for Drug Evaluation and Research. EOP = End of Phase. DARRTS = Document Archiving, Reporting, and Regulatory Tracking System. EDR = Electronic Document Room. MAPP = Manual of Policies and Procedures. SOPP = Standard Operating Procedure and Policy.

2.3 Sample of Active Commercial INDs

ERG defined the *universe* of INDs for this assessment as active commercial INDs: that is, commercial INDs with any type of sponsor submission (except annual report) or meeting during the past year. ERG excluded active commercial INDs with an NDA or BLA submitted by the sponsor in the past two years. These INDs were less likely to have meeting activity after the submission of an NDA or BLA. ERG defined the *sample cohort* as a selection of commercial INDs in the universe likely to have communication activity between July 31, 2018 and July 31, 2019. ERG defined a complete set of inclusion and exclusion criteria for the sample as part of the detailed assessment approach. In addition, ERG ensured that the sample of active commercial INDs represented traits of interest, based on their historical representation in active commercial INDs from PDUFA V:

1. **Sponsor size:** Small, medium, large, and private.
2. **Breakthrough Therapy Designation:** INDs with and without BTD.
3. **Regenerative Medicine Advanced Therapies:** INDs with and without RMAT designation.
4. **Clinical review office[1]:** INDs in each of the 17 offices in FDA Center for Drug Evaluation and Research (CDER) offices and 4 offices in Center for Biologics Evaluation and Research (CBER).
5. **Meeting types:** INDs with Type A, B, B (EOP), and C meetings during the data collection period.
6. **Commercial IND phase:** Commercial INDs in Phases 1, 2, and 3.

From this universe, ERG randomly selected 150 INDs and examined them for conformance with the desired distribution of traits of interest. To achieve the desired distribution, ERG replaced some INDs with randomly selected INDs with the desired traits. During the assessment period, ERG removed three INDs due to lack of conformance with inclusion criteria for the sample, resulting in a sample size of 147 INDs.

Throughout the one-year assessment period (July 31, 2018 to July 31, 2019), ERG tracked actual and projected IND communication activity to estimate whether the sample would include enough activity for analysis. To increase activity within the sample, ERG conducted systematic replacements of sample INDs at five points during the assessment period: September 2018, November 2018, January 2019, May 2019, and July 2019 (CBER only). At each of these points, ERG replaced INDs that were unlikely to have activity with INDs having similar traits that were more likely to have activity. ERG also monitored the activity of INDs in the sample by traits of interest, including representation across Centers and review Offices and Divisions. In July 2019, ERG replaced some CBER INDs to ensure the desired representation of CBER INDs with communication activity. To permit time to assess communication activity for these INDs, ERG extended the assessment period for the CBER INDs by one month, through August 31, 2019. At the end

[1] As part of FDA's initiative to modernize the New Drugs Regulatory Program, the Center for Drug Evaluation and Research (CDER) has since undergone a reorganization of the Office of New Drugs (OND). The offices and divisions discussed in this report reflect the structure organization at the time of data collection. A summary of these organizational changes can be found on FDA's *website.*

of the assessment period most INDs had some type of communication activity (Table 3-1). Unless otherwise noted, ERG included all INDs in the sample when calculating metrics.

2.4 Data Collection

For the 147 commercial INDs in the sample, ERG collected data on communication activity that took place during the assessment period. ERG collected all data, both qualitative and quantitative, in accordance with the procedures specified in its evaluation protocols and instruments. ERG entered data into a Program Evaluation Tracking Tool (PETT) that ERG developed to store raw data and compute metrics values.

To protect proprietary and non-public information, ERG performed all data collection and analysis on secure computers with secure FDA email. All ERG personnel also hold security clearances and signed Non-Disclosure Agreements. To protect the privacy of interview and survey respondents, ERG maintained identifying information only for the purpose of sending surveys and scheduling interviews and kept this information in a secure environment inaccessible to anyone outside ERG's internal project team. ERG anonymized and aggregated survey and interview results for analysis and reporting purposes.

2.5 Data Analysis

ERG analyzed the data collected to generate meaningful information to use in answering the assessment questions. ERG performed three types of data analysis:

- **Descriptive analysis—**to quantitatively describe characteristics of the IND sample, characteristics of FDA-sponsor communications, and differences in these characteristics based on IND traits of interest (sponsor size, special designations, FDA review Office or Division, meeting type, and IND phase).
- **Statistical analysis—**to determine whether differences observed by traits of interest are statistically significant.
- **Qualitative analysis—**to gain insights into communication practices and identify common themes (and outlier situations). ERG used NVivo, a qualitative analysis software tool, to analyze the qualitative observations and interview responses.

2.6 Findings and Recommendations

Based on the analyses described above, ERG developed cohesive, integrated answers to the assessment questions. ERG then distilled all results into a set of findings and recommendations.

2.7 Study Limitations

Study limitations included the following:

1. Sample sizes were too small to determine whether differences seen with less prevalent traits of interest (e.g., RMAT designation) were statistically significant.
2. Qualitative information from interviews and surveys was valuable in understanding good communication practices, challenges, and opportunities for improvement, but could not be used for quantification or statistical analysis.

3. Results

In Section 3, ERG presents PDUFA VI IND communications assessment results as follows:

- Section 3.1 Overview of Composition of and Activity in IND Sample
- Section 3.2 General Feedback About IND Communications in PDUFA VI
- Section 3.3 Meeting Requests
- Section 3.4 Meeting Request Responses
- Section 3.5 Meeting Packages
- Section 3.6 Preliminary FDA Comments
- Section 3.7 Meetings
- Section 3.8 Meeting Minutes (Including WROs)
- Section 3.9 IRs and Amendments
- Section 3.10 Email and Phone Communications
- Section 3.11 Use of Templates
- Section 3.12 Use of Regulatory and Guidance Language
- Section 3.13 Changes in FDA Advice
- Section 3.14 Changes in FDA Review Teams

3.1 Overview of Composition of and Activity in IND Sample

Key Points

- The sample consisted of 147 active commercial INDs.
- Compared to PDUFA V INDs, the sample was representative for traits of interest: sponsor size, BTD, RMAT designation, FDA review office, IND phase, and meeting type; the sample included slightly more Type C and slightly fewer Type B meetings than the PDUFA V cohort.
- The INDs in the sample had robust communication activity, with just over one meeting and numerous other communications per IND (on average).

Composition of Sample

Before creating a sample of INDs for this assessment, ERG analyzed a historical universe of active commercial INDs (from PDUFA V) to establish targets for the following traits of interest: sponsor size, BTD, RMAT designation, FDA review office, meeting type, and IND phase. As shown in Table 3-1, the composition of the assessment sample is consistent with the established targets, except for meeting type. By randomly selecting INDs for the sample, ERG could not know in advance what types of meetings would take place for the INDs. At the end of the assessment period, Type C meetings were somewhat overrepresented and Type B meetings were somewhat underrepresented in the sample. Additionally, some INDs had multiple clinical trials in different phases, leading to the appearance of differences in representativeness compared to the PDUFA V cohort.

Table 3-1. Distribution of Traits of Interest Across Active Commercial INDs in Assessment Sample (n=147)

IND Trait	Categories	Prevalence in PDUFA V	Target Allocation *(+/- 5 percentage points)*	Sample Representation
Sponsor size	Small	39%	**39% (58 of 150)** *34-44% (51-66 of 150)*	**59 (40%)** *Within range*
	Medium	11%	**11% (17 of 150)** *6-16% (9-24 of 150)*	**18 (12%)** *Within range*
	Large	24%	**24% (36 of 150)** *19-29% (28-44 of 150)*	**37 (25%)** *Within range*
	Private	26%	**26% (39 of 150)** *21-31% (31-47 of 147)*	**33 (23%)** *Within range*
BTD	With BTD	4%	**4% (6 of 150)** *1-9% (2-14 of 150)*	**13 (9%)** *Within range*
RMAT	With RMAT	1%	**1% (1 of 150)** *1-6% (1-9 of 150)*	**6 (4%)** *Within range*
FDA review office*	OAP *DAIP* *DAVP* *DTOP*	12%	**12% (17 of 150)** *6-16% (9-24 of 150)*	**17 (12%)** *Within range*
	ODEI *DCRP* *DNP* *DPP*	16%	**16% (24 of 150)** *11-21% (17-32 of 150)*	**24 (16%)** *Within range*
	ODEII *DAAAP* *DDDP* *DMEP* *DPARP*	17%	**17% (26 of 150)** *12-22% (18-33 of 150)*	**25 (17%)** *Within range*
	ODEIII *DBRUP* *DDDP* *DGIEP*	14%	**14% (21 of 150)** *9-19% (14-29 of 150)*	**19 (13%)** *Within range*
	ODEIV *DMIP* *DNDP* *DPMH*	2%	**2% (3 of 150)** *1-7% (2-11 of 150)*	**8 (5%)** *Within range*
	OHOP *DHP* *DOP1* *DOP2*	21%	**21% (32 of 150)** *16-26% (24-39 of 150)*	**26 (18%)** *Within range*

CDER

IND Trait	Categories	Prevalence in PDUFA V	Target Allocation *(+/- 5 percentage points)*	Sample Representation
CBER	OBRR	2%	**2% (3 of 150)** *1-7% (2-11 of 150)*	**6 (4%)** *Within range*
	OCBQ	0%	**0% (0 of 150)** *0-5% (0-8 of 150)*	**0 (0%)** *Within range*
	OVRR	4%	**4% (6 of 150)** *1-9% (2-14 of 150)*	**6 (4%)** *Within range*
	OTAT	12%	**12% (18 of 150)** *7-17% (11-26 of 150)*	**16 (11%)** *Within range*
Meeting type requested**	Type A	4%	**4% (6 of 150)** *1-9% (2-14 of 150)*	**7 (3%)** *Within range*
	Type B	48%	**48% (72 of 150)** *43-53% (64-80 of 150)*	**74 (30%)** *Underrepresented*
	Type B (EOP)	12%	**12% (18 of 150)** *7-17% (11-26 of 150)*	**51 (21%)** *Within range*
	Type C	36%	**36% (54 of 150)** *31-41% (46-62 of 150)*	**115 (46%)** *Overrepresented*
IND phase***	Phase 1	37%	**37% (56 of 150)** *32-42% (48-63 of 150)*	**16 (11%)**
	Phase 2	47%	**47% (70 of 150)** *42-52% (63-78 of 150)*	**31 (21%)**
	Phase 3	16%	**16% (24 of 150)** *11-21% (16-32 of 150)*	**61 (41%)**
	Multiple Phases	-	-	**35 (24%)**
	Other	-	-	**4 (3%)**

*As part of FDA's initiative to modernize the New Drugs Regulatory Program, the Center for Drug Evaluation and Research (CDER) has undergone a reorganization of the Office of New Drugs (OND). The offices and divisions discussed in this report reflect the structure at the time of data collection. A summary of these organizational changes can be found on FDA's *website*.
**Meetings requested sum to 249; two meeting requests did not specify meeting type, so meeting types requested sum to 247.
***For IND phase, ERG used the most recent phase(s) that sponsors included in documents submitted to FDA.
CDER Offices: OAP = Office of Antimicrobial Products. DAIP = Division of Anti-Infective Products. DAVP = Division of Anti-Viral Products. DTOP = Division of Transplant and Ophthalmology Products. ODEI = Office of Drug Evaluation I. DCRP = Division of Cardiovascular and Renal Products. DNP = Division of Neurology Products. DPP = Division of Psychiatry Products. ODEII = Office of Drug Evaluation II. DAAAP = Division of Anesthesia, Analgesia, and Addiction Products. DDDP = Division of Dermatology and Dental Products DMEP = Division of Metabolism and Endocrinology Products. DPARP = Division of Pulmonary, Allergy, Rheumatology Products. ODEII = Office of Drug Evaluation III. DBRUP = Division of Bone, Reproductive, and Urologic Products. DDDP = Division of Dermatology and Dental Products. DGIEP = Division of Gastroenterology and Inborn Errors Products. ODEIV = Office of Drug Evaluation IV. DMIP = Division of Medical Imaging Products. DNDP = Division of Non-prescription Drug Products. DPMH = Division of Pediatrics and Maternal Health. OHOP = Office of Hematology and Oncology Products. DHP = Division of Hematology Products. DOP1 = Division of Oncology Products I. DOP2 = Division of Oncology Products II. **CBER Offices:** OBRR = Office of Blood Research and Review. OCBQ = Office of Compliance and Biologics Quality. OVRR = Office of Vaccines Research and Review. OTAT = Office of Tissues and Advanced Therapies.

Activity in Sample

The commercial INDs in the assessment sample demonstrated robust communication activity during the data collection period, as evidenced by an average of one meeting and numerous IRs and amendments per IND (Table 3-2). In calculating metrics, ERG included data for all INDs in the sample regardless of the volume of meeting-related activity.

Table 3-2. Communications Activity in Sample of Active Commercial INDs (n=147) During the One-Year Assessment Period (July 31, 2018 to July 31, 2019)

Category	Communication Type	Number in Sample
Meeting-Related Communication	Meeting Requests	249
	Meeting Request Responses	237
	Meeting Packages	216
	Preliminary Comments	154
	Meetings Held (Including WROs)*	161
	Meeting Minutes (Including WROs)*	152
Other	FDA IRs**	647
	Sponsor Amendments**	2,137
	Sponsor Questions and FDA Answers***	369

*FDA considers WROs to be meetings and the final written communications (minutes) for these meeting. Therefore, ERG counted WROs as meetings held and as meeting minutes. For the assessment, ERG examined WROs differently for these two purposes; that is, ERG examined WROs against meeting metrics in the analysis of meetings and against meeting minute metrics in the analysis of meeting minutes.

**Number of individual FDA questions and sponsor amendments, regardless of whether they were transmitted singly or in groups.

***Outside of FDA IRs and sponsor amendments.

3.2 General Feedback About IND Communications in PDUFA VI

Key Points

- Overall, sponsors and FDA reviewers described their IND communications as clear, effective, efficient, collaborative, and timely, with RPMs playing a key role in this regard.
- Sponsors and FDA reviewers identified two good communication practices: (1) sponsor and FDA establish preferred frequency and methods of communication at the start of the relationship, and (2) FDA provides timelines for responses to sponsor questions submitted via email or telephone communication when possible.
- Sponsors and FDA reviewers identified several pain points: (1) heavy FDA workloads and staff shortages, (2) lack of timelines for responses to questions submitted via email or telephone calls, (3) technical problems with teleconference systems during industry meetings, and (4) inconsistent levels of responsiveness (uncommon).
- Some sponsors and FDA reviewers also acknowledged a challenging balancing act in which sponsors would like development program-specific advice as early as possible, while FDA reviewers instead direct sponsors to guidance when the data are too premature to support specific advice.
- Sponsors and FDA reviewers offered two suggestions: (1) add guidelines for email and telephone communications, and (2) inform sponsors as soon as possible of changes in RPM.
- Sponsors emphasized the essential role that FDA feedback and advice play in drug development, especially in areas without established regulatory precedence.

For the 147 INDs in the assessment sample, ERG solicited feedback about communication practices from IND sponsors and FDA review teams via surveys (sent directly after formal meetings) and interviews (conducted after 6-8 months of communication activity). This section highlights general feedback. ERG presents feedback related to specific communication topics in the sections that follow.

Feedback from IND sponsors and FDA reviewers was largely positive, with most describing their communications as clear, effective, efficient, collaborative, and timely. They highlighted the importance of RPMs in facilitating positive communications. Other common themes that emerged relating to good practices, pain points, and suggestions are summarized in Table 3-3.

Patterns by Traits of Interest

ERG examined IND sponsor and FDA reviewer feedback to identify any patterns by IND traits of interest. ERG found no clear patterns in the interview and survey data. Some interviewees offered anecdotal observations:

- **Sponsor Size:** Smaller or less experienced sponsors tend to have more frequent communication with the FDA RPM and review team than larger or more experienced sponsors.
- **IND Phase:** Communications tends to be most frequent before the beginning of large, pivotal trials and before submission of an NDA or BLA.
- **BTD** and **RMAT**: Both BTD and RMAT provide opportunities for increased communication with the FDA review team. BTD also provides an opportunity for creation of a Formal Communication Plan that lays out when and how FDA-sponsor communications will occur.

Table 3-3. IND Sponsor and FDA Reviewer Feedback about IND Communications from Interviews and Surveys: Common Themes

Topic	**Feedback from IND Sponsors** (31 survey responses and 98 interviews*)	**Feedback from FDA Reviewers** (152 survey responses and 132 interviews*)	**Additional Information**
Overall	Communication with FDA was clear, efficient, effective, collaborative, and timely. Formal communications were effective for gaining insight into FDA's rationales and delving into complex scientific issues, while email and telephone communication was effective for smaller issues and clarifications. PDUFA VI timelines for formal communications are appropriate.	Communication with sponsors was effective. FDA guidances were helpful in managing effective communications. Frequency of communication depended on proximity to major development milestones, complexity of development program, and level of sponsor experience. PDUFA VI timelines for formal communications are appropriate.	N/A
Good practices	Collaborative, proactive, and responsive relationship with the RPM. Working with RPMs to determine preferred frequency and methods of communications. RPMs providing estimates for when they will respond to sponsor questions.	Effective communication between the RPM, review team, and sponsors, including being responsive to formal communication as well as email and telephone calls. Providing estimates for when FDA will respond to questions from sponsors sent via email or telephone calls with the RPM. Involvement of additional staff (e.g., CDRH, other divisions) early in the IND process.	While not specified in FDA's guidances, some RPMs gave sponsors estimates for when they would respond to questions. This was helpful for sponsors to know when they will receive feedback and plan accordingly.

Topic	Feedback from IND Sponsors (31 survey responses and 98 interviews*)	Feedback from FDA Reviewers (152 survey responses and 132 interviews*)	Additional Information
Challenges or pain points	Lack of timelines for FDA responses to questions from sponsors sent via email or telephone calls. Technical issues with the teleconference system. Occasional: FDA directing sponsors to guidance rather than offering program-specific advice. Uncommon: RPMs being less responsive than typical.	Heavy workloads exacerbated by staff shortages. Technical issues with the teleconference system. Occasional: Sponsors requesting FDA advice about their development program before data are sufficient to address their questions. Uncommon: Sponsors communicating with FDA reviewers directly rather than via the RPM. Uncommon: Sponsors being less responsive than typical.	Some FDA reviewers cited challenges stemming from staff shortages and heavy workloads, sometimes leading to burnout. They also cited scheduling meetings with large number of participants as a challenge, as calendars often conflict, and conference rooms are often overbooked. In general, sponsors find it helpful to receive FDA advice as early as possible in order to fine-tune their development programs and pursue regulatory pathways with precision and confidence. Because they want to provide data-driven, scientifically sound advice, FDA reviewers sometimes feel unable to provide advice as early as sponsors would like, so they direct sponsors to guidance instead. For the INDs in the assessment sample, balancing these desires was occasionally challenging. Outlier: In rare cases when a sponsor has lengthy history with FDA and knows the staff, they contacted a reviewer or division-level manager directly. This practice disrupts the flow of information between the sponsor and RPM and other reviewers.

Topic	Feedback from IND Sponsors (31 survey responses and 98 interviews*)	Feedback from FDA Reviewers (152 survey responses and 132 interviews*)	Additional Information
Suggestions	Encourage RPMs and sponsors to explicitly identify preferred communication modes and frequency. Encourage all RPMs to tell sponsors when they can expect a response from FDA about a question or issue. Notify the sponsor of any changes in RPM as soon as possible. Outlier: Provide a forum to discuss emerging and scientific topics in special circumstances, such as for new types of drugs/biologics or therapeutic approaches or when patient perspectives would be useful. Outlier: Provide program- specific regulatory advice, rather than directing sponsors to guidances.	Provide response timelines for email and telephone communication. Provide additional guidelines on the appropriate number or scope of questions.	Sponsors appreciate the measures FDA has taken to optimize transparency and predictability. More consistently letting them know when to expect responses from FDA would further enhance these efforts.
Impact on development program	Early and ongoing FDA feedback provides direction for regulatory pathways that sponsors might decide to pursue and can help sponsors identify future review issues. Early and ongoing communications with FDA are essential in programs with novel drug candidates or surrogate endpoints without regulatory precedence.	**	N/A

*Each interview included multiple people, so the total number of individuals interviewed was much greater than the number of interviews conducted.

**This was a sponsor-specific topic of conversation during interviews.

CDRH = Center for Devices and Radiological Health.

3.3 Meeting Requests

Key Points

- The mean number of meeting requests per IND in the sample was 1.7. This value was higher for INDs with BTD (2.7) and for INDs submitted to ODEII (1.9), and lower for INDs submitted to OBRR (0.5).
- The type of meeting most often requested was Type C, followed by Type B and Type B (EOP). The meeting format most often requested was face-to-face, followed distantly by teleconference and WRO.
- Roughly half of meeting requests included suggested dates that fell within FDA guidance, and about half included all items required by guidance.
- In cases where sponsors provided both a list of requested FDA staff and questions listed by discipline, the disciplines of the questions aligned with the disciplines of the requested FDA staff in 90% of cases.

During the IND stage of development, sponsors can request meetings with FDA reviewers to discuss questions and issues related to obstacles in development, upcoming submissions, major development milestones, or other topics. In these situations, the sponsor submits a written request to FDA.

ERG collected data on all 249 meeting requests submitted between July 31, 2018 and July 31, 2019 for the 147 active commercial INDs in the sample. Data on metrics related to meeting requests appear in Table 3-4. The mean number of meeting requests per IND was 1.7. Of the 147 INDs in the sample, 128 were associated with meeting requests during the one-year assessment period.

Table 3-4. Data for Evaluation Metrics Related to Meeting Requests (n=249) for INDs in Sample (n=147)

Metrics	Result
Number of meeting requests per IND: **Mean**	1.7
Number of meeting requests per IND: **Median**	1
Number of meeting requests per IND: **Range**	6 [0, 6]
Number of questions per meeting request: **Mean**	7
Number of questions per meeting request: **Median**	6
Number of questions per meeting request: **Range**	30 [1, 31]
Percent of suggested meeting dates within timelines suggested in guidance*	57%
Percent of meeting requests that are complete**	54%
Percent of meeting requests with all recommended items included***	29%
Percent of meeting requests for: **Type A**‡	3%
Percent of meeting requests for: **Type B**‡	30%
Percent of meeting requests for: **Type B (EOP)** ‡	20%
Percent of meeting requests for: **Type C**‡	46%
Percent of meeting requests for: **Face-to-face**‡‡	69%
Percent of meeting requests for: **Teleconference**‡‡	17%

Metrics	Result
Percent of meeting requests for: **Videoconference**‡‡	0%
Percent of meeting requests for: **Written response only (WRO)** ‡‡	9%
Percent of meeting requests that include pediatric study plans	22%
Percent of meeting requests that include human factors engineering plan	9%
Percent of meeting requests that align questions with review disciplines requested to attend*	90%

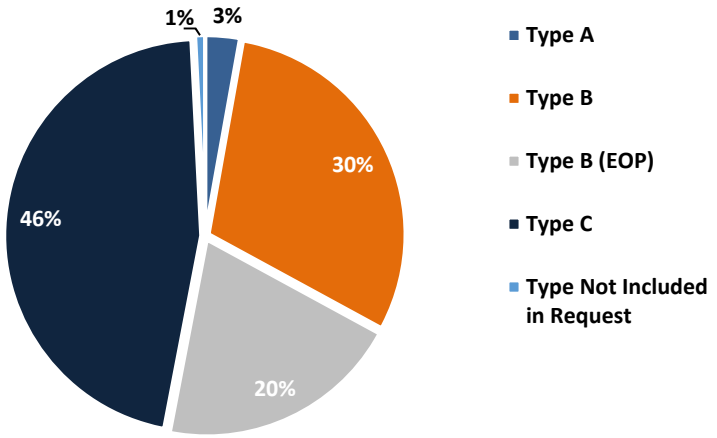
*Excludes WRO requests because suggested meeting dates and FDA attendees are not necessary when requesting WRO.
**Excludes proposed agendas and lists of sponsor and FDA attendees when determining completeness for WRO requests.
*** Excludes "if applicable" items such as pediatric study plans, human factors engineering plans, and combination product information.
‡Values do not sum to 100% because 1% of requests did not include requested meeting type.
‡‡ Values do not sum to 100% because 3% of requests included multiple meeting formats and 2% did not include a format.

Meeting types. Nearly all meeting requests included the type of meeting requested. The type requested most often was Type C, followed by Type B and Type B (EOP) (Figure 3-1).

Suggested meeting dates. FDA's meeting guidance specifies timelines (number of days after FDA receives meeting request) for the scheduled meeting date of meetings that sponsors request. These are 30 days for Type A, 60 days for Type B, 70 days for Type B (EOP), and 75 days for Type C meetings. FDA recommends that sponsors include a suggested meeting date in their meeting requests, unless they request a WRO in which case a meeting date is unnecessary. Of the 93% of meeting requests that contained suggested meeting dates, about half of the sponsors' suggested meeting dates fell within the timelines specified in FDA's guidance (Table 3-4).

Of the meeting requests with suggested meeting dates that fell outside of the timelines in FDA guidance, the majority were requests for Type B meetings, followed by Type C and Type B (EOP) meetings. Suggested meeting dates in Type B requests were the closest to the guidance timelines (mean 9 days, range 1-64 days after guidance timeline). Suggested meeting dates in Type B (EOP) and Type C requests were somewhat later (mean 21 days, range 11-42 days after guidance timeline).

Figure 3-1. Types of Meetings Requested (n=249) in Sample of Active Commercial INDs (n=147)



Completeness of meeting requests. Meeting requests should include adequate information for FDA to assess the potential utility of the meeting and to identify FDA staff necessary to discuss proposed agenda items. FDA guidance specifies 7 required items and 11 recommended items for meeting requests (see text box at right). For the purpose of this assessment, ERG defined meeting requests as complete when all required items were present. Meeting requests for WROs do not require a proposed agenda or a list of sponsor or FDA attendees, so ERG considered these complete if the requests included the first four items in the required list. By this definition, 54% of the 249 meeting requests in the sample were complete (Table 3-4). Most meeting requests included a requested meeting format, purpose, planned attendees, and objectives. About a quarter of the meeting requests lacked a date for meeting package submission and a list of requested FDA attendees.

Required Items for Meeting Requests*

- Proposed meeting format
- Date of background package submission
- Purpose of meeting
- Specific objectives of meeting
- Proposed agenda**
- List of sponsor attendees
- List of requested FDA attendees**

Recommended Items for Meeting Requests*

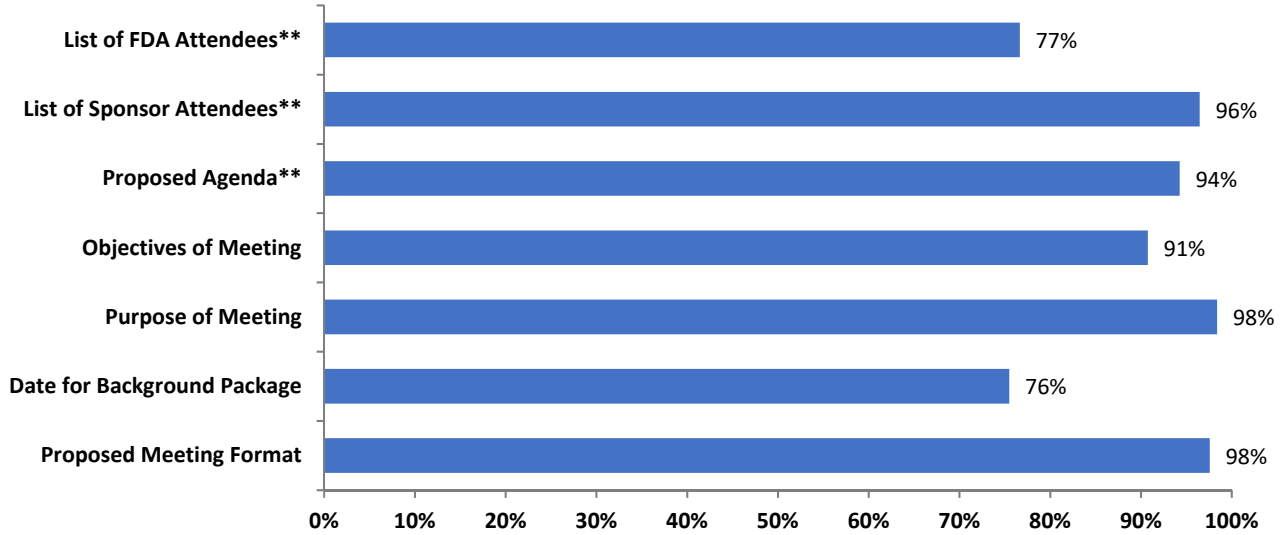
- Application number
- Product name
- Chemical/established name/structure
- Proposed regulatory pathway
- Proposed indication
- Requested meeting type
- Pediatric study plans, if applicable
- Human factors engineering plans, if applicable
- Combination product information, if applicable
- Suggested meeting dates and times
- List of proposed questions, grouped by FDA discipline

*Per FDA Guidance: U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2017). Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA.

**Not required for WRO requests.

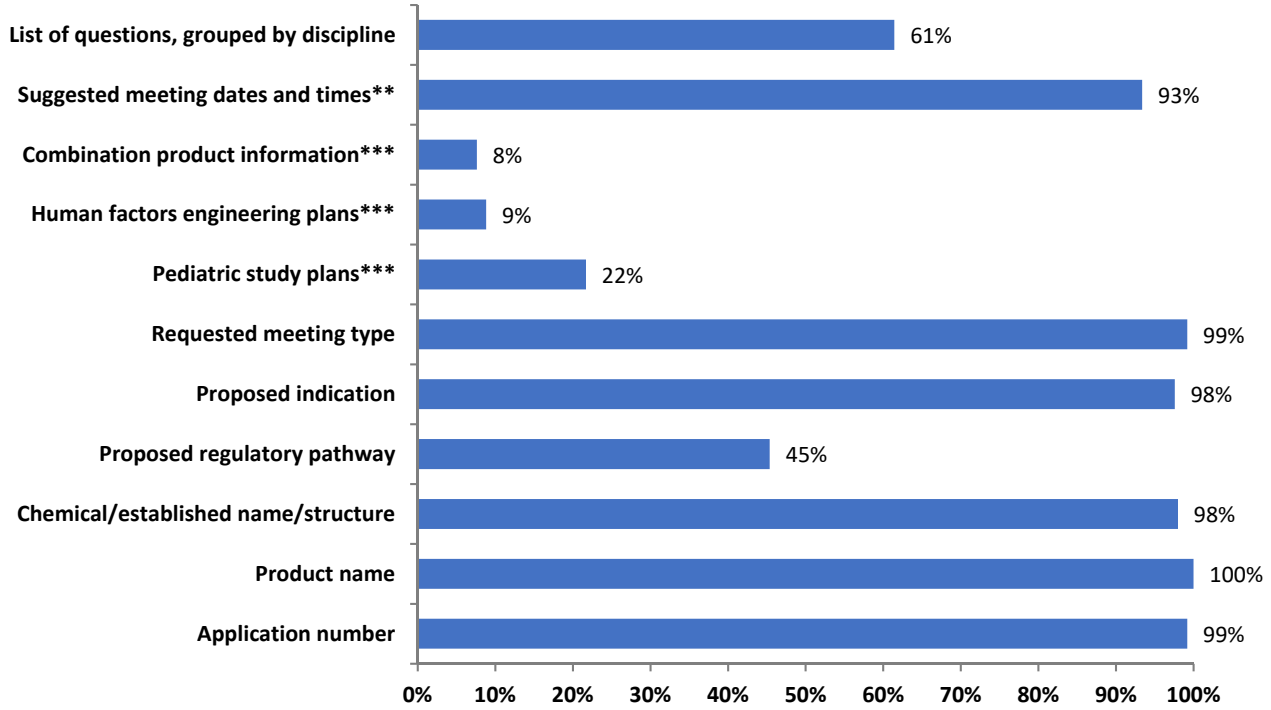
For this assessment, ERG excluded "if applicable" items when determining the percentage of meeting requests that included all recommended items. About 29% of sponsor meeting requests included all recommended items (Table 3-4). Most meeting requests included application number, product name, established name/structure, proposed indication, requested meeting type, and suggested meeting date. The proposed regulatory pathway and a list of questions grouped by FDA discipline were sometimes omitted. Most meeting requests lacked the "if applicable" specialized items: pediatric study plans, human factors engineering plans, and combination product information (Figure 3-3).

Figure 3-2. Rate of Inclusion of Required Items* in Sponsor Meeting Requests (n=249) for INDs in Sample (n=147)



*Per FDA guidance: U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2017). Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA.
** These percentages exclude requests for a WRO.

Figure 3-3. Rate of Inclusion of Recommended Items* in Sponsor Meeting Requests (n=249) for INDs in Sample (n=147)



*Per FDA guidance: U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2017). Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA.
**This percentage excludes requests for a WRO.
***These items are listed as "if applicable" in the guidance.

Meeting format. Sponsors may request one of three meeting formats: face-to-face meeting, teleconference or videoconference, or WRO. In the 249 meeting requests that FDA received for the 147 INDs in the sample during the one-year assessment period, about 69% of sponsors requested face-to-face meetings, 17% requested teleconferences, and 9% requested WRO (Table 3-4). About 3% requested a combination of meeting formats, and 2% did not request a meeting format.

Alignment of Disciplines and FDA Staff Requested. Meeting requests must include a list of requested FDA staff by discipline and are recommended to include a list of questions grouped by discipline. ERG examined these lists to determine the extent to which the disciplines associated with questions aligned with the disciplines of the FDA staff requested. These disciplines aligned in 90% of meeting requests where sponsors provided both questions grouped by discipline and requested FDA staff. ERG found no patterns in the cases where the disciplines did not align.

Interview feedback. In interviews, many FDA reviewers cited a good practice related to meeting requests that facilitated effective communication: submit meeting requests for substantive questions instead of asking for advice via email and telephone calls. Both FDA reviewers and sponsors agreed that this practice ensures that questions are vetted across the appropriate review staff so FDA can fully address the sponsor's questions, with a written record of the communications available for reference.

Patterns by Traits of Interest

ERG analyzed meeting request data to identify any patterns by traits of interest in the sample of active commercial INDs. ERG found no striking differences by sponsor size, RMAT designation, or IND phase. ERG found some variations by the following traits:

- **FDA Review Office:** INDs reviewed in CBER's OBRR were associated with a lower mean number of meeting requests per IND (0.5) than the sample as a whole (1.7). INDs reviewed in CDER's ODEII were associated with a greater mean number of meeting requests per IND (1.9) than the sample as a whole (1.7). These differences are statistically significant at $p<0.05$.
- **BTD:** INDs with BTD were associated with a greater mean number of meeting requests per IND (2.7) than the sample as a whole (1.7). This difference is statistically significant at $p<0.05$. *Note: The mean number of meeting requests (and other meeting activities) per IND was not significantly higher for INDs with RMAT designation than the sample as a whole.*

3.4 Meeting Request Responses

Key Points

- The mean number of meeting requests per IND in the sample was 1.7, and the mean number of meeting requests *granted* per IND in the sample was 1.6. The number of meeting requests granted was higher for INDs with BTD (2.7) and lower for INDs submitted to OBRR (0.5).
- FDA granted sponsors' suggested meeting dates in 72% of meeting request responses. Some of these dates fell outside of FDA guidance timelines, and FDA staff sometimes could not find a meeting room or a time when all participants were available on the suggested dates.
- In most cases, FDA granted the meeting type and format requested by the sponsor.
- In interviews, FDA reviewers indicated that WROs were helpful when the questions were straightforward or if the path for development was well established.

Upon receiving a meeting request, FDA assesses the request to determine whether a meeting will be granted and, if so, what the meeting type and format will be. In the case of pre-IND and most Type C meetings (except those pertaining to new surrogate endpoints), FDA may determine that a WRO is more appropriate than a meeting. FDA must notify the sponsor of its decision and if a meeting is granted, schedule the meeting within a certain period of time that depends on what type of meeting was requested.

ERG collected data on all 237 meeting request responses that FDA sent to sponsors between July 31, 2018 and July 31, 2019 for the 147 active commercial INDs in the sample. The number of meeting request responses (237) is lower than the number of meeting requests (249) because sponsors withdrew meeting requests or submitted them so late in the assessment period that FDA's response occurred after the assessment period ended (n=12). Of the 237 meeting request responses, 232 (98%) indicated that FDA granted a meeting, including cases where FDA converted a face-to-face or teleconference meeting to a WRO. When denying meeting requests (n=5), FDA typically gave one of the following reasons: discussion of the meeting topics is premature, or the meeting request is incomplete.

Response Timelines. When a meeting request is received, FDA must respond to the request within 14 days of the date the meeting request was sent for Type A meetings, 21 days for Type B meetings, 14 days for Type B (EOP) meetings, and 21 days for Type C meetings. FDA met these timelines for 82% of the response letters sent during the assessment period. FDA also must schedule meetings a within 30 days of the date the meeting request was sent for Type A meetings, 60 days for Type B meetings, 70 days for Type B (EOP) meetings, and 75 days for Type C meetings. FDA met these timelines for 44% of meetings scheduled. Additionally, in instances that sponsors requested meeting dates outside of these timelines (43%) (Table 3-4), FDA is still expected to grant a meeting date within 14 days of the sponsors' suggested dates and did so in 80% of request responses.

Meetings granted. The mean number of meeting requests per IND in the sample was 1.7 (n=249 meeting requests), and the mean number of meetings granted per IND in the sample was 1.6 (n=232 meetings granted) (Table 3-5). As shown in Figure 3-4, 44% of the INDs in the sample had one meeting granted, 24% had two meetings granted, and 20% had three or more meetings granted during the one-

year assessment period; 12% of the INDs in the sample had no meeting requests and therefore no meetings granted.

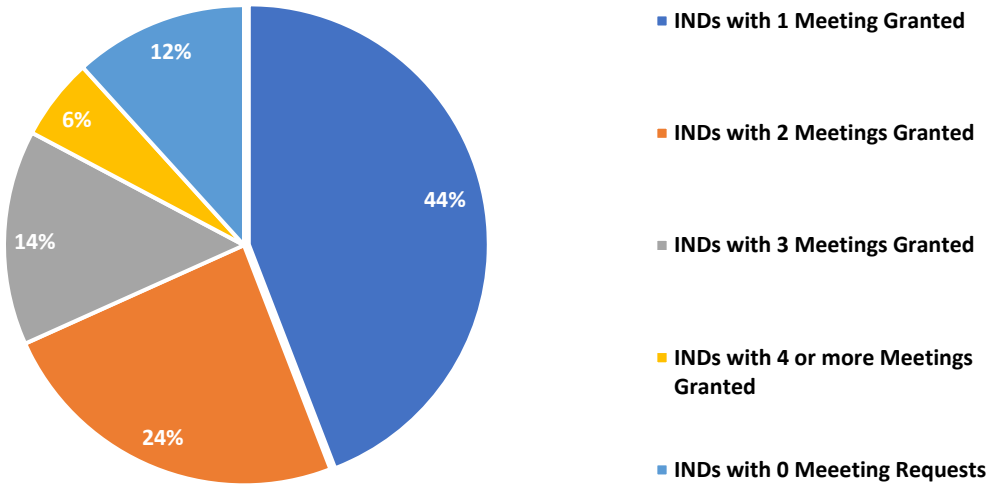
Meeting dates granted. FDA granted the sponsor's suggested meeting date for 72% of the meeting requests that included a suggested date from the sponsor. In interviews, FDA reviewers cited the following reasons for not granting the sponsor's suggested date: suggested date was outside timelines specified in FDA guidance, the RPM was unable to find a time on that date when all needed FDA staff were available, and the RPM could not find a meeting room on that date.

Table 3-5. Data for Evaluation Metrics Related to Meeting Request Responses (n=237*) for INDs in Sample (n=147)

Metrics	Result
Number of meetings granted per IND: **Mean**	1.6
Number of meetings granted per IND: **Median**	1
Number of meetings granted per IND: **Range**	6 [0, 6]
Of meeting requests received, percent with meeting request granted	98%
Percent of suggested meeting dates granted**	72%
Percent of meeting request response letters sent on time	82%
Percent of meeting dates scheduled on time	44%
Percent of meeting dates granted within 14 days of requested meeting dates, when requested dates are outside guidance timelines	80%

*The number of meeting request responses (237) is lower than the number of meeting requests (249) because sponsors withdrew meeting requests or submitted them so late in the assessment period that FDA's response occurred after the assessment period ended (n=12).
**Meetings that were granted and scheduled within 14 days of the originally requested date were included in this calculation

Figure 3-4. INDs in Sample (n=147) by Number of Meetings Granted



Meeting type and format granted. Of the meetings that FDA granted, 3% were Type A meetings, 31% were Type B meetings, 50% were Type C meetings, and 16% were Type B (EOP) meetings. When FDA grants meetings, the Agency may accept or adjust the sponsor's requested meeting type, format, and date. In most cases, FDA granted the sponsor's requested meeting type (91% of meeting request responses) and format (77% of meeting request responses). Of the 23 meeting request responses in which FDA adjusted the meeting type:

- 8 changed from Type B (EOP) to Type B.
- 5 changed from Type B (EOP) to Type C.
- 4 changed from Type B to Type C.
- 2 changed from Type C to Type B (EOP).
- 2 changed from Type C to Type B.
- 1 changed from Type A to Type C.
- 1 changed from Type B to Type B (EOP).

FDA adjusted the meeting format in 46 cases, resulting in these changes:

- Of the 172 requests for face-to-face meetings, 22 changed to teleconference.
- Of the 172 requests for face-to-face meetings, 18 changed to WRO.
- Of the 41 requests for teleconference meetings, 5 changed to WRO.
- Of the 41 requests for teleconference meetings, 1 changed to face-to-face.

Interview feedback. In interviews, FDA reviewers cited a good practice related to meeting request responses that facilitated effective communication: WROs were helpful when the questions were straightforward or if the path for development is well established.

Additionally, some FDA staff stated that the volume and complexity of questions in some meeting packages were overly ambitious and could not reasonably be addressed in a standard one-hour meeting. Some staff suggested a need for more information for sponsors about the appropriate scope and timing of questions for meetings.

Patterns by Traits of Interest

ERG examined patterns in meeting request responses by traits of interest in the sample of active commercial INDs. ERG found no striking differences by sponsor size, RMAT designation, meeting type, or IND phase. ERG found some variations by the following traits:

- **FDA Review Office:** As expected given the lower number of meeting requests, INDs reviewed in CBER's OBRR were associated with a lower mean number of meeting request responses per IND (0.5) than the sample as a whole (1.6). This difference was statistically significant at $p<0.05$.
- **BTD:** As expected given the greater number of meeting requests, INDs with BTD were associated with a greater mean number of meeting request responses per IND (2.7) than the sample as a whole (1.6). This difference was statistically significant at $p<0.05$.

3.5 Meeting Packages

Key Points

- The mean number of meeting packages per IND in the sample was 1.5. This number was greater for INDs with BTD (2.5). The number was lower for INDs submitted to OBRR (0.3).
- For the INDs in the sample, about a third of meeting packages included all items recommended in FDA guidance; proposed regulatory pathway was omitted in about half of meeting packages.
- Sponsors submitted most meeting packages by or close to dates specified in FDA guidance. Of meeting packages submitted late, 65% were for Type C meetings.
- In interviews, some reviewers suggested providing guidance for sponsors on appropriate length (number and complexity of questions) for a meeting package.

After FDA grants a meeting, the sponsor submits a meeting package with background information related to the meeting topics. The meeting package helps FDA staff prepare for the meeting.

ERG collected data on all 216 meeting packages that sponsors submitted between July 31, 2018 and July 31, 2019 for the 147 active commercial INDs in the sample; this includes meeting packages for WROs. The number of meeting packages (216) is lower than the number of meetings granted (232) because some sponsors withdrew their meeting requests before submitting a meeting package and some submitted their meeting packages after the assessment period ended.

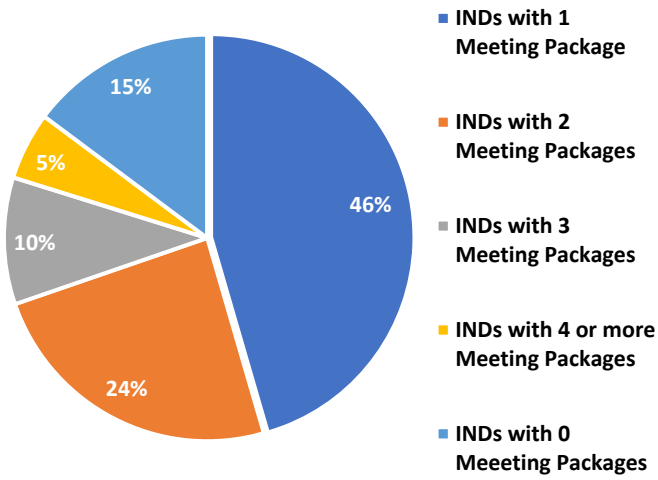
The mean number of meeting packages submitted per IND was 1.5 (Table 3-6). As shown in Figure 3-5, 46% of the INDs in the sample had one meeting package, 24% had two meeting packages, 10% had three meeting packages, 5% had four or more meeting packages during the one-year assessment period; 15% of INDs had no meeting packages.

Table 3-6. Data for Evaluation Metrics Related to Meeting Packages (n=216) for INDs in Sample (n=147)

Metrics	Result
Number of meeting packages per IND: **Mean**	1.5
Number of meeting packages per IND: **Median**	1
Number of meeting packages per IND: **Range**	5 [0, 5]
Percent of meeting packages with all recommended items included*	35%
Percent of meeting packages submitted on time	79%

*Excludes "if applicable" items such as pediatric study plans, human factors engineering plans, and combination product information.

Figure 3-5. INDs in Sample (n=147) by Number of Meeting Packages



Completeness of meeting packages. Meeting packages are considered complete if they include all recommended items except those applicable to only some INDs. Of the 216 meeting packages in the sample, 35% included all such recommended items. Of the 65% of meeting packages that did not include all generally recommended items, proposed regulatory pathway was the item most often omitted (Figure 3-6); proposed meeting agenda and a list of sponsor attendees were omitted in just over one-third of meeting packages.

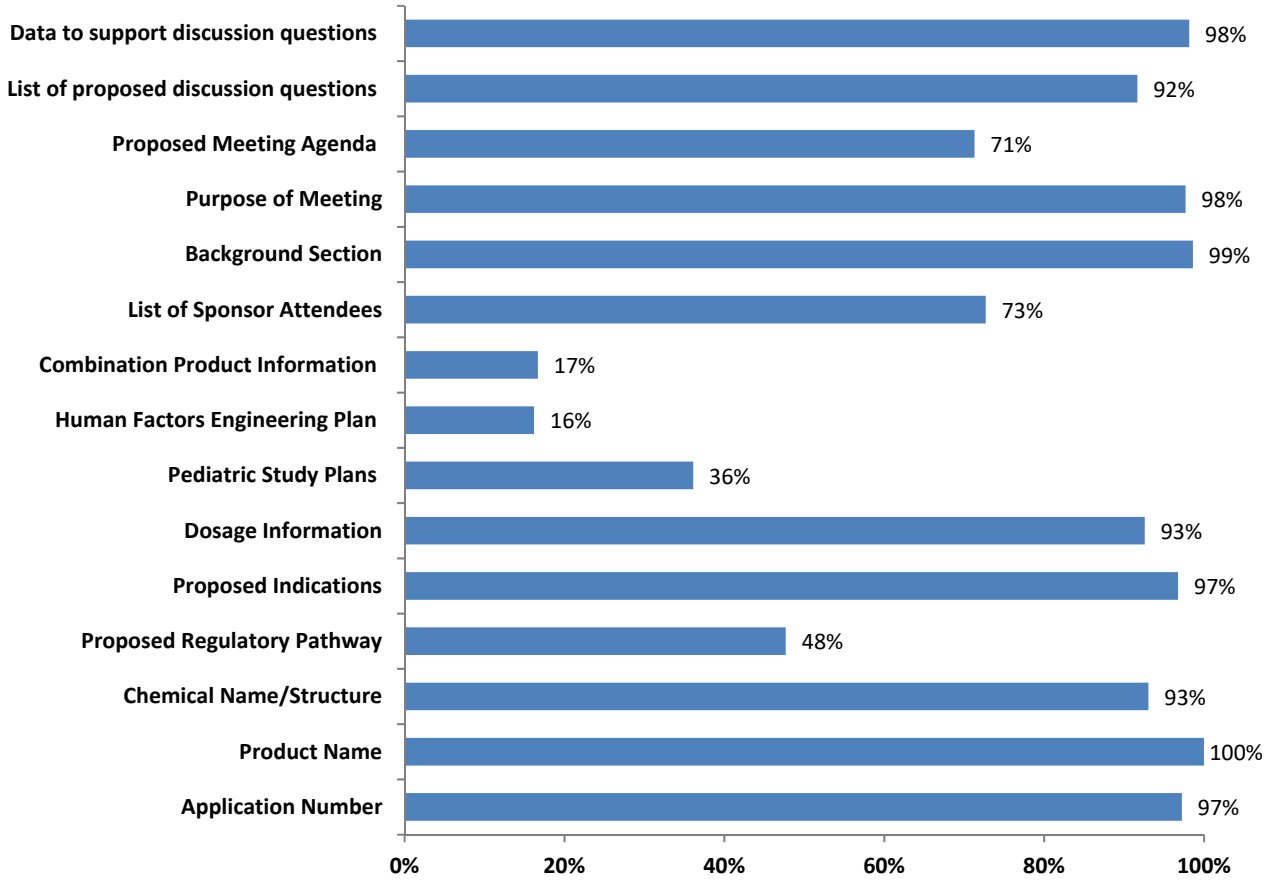
Timing of meeting packages. Meeting packages must be submitted as early as possible so FDA can review the information in the package and prepare preliminary comments in a timely manner. According to FDA's meeting guidance, sponsors should submit meeting packages at least 30 days (Type B), 50 days (Type B (EOP)), or 47 days (most Type C) before the requested meeting date. Sponsors should submit meeting packages with their requests for Type A meetings and or Type C meetings requested to discuss new surrogate endpoints. Sponsors submitted 79% of meeting packages within these timelines.

Recommended Items for Meeting Packages*

- Application number
- Product name
- Chemical/established name/structure
- Proposed regulatory pathway
- Proposed indication
- Dosage form, route of administration, and dosing regimen
- Pediatric study plans, if applicable
- Human factors engineering plans, if applicable
- Combination product information, if applicable
- List of all individuals from the sponsor's organization that will be attending the meeting
- A background section including: a brief history of development, substantive changes in product development plans, and the current status of development
- A statement summarizing the purpose of the meeting
- A proposed agenda, including estimated times needed for discussion
- A list of final questions, grouped by discipline, with context for the question.
- Data to support discussion, organized by discipline and question

*Per FDA Guidance: U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2017). Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA. Products Guidance for Industry

Figure 3-6. Rate of Inclusion of Recommended Items* for Meeting Packages (n=216) for INDs in Sample (n=147)

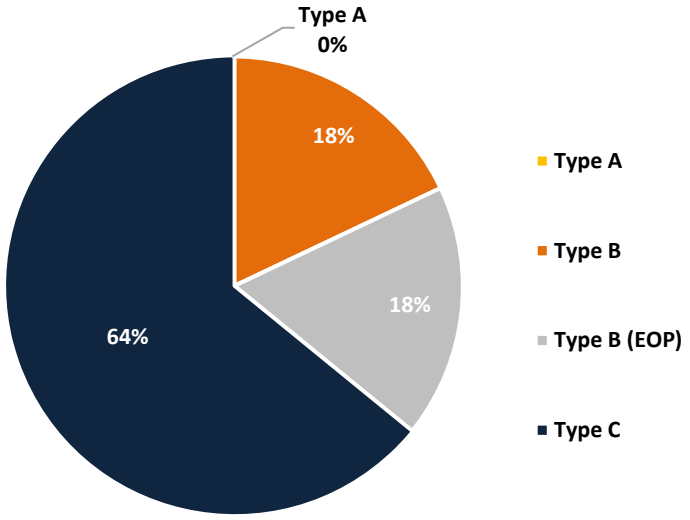


*Per FDA guidance: U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2017). Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA.

Of the 21% of meeting packages that were submitted outside the timelines specified in FDA guidance, the majority were for Type C meetings; a few were for Type B or Type B (EOP) meetings (Figure 3-8). In most cases, sponsors submitted their meeting packages within two weeks of the timeline specified in guidance. For example, of the 45 meeting packages submitted outside the timelines specified in guidance, the number of days late was:

- Type B (EOP) (n=12): mean 5 days, range 1-8 days after timeline in guidance.
- Type B (n=6): mean 8 days, range 1-20 days after timeline in guidance.
- Type C (n=27): mean 19 days, range 1-33 days after timeline in guidance.

Figure 3-7. Types of Meeting Packages Submitted After Timelines in FDA Guidance (n=39) for INDs in Sample (n=147)



Interview feedback. In interviews, FDA reviewers and IND sponsors cited good practices related to meeting packages that facilitated efficient communication for INDs in the sample:

- Ensure that meeting packages are mostly complete at the time of meeting request submission.
  This practice helps sponsors submit meeting packages on time and include all the information necessary for FDA to review and prepare preliminary comments.
- Ensure meeting packages are an appropriate length (i.e., the number and complexity of questions are appropriate) for the meeting requested.
  This practice helps FDA review the information in a timely manner and answer questions during the time allotted for the meeting.

Patterns by Traits of Interest

ERG examined patterns in meeting packages by traits of interest in the sample of active commercial INDs. ERG found no striking differences by sponsor size, RMAT designation, meeting type, or IND phase. ERG found some variations by the following traits:

- **FDA Review Office:** As expected given the lower number of meeting requests, INDs reviewed in CBER's OBRR were associated with a lower mean number of meeting packages per IND (0.3) than the sample as a whole (1.5). This difference was statistically significant at $p<0.05$.
- **BTD:** As expected given the greater number of meeting requests, INDs with BTD were associated with a greater mean number of meeting packages per IND (2.2) than the sample as a whole (1.5) and INDs without BTD (1.4). This difference was statistically significant at $p<0.05$.

3.6 Preliminary Comments from FDA

Key Points

- The mean number of preliminary comments per IND in the sample was 1.0. This number was higher for INDs with BTD (2.5).
- FDA sent most preliminary comments to sponsors within the expected timelines.
- In 22% of cases, sponsors cancelled a meeting after receiving FDA's preliminary comments.
- In 34% of preliminary comments, FDA stated that the sponsor's information was insufficient to answer at least one of the questions. FDA raised additional issues (not asked by the sponsor) in 73% of preliminary comments.
- FDA included regulatory/statutory or advisory language in most preliminary comments. In all cases, this language was used appropriately to distinguish between requirements and recommendations.

After reviewing a sponsor's meeting package, FDA holds an internal meeting to prepare and sends preliminary comments (responses to the sponsor's questions). In most cases, the preliminary comments then serve as a foundation for discussion during the meeting that FDA granted. If the sponsor feels that the preliminary comments answer their questions fully, so they no longer need further discussion in a meeting, they may cancel the meeting; in that case, the preliminary comments serve as the final meeting record.

ERG collected data on all 154 sets of preliminary comments that FDA sent to sponsors between July 31, 2018 and July 31, 2019 for the 147 commercial INDs in the sample. The number of preliminary comments (154) is lower than the number of meeting packages (216) in the assessment sample because WROs have no preliminary comments and because FDA sent preliminary comments for some meetings after the assessment period ended (because the Agency received the meeting packages near the end of this time period).

Data on metrics related to preliminary comments appear in Table 3-7. The mean number of preliminary comments per IND was 1.0.

Timeliness. For PDUFA VI, FDA committed to specific timelines for sending preliminary comments to sponsors: at least 5 days before the scheduled meeting date for Type B (EOP) and Type C meetings. FDA has internal goals of at least 2 days before the meeting date for Type A and Type B meetings. For INDs with Type B (EOP) or Type C meetings, FDA sent 84% of preliminary comments within the PDUFA timelines. For INDs with Type A or Type B meetings, FDA sent 98% of preliminary comments within the internal goals. According to FDA reviewers, the few delays were attributable to late or incomplete meeting packages from sponsors, heavy FDA workload, or unexpected FDA closings (e.g., due to weather).

Meeting cancellation. For INDs in the sample, sponsors cancelled 22% of scheduled meetings after receiving FDA's preliminary comments.

Table 3-7. Data for Evaluation Metrics Related to Preliminary Comments (n=154) for INDs in Sample (n=147)

Metrics	Result
Percent of preliminary comments sent on time	84%
Percent of preliminary comments resulting in a withdrawal or cancellation of meeting	22%
Percent of meeting packages where inadequate sponsor information precludes an answer from FDA in preliminary comments or WROs	34%
Percent of preliminary comments that address issues not identified by sponsors	73%
Percent of preliminary comments prepared with a template	97%
Percent of preliminary comments where FDA staff used statutory/regulatory or advisory language	98%
Of preliminary comments where FDA staff used statutory/regulatory or advisory language, percent where they used appropriate language	100%
Percent of preliminary comments that direct sponsors to a published guidance	64%

Preliminary comments content. If a sponsor submits a meeting package without enough information for FDA to answer a question, FDA will state this in the preliminary comments; this occurred in 34% of preliminary comments. ERG found no patterns in the types of sponsor questions that led to an FDA statement of insufficient information. FDA may also raise additional issues in preliminary comments if reviewers encounter topics where further information or analysis is needed. FDA did so in 73% of preliminary comments. In these cases, the issues that FDA raised were specific to the development program; ERG found no patterns beyond that.

Regulatory/statutory and advisory language. In preliminary comments, FDA may use regulatory/statutory or advisory language. Regulatory/statutory language includes words such as “must” and “required”. Advisory language uses words such as “recommend” and “advise”. Most (98%) of FDA’s preliminary comments included this kind of language; in all cases, FDA used the language appropriately to distinguish between legal requirements and FDA advice.

Referrals to guidance. FDA reviewers direct sponsors to published guidance if they feel that this can best answer the sponsor’s questions; 64% of preliminary comments included references to guidance. These, too, were specific to the development programs, with no major commonalities. As explained in Table 3-3 (in Section 3.2), occasionally sponsors were unsatisfied with referrals to guidance when they wanted development program-specific advice instead; in these instances, FDA reviewers felt that it would be premature to provide specific advice because the data available were insufficient.

Interview feedback. In interviews, FDA reviewers and sponsors cited a good practice related to preliminary comments that facilitated efficient communication: send preliminary comments as early as possible to the sponsor, even when there are no PDUFA goals for timing. This practice helps sponsors determine if meetings should be cancelled, or it helps sponsors focus their remaining questions and utilize the meeting effectively.

Patterns by Traits of Interest

ERG examined patterns in FDA preliminary comments by traits of interest in the sample of active commercial INDs. ERG found no striking differences by sponsor size, RMAT designation, FDA review office, meeting type, or IND phase. ERG found some variations by the following trait:

- **BTD:** As expected given the greater number of meeting requests, INDs with BTD were associated with a greater mean number of preliminary comments per IND (2.5) than the sample as a whole (0.98). This difference was statistically significant at $p<0.01$.

3.7 Meetings

Key Points

- The mean number of meetings per IND in the sample was 1.1. This number was higher for INDs with BTD (2.0).
- Most meetings in the sample were Type C or Type B meetings, about half were held face to face, the average duration was 47 minutes, and most addressed clinical topics.
- Face-to-face meetings typically involve more people (mean, 21) than teleconferences (mean, 19).

After receiving FDA's preliminary comments for Type B (EOP) and Type C meetings, sponsors must notify FDA within 3 days that they would like to proceed with the meeting. Sponsors may also respond to the preliminary comments, usually to identify which questions they wish to focus on during the meeting; FDA guidance does not specify a timeline for these responses. In general, sponsors should not submit new information or questions in their responses, as FDA reviewers might not have enough time to review new information prior to the meeting. After the sponsor's response, FDA and sponsor staff meet to discuss the sponsor's questions.

ERG collected data on all 161 completed meetings, including WROs, conducted between July 31, 2018 and July 31, 2019 for the 147 active commercial INDs in the sample; for CBER INDs, ERG extended the assessment period to August 31, 2019 to capture more meetings in CBER. The number of meetings (161) is greater than the number of preliminary comments (154) because FDA considers WROs to be meetings without preliminary comments. The number of meetings (161) is less than the number of meeting requests (249) because some were denied, withdrawn, cancelled, or held after the assessment period. Data on meeting metrics appear in Table 3-8. The mean number of meetings per IND was 1.1.

Table 3-8. Data for Evaluation Metrics Related to Meetings Held (n=161) for INDs in Sample (n=147)

Metrics	Result
Meeting Format: **Face-to-Face**	48%
Meeting Format: **Teleconference**	25%
Meeting Format: **Videoconference**	0%
Meeting Format: **Written Response Only**	27%
Meeting Type: **Type A**	3%
Meeting Type: **Type B**	30%
Meeting Type: **Type B (EOP)**	14%
Meeting Type: **Type C**	53%
Meeting Duration: **Mean***	47 minutes
Meeting Duration: **Median***	50 minutes
Meeting Duration: **Range***	72 minutes [13, 85]
Percent of INDs with an initial comprehensive multidisciplinary BTD/RMAT meeting	1%
Percent of meetings related to BTD/RMAT designation	17%

*Face-to-face and teleconferences only; WROs are excluded.

Meeting type, format, and duration. Most meetings in the sample were Type C or Type B, and about half were held as face-to-face meetings (Figure 3-8). On average, meetings lasted 47 minutes (range, 13 to 85 minutes). Face-to-face meetings tended to be somewhat longer than teleconferences (mean 50 minutes versus 38 minutes), and Type B (EOP) meetings tended to be somewhat longer than Type C meetings (mean 54 minutes versus 48 minutes).

Meeting topics. A majority (65%) of meeting topics discussed were clinical. The other topics discussed pertained to a scattered distribution of disciplines.

Meeting attendees. ERG had access to information about the roles of meeting attendees only for CDER meetings. The results presented here are therefore for CDER only. As expected, most FDA attendees were reviewers, team leads, directors, and RPMs, with a scattering of other roles present as needed (Figure 3-9). On the sponsor side, most attendees were directors, vice presidents, consultants, researchers, chief executives, and managers (Figure 3-10). The numbers of meeting attendees were:

- *Face-to-face meetings:* In total, mean 21 people (range 7 to 44), comprised of sponsor staff (mean 9, range 3 to 18) and FDA staff (mean 12, range 4 to 26).
- *Teleconferences:* In total, mean 19 people (range 7 to 38), comprised of sponsor staff (mean 10, range 4 to 16) and FDA staff (mean 9, range 3 to 22).

Interview feedback. In interviews, most sponsors characterized FDA's meeting guidance as useful in helping them understand what to expect during meetings. FDA staff and sponsors both commented that the OND Meeting Support Team was very helpful in scheduling meetings and processing visitors, which helped meetings be more efficient.

Some sponsors and FDA staff noted that the short time between preliminary comments and meetings is a challenge. For some sponsors, receiving preliminary comments 48 hours before a meeting sometimes made it difficult to respond to FDA's comments and plan travel to FDA. For some FDA reviewers, receiving additional data or questions from the sponsor within 48 hours of a meeting did not provide enough time to review materials, especially when the meeting package already contained numerous or complex questions or questions that were premature based on stage of development.

Nevertheless, most FDA staff and sponsors interviewed for this assessment stated that the meetings for their INDs effectively addressed the sponsor's questions. According to FDA reviewers, this was especially true when sponsors included enough background information in their meeting packages and clearly communicated their questions.

Patterns by Traits of Interest

ERG examined patterns in meetings by traits of interest in the sample of active commercial INDs. ERG found no striking differences by sponsor size, FDA review office, or IND phase. ERG found some variations by the following trait:

- **BTD:** As expected given the greater number of meeting requests, INDs with BTD were associated with a greater mean number of meetings per IND (2.0) than the sample as a whole (1.1) and INDs without BTD (0.9). These differences are statistically significant at $p<0.05$.

Figure 3-8. Meetings (n=161) for INDs in the Sample (n=147), by Format and Type

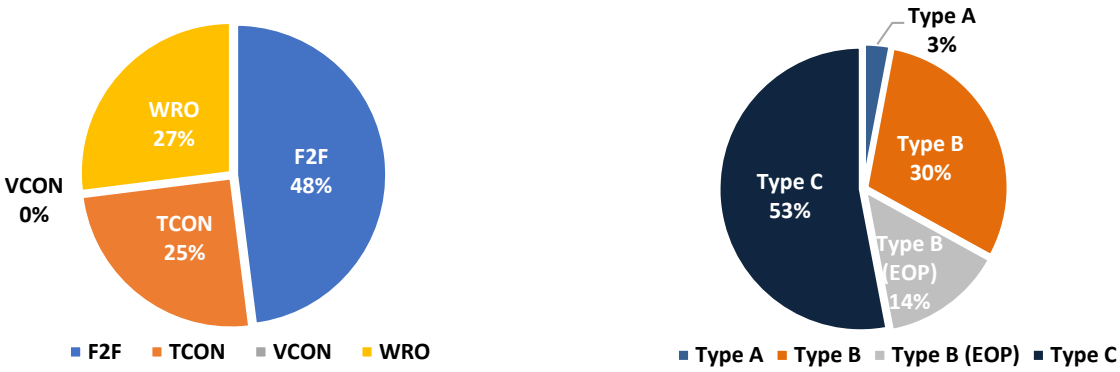


Figure 3-9. Roles of FDA Attendees at CDER Meetings (n=91) for INDs in Sample (n=147)

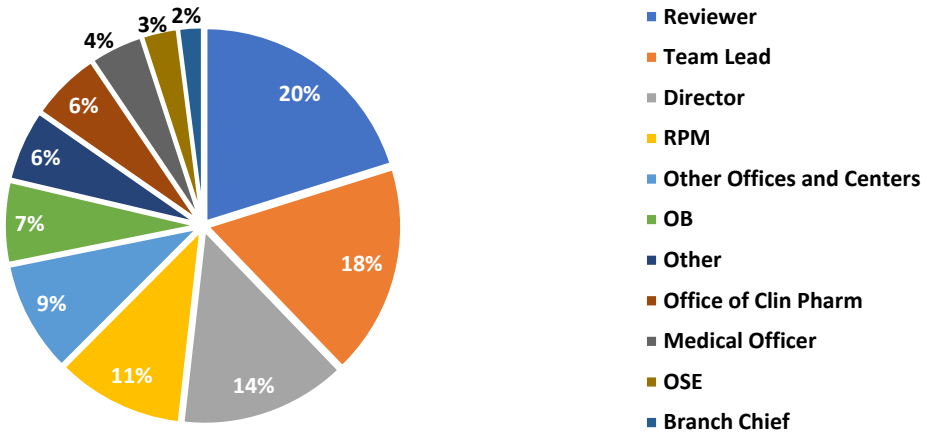
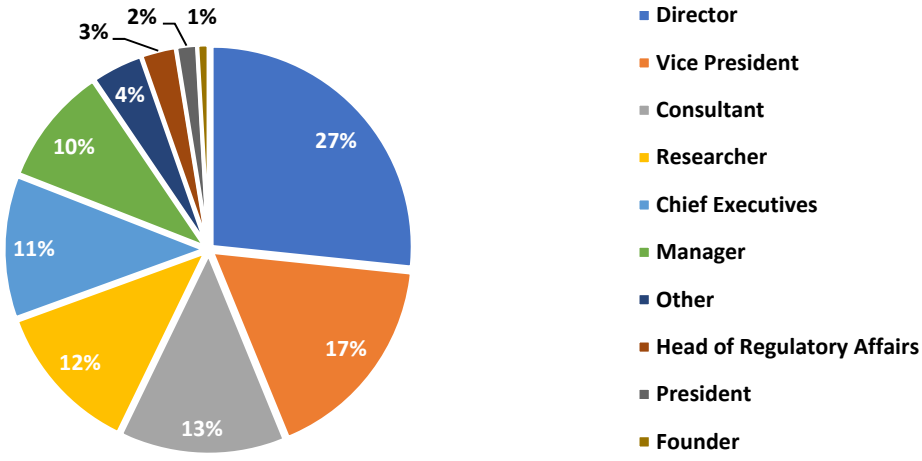


Figure 3-10. Roles of Sponsor Attendees* at CDER Meetings (n=91) for INDs in Sample (n=147)



*Occasionally, sponsor attendees have more than one role.

3.8 Meeting Minutes (Including WROs)

Key Points

- The mean number of meeting minutes per IND in the sample was 1.0. This was higher for INDs with BTD (2.0).
- For meetings in the sample, FDA issued minutes within the expected 30 days in 89% of cases.
- In all cases, minutes were consistent with topics discussed in the meeting. In about half of cases, FDA grouped the list of agreements and decisions by discipline. In more than half of cases, the minutes reflected topics that had not been identified by sponsors in their meeting packages; this was less likely to occur for INDs with BTD.
- In most meeting minutes, FDA used regulatory/statutory and advisory language to distinguish between requirements and recommendations, and often included references to guidance.

FDA guidances state that within 30 days of a meeting, FDA should prepare and send meeting minutes to sponsors. FDA RPMs utilize established meeting minute templates for this purpose. Preliminary comments that lead to meeting cancellation are also considered meeting minutes.

ERG collected data for all 152 sets of meeting minutes (including WROs) issued between July 31, 2018 and July 31, 2019 (for CDER) or September 10, 2019 (for CBER) for the 147 active commercial INDs in the sample. The number of meeting minutes (152) is lower than the number of meetings (161) in the assessment sample because minutes for meetings held late in the assessment period were not available for this analysis.

Data for evaluation metrics related to meeting minutes appear in Table 3-9. The mean number of meeting minutes per IND in the sample was 1.0. All minutes conformed to FDA's template.

Table 3-9. Data for Evaluation Metrics Related to Meeting Minutes (n=152) for INDs in Sample (n=147)

Metrics	Result
Percent of meeting minutes sent on time	89%
Percent of meeting minutes prepared with a template	100%
Percent of meeting minutes that present the same key topics (paths forward, action items, decisions) as observed during the meetings*	100%
Percent of meeting minutes that include a list of agreements/decisions by discipline*	70%
Percent of meeting minutes that address issues not identified by sponsors in meeting packages	55%
Percent of meeting minutes that contain statutory/regulatory or advisory language	95%
Of meeting minutes that contain statutory/regulatory or advisory language, percent that use appropriate language	100%
Percent of meeting minutes that direct sponsors to a published guidance	54%

*For face-to-face meetings and teleconferences only; excludes WROs.

Timeliness. In 89% of cases, FDA issued meeting minutes within the expected 30 days of the meeting (Table 3-9). The remaining handful of cases were Type C WROs that FDA issued within 46 to 87 days of the cancelled meeting date.

Content. All the meeting minutes in the sample presented the same key topics as observed during the meetings. This is consistent with feedback from sponsors, who stated that FDA's minutes reflected their understanding of the content discussed during meetings. According to these sponsors, in the rare instances where the minutes diverge from their expectations, the issues are typically minor and readily resolved via follow up with FDA.

In meeting minutes, some FDA reviewers and sponsors find it helpful to see a list of agreements and decisions made during the meeting organized by discipline. For meetings held for the INDs in the sample (excluding WROs), more than half included such a list. In the remaining meeting minutes, FDA typically included a list of agreements and decisions with the associated disciplines designated (but not sorted or grouped by discipline). This often happened when the questions in meeting packages were not grouped by discipline.

About half of meeting minutes for INDs in the sample addressed topics or issues not included in the sponsor's premeeting package. In general, these were topics that FDA raised in order to bring attention to considerations that sponsors should plan to address in their development programs, such as aspects of clinical trial protocols for safety and efficacy. In many cases, FDA raised these topics during the meeting and documented them in the minutes. In some cases, FDA added them to meeting minutes as post-meeting comments. In some cases, the minutes were WROs, so there was no verbal discussion.

Regulatory/statutory and advisory language. In meeting minutes (as with preliminary comments), FDA may use regulatory/statutory or advisory language to specify what is required versus recommended. The majority of meeting minutes contained such language, and the language was always used appropriately to distinguish between requirements and advice.

References to guidance. About half of meeting minutes in the sample included references to published FDA guidance, such as:

- *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*
- *Guidance for Industry entitled Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*
- *Photosafety Evaluation of Pharmaceuticals*
- *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*
- *Guidance for Industry Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*
- *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims (Patient-Focused Endpoints)*
- *Guidance on Safety Considerations for Product Design to Minimize Medication Errors*
- *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*

Patterns by Traits of Interest

ERG examined patterns in meeting minutes by traits of interest in the sample of active commercial INDs. ERG found no striking differences by sponsor size, FDA review office, or IND phase. ERG found some variations by the following traits:

- **BTD:** As with meeting requests, responses, packages, preliminary comments, and meetings, the mean number of meeting minutes per IND was higher for INDs with BTD (2.0) compared to the sample as a whole (1.0) and INDs without BTD (0.9). These differences are statistically significant at $p<0.05$.
- **BTD/RMAT Designation:** Fewer meeting minutes addressed topics not raised by sponsors in meeting packages for INDs with BTD or RMAT designation (37%) than for INDs in the sample as a whole (56%) or INDs without BTD or RMAT designation (58%). These differences are statistically significant at $p<0.05$. BTD and RMAT designation offer opportunities for more frequent communication with FDA, which might lead to a reduced need for FDA to address topics that sponsors did not raise.

3.9 IRs and Amendments

Key Points

- The mean number of IRs per IND in the sample was 4.4, and the mean number of amendments per IND was 14.3. These numbers were statistically significantly higher for INDs with BTD and for INDs in Phase 1.
- For INDs in the sample, a majority of IRs, amendments, and sponsors questions pertained to clinical topics.
- FDA included a due date for responses in about a quarter of IRs; the mean due date was 7 days.
- Some sponsors suggested that FDA provide adequate time for sponsors to respond to IRs and to provide scientific rationale whenever possible.
- Some sponsors also stated that it's helpful for FDA to provide an estimate of when they will provide answers to sponsor questions.

During the IND stage of drug development, FDA may request information from sponsors in the form of IRs. FDA issues IRs to clarify information already received or ask for additional data. Sponsors submit amendments to respond to FDA's IRs (solicited amendments) or to provide other information that has not been requested (unsolicited amendments). Sponsors may also ask questions of FDA. These exchanges represent another form of communication between FDA reviewers and sponsors.

IRs and amendments. ERG collected data on all 647 IRs issued and 2,137 amendments submitted between July 31, 2018 and July 31, 2019 for the 147 active commercial INDs in the sample. As shown in Table 3-10, the mean number of IRs per IND (4.4) was lower than the mean number of amendments per IND (14.3) because (1) sponsors sometimes sent multiple amendments to respond to a single IR, and (2) sponsors submitted unsolicited amendments to offer additional information for FDA consideration.

Table 3-10. Data for Evaluation Metrics Related to IRs (n=647), Amendments (n=2,137), Sponsor Questions (n=369), and FDA Responses (n=369) for INDs in Sample (n=147)

Metrics	Result*
Number of FDA IRs per IND: **Mean**	4.4
Number of FDA IRs per IND: **Median**	1
Number of FDA IRs per IND: **Range**	74 [0, 74]
Number of sponsor amendments per IND: **Mean**	14.3
Number of sponsor amendments per IND: **Median**	10.5
Number of sponsor amendments per IND: **Range**	71 [0, 71]
Number of sponsor questions per IND: **Mean**	2.5
Number of sponsor questions per IND: **Median**	0
Number of sponsor questions per IND: **Range**	98 [0, 98]
Number of FDA responses per IND: **Mean**	2.5
Number of FDA responses per IND: **Median**	0
Number of FDA responses per IND: **Range**	98 [0, 98]

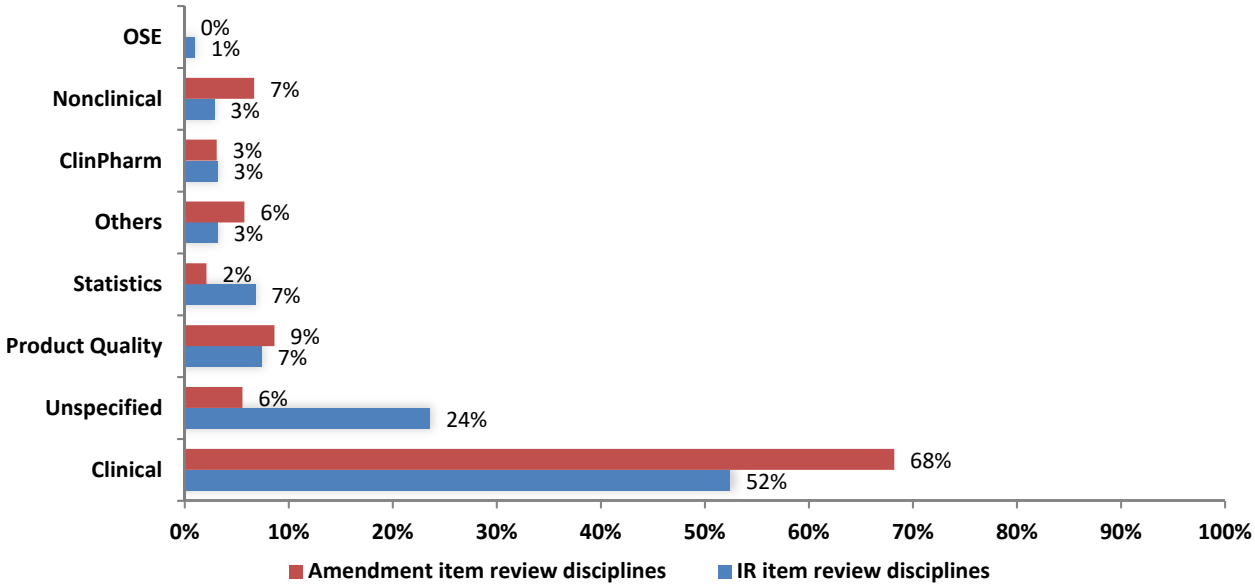
**These are counts of individual IR and amendment items, regardless of whether they were transmitted individually or in groups.*

FDA databases do not link IRs and amendments, so ERG is unable to offer accurate estimates of the number of solicited versus unsolicited amendments, or the number of amendments per IR.

For INDs in the sample, FDA provided due dates with 25% of IRs. The mean due date was 7 days (median 6 days, range 47 days) from IR transmittal. In interviews, FDA reviewers and sponsors stated that sponsors usually met these due dates, with FDA providing additional time when needed. FDA reviewers and sponsors did not indicate an ideal due date for IR responses because timing depends on so many factors such as the number and complexity of IRs to be addressed, proximity to major milestones or submissions, and geographic locations of members of the sponsor team (and whether they must coordinate across distant time zones).

As shown in Figure 3-11, a majority of IRs (52%) and amendments (68%) pertained to clinical topics. The remaining IRs and amendments were scattered across other disciplines and topics.

Figure 3-11. Distribution of Disciplines in IRs (n=647) and Amendments (n=2,137) for INDs in Sample (n=147)



Sponsor questions and FDA responses. Just as FDA may submit IRs to sponsors, sponsors may send questions or requests for comments to FDA. Counts of such sponsor questions and FDA responses for INDs in the sample appear in Table 3-10 (on the previous page). Most sponsor questions were about clinical trials. Sponsors also asked for feedback on additional clinical protocols or changes to existing protocols.

Interview feedback. In interviews, FDA reviewers and sponsors cited good practices related to IRs, amendments, and questions that facilitated efficient communication about the INDs in the sample:

- Provide sponsors with adequate time to respond to IRs, especially during the 30-Day Safety Review period, or be willing to negotiate deadline extensions. *This practice helps sponsors organize IRs and ensure that they can provide needed information by the due date.*

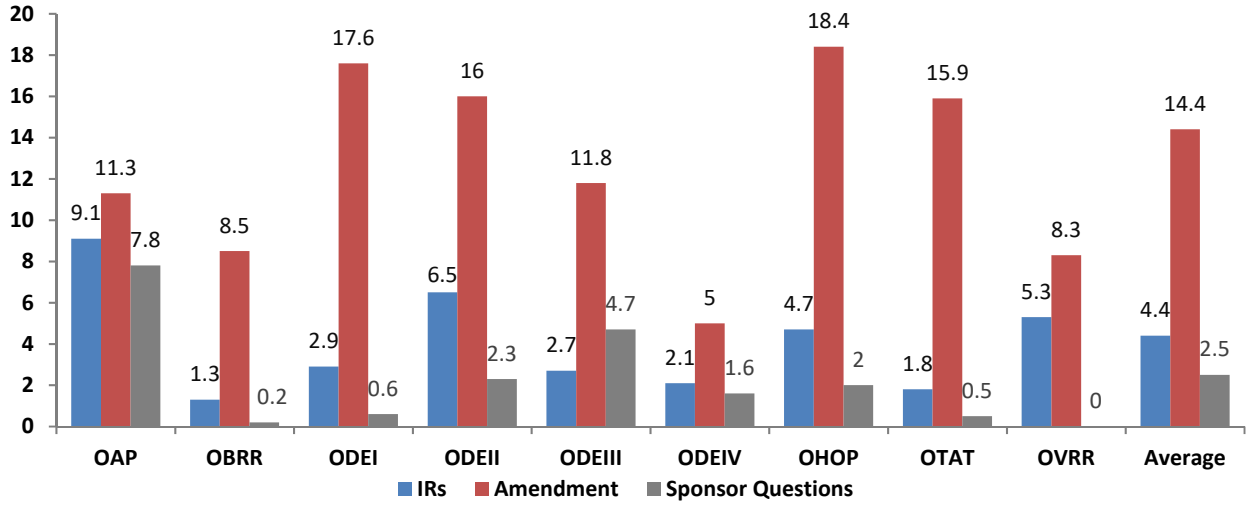
- Provide scientific rationales for IRs whenever possible. *This practice gives sponsors context for FDA's IRs and helps sponsors provide all relevant information.*
- Give sponsors estimates for when FDA will respond to their questions. *This practice gives sponsors an expected timeline for questions, which do not have PDFUA goal dates.*

Patterns by Traits of Interest

ERG examined patterns in IRs, amendments, and sponsor questions by traits of interest in the sample of active commercial INDs. ERG found some variations by the following traits:

- **BTD:** INDs with BTD had more IRs, amendments, and sponsor questions per IND (mean 26.5, 12.8, and 9.9, respectively) than INDs without BTD (mean 13.2, 3.6, and 1.8, respectively). These differences are statistically significant at $p<0.01$.
- **IND Phase:** INDs in Phase 1 had a greater mean number of IRs per IND (7.0) than INDs in Phase 2 (2.4). This difference is statistically significant at $p<0.05$.
- **Sponsor size:** Small sponsors received more IRs per IND (mean 6.3) compared to the sample overall (mean 4.4) and large companies (mean 4.0). Small sponsors also sent more questions per IND (mean 3.8) to FDA compared to large companies (mean 2.3). At this sample size, these differences are not statistically significant.
- **FDA review division:** The mean number of IRs, amendments, and sponsor questions across offices can be grouped into low-, mid-, and high-volume groups (Figure 3-12). For IRs, the low-volume group had a mean of 1-3 IRs per IND (OBRR, OTAT, ODEIV, ODEIII, ODEI), the mid-volume had a mean of 4-6 IRs per IND (OHOP, OVRR, ODEII), and the high-volume group had 9 IR items (OAP). For sponsor amendments, the low-volume group had a mean of 5-8 amendments per IND (ODEIV, OVRR, OBRR), the mid-volume group had a mean of 11-16 amendments per IND (OAP, ODEIII, OTAT, ODEII), and the high-volume group had a mean of 17-18 amendments per IND (ODEI, OHOP). For sponsor questions, the mean numbers of questions per IND were 0-1 (low volume: OVRR, OBRR, OTAT, ODEI), 2-3 (mid volume: ODEIV, OHOP, ODEII), and 4-8 (high volume: ODEIII, OAP). At this sample size, these differences are not statistically significant.
- **RMAT Designation:** INDs without RMAT designation had more IRs per IND (mean 4.5) than INDs with RMAT (mean 1.5). At this sample size, this difference is not statistically significant. There were no differences in the numbers of amendments and sponsor questions per IND for INDs with and without RMAT designation.

Figure 3-12. Distribution of Mean Number of IRs (n=647), Amendments (2,137), and Sponsor Questions (n=369) per IND for INDs in Sample (n=147), by FDA Office



3.10 Email and Phone Communications

Key Points

- Sponsors almost always communicated with FDA via RPMs. Rarely, sponsors communicated directly with reviewers, particularly when the sponsors were experienced and had prior relationships with the reviewers.
- Most sponsors praised FDA's RPMs for their availability and responsiveness.
- A majority of sponsors and FDA RPMs preferred to conduct communication via email, in part because the email thread provides documentation of the communication for reference.
- Sponsors and FDA reviewers generally agreed that email and telephone communication is best used for routine status updates and straightforward questions.

IND sponsors often communicate with FDA staff via email and telephone calls to discuss IND-related matters. Using surveys and interviews, ERG collected data about communications that took place between July 31, 2018 and July 31, 2019 and throughout the lifetime for the 147 INDs in the sample. Because this is qualitative rather than quantitative data, ERG does not present quantitative metrics here.

Role of RPM. For INDs in the sample, nearly all email and telephone communications between sponsors and FDA involved the Agency's RPMs for the INDs. RPMs consulted with FDA reviewers, or arranged teleconference calls between sponsors and FDA reviewers, when needed to address sponsor questions – that is, when these questions could be answered over email rather than through the formal meeting process. Rarely, sponsors and FDA reviewers reported instances of sponsors contacting FDA reviewers directly (without going through the RPM); this occurred with a few sponsors who had previously established relationships with FDA reviewers for other INDs.

Satisfaction. Most sponsors and FDA reviewers expressed satisfaction with the frequency, timeliness, and nature of email and telephone communications. Some noted that it was helpful to establish the desired frequency (e.g., monthly, as needed) and method (e.g., email, phone call) of these communications at the beginning of the relationship. Most sponsors praised the availability and responsiveness of FDA's RPMs; a small number indicated that the RPM was not as responsive as desired. Most FDA staff stated that their communications with sponsors were constructive and effective; a small number indicated frustration with sponsors who contacted FDA reviewers directly.

Communication method. Most sponsors and FDA RPMs reported a preference for email as a main vehicle for communications outside of formal meetings and IRs and amendments. This practice provides documentation of the communications for reference and helps to ensure a shared understanding of communication content.

Topics. Sponsors and FDA reviewers generally agreed that topics best addressed through email or telephone calls include small, simple, or readily answerable questions about the development program, regulatory requirements, or guidance; updates about the status of the sponsor's development program or sponsor/FDA responses to questions; courtesy copies of submissions and confirmations of receipt of information; and logistical questions about upcoming meetings or milestones.

Patterns by Traits of Interest

ERG observed no patterns in email and telephone communication by traits of interest for INDs in the sample.

3.11 Use of Templates

Key Points

- FDA RPMs used established templates to prepare all meeting minutes and nearly all preliminary comments.
- Those who commented on the templates stated that they are useful.

FDA has established templates for two types of documents that reviewers prepare during the meeting process: preliminary comments and meeting minutes (including WROs). Using these templates fosters consistent and accurate transmission of information to other FDA staff and to sponsors.

ERG collected data on the use of FDA templates for all 154 preliminary comments and 152 meeting minutes issued between July 31, 2018 and July 31, 2019 for active commercial INDs in the sample.

Use of established templates for preliminary comments and meeting minutes was nearly universal (Table 3-11). FDA RPMs were so accustomed to using these templates that they rarely commented on them during the interviews that ERG conducted. The few who did stated that the templates are useful.

Patterns by Traits of Interest

Because use of templates for preliminary comments and meeting minutes is nearly universal, ERG found no patterns in their use by traits of interest in the sample of active commercial INDs.

Table 3-11. Data for Evaluation Metrics Related to Use of FDA Templates for Preliminary Comments (n=154) and Meeting Minutes (n=152) for INDs in Sample (n=147)

Metrics	Result
Percent of preliminary comments prepared with a template	97%
Percent of meeting minutes prepared with a template	100%

3.12 Use of Regulatory/Statutory and Advisory Language and Guidance

Key Points

- Nearly all preliminary comments and meeting minutes included regulatory/statutory and advisory language, and the use of this language was appropriate to distinguish between legal requirements and FDA advice.
- Most sponsors stated that FDA clearly distinguished between requirements and recommendations/advice.
- Over half of preliminary comments and meeting minutes also included references to FDA guidance documents.

In meeting-related documents, FDA may use regulatory/statutory language (words such as "must" and "required") and advisory language (words such as "recommend" and "advise") to distinguish between requirements and recommendations. ERG collected data on the use of such language in all 154 preliminary comments and 152 meeting minutes issued between July 31, 2018 and July 31, 2019 for the 147 INDs in the sample. Use of regulatory/statutory and advisory language in these documents was nearly universal and appropriate (Table 3-12). In surveys and interviews, nearly all sponsors indicated that the distinction between requirements and advice was clear in these written materials (and in verbal conversations as well).

FDA reviewers also directed sponsors to published guidance if they felt that this could best answer the sponsor's questions. They did so in over half of preliminary comments (61%) and meeting minutes (54%).

Table 3-12. Data for Evaluation Metrics Related to Use of Regulatory/Statutory and Advisory Language and References to Guidance in Preliminary Comments (n=154) and Meeting Minutes (n=152) for INDs in Sample (n=147)

Metrics	Result
Percent of preliminary comments that contain statutory/regulatory or advisory language	98%
Of preliminary comments that contain statutory/regulatory or advisory language, percent where they used appropriate language	100%
Percent of preliminary comments that direct sponsors to a published guidance	64%
Percent of meeting minutes that contain statutory/regulatory or advisory language	95%
Of meeting minutes that contain statutory/regulatory or advisory language, percent that use appropriate language	100%
Percent of meeting minutes that direct sponsors to a published guidance	54%

3.13 Changes in FDA Advice

Key Points

- According to IND sponsors and FDA reviewers who responded to ERG surveys and interviews, most INDs experienced no changes in FDA advice during the IND's lifetime (defined as the period from IND inception through the end of the assessment period).
- When changes in advice did occur, the reason usually was receipt of new or updated data from the sponsor.
- Sponsors reported no major impacts on their development programs due to changes in FDA advice.

During the IND stage of drug/biologic development, FDA provides sponsors with advice about various aspects of the development program, such as the design of clinical trials, data sets, and upcoming milestones and submissions. The Agency would like to understand the extent to which this advice changes during the lifespan of the IND. ERG collected data on changes in FDA advice throughout the lifetime of all 147 active INDs in the sample, where lifetime is defined as the period from the inception of the IND through the end of the assessment period. For the INDs in the assessment sample, the mean IND lifetime was 6.1 years (median 4.6 years, range 0.4 to 29.0 years).

According to IND sponsors and FDA reviewers who responded to ERG's surveys and interviews, Agency advice remained consistent throughout the lifetime for most of the INDs in the sample (Table 3-13). Sponsors were slightly more likely than FDA reviewers to report changes in advice, but this difference was not statistically significant.

According to IND sponsor and FDA reviewer feedback during interviews with ERG, the main reason for changes in advice was the availability of new or updated data that provided more (or different) information as the basis for advice. A few FDA interviewees cited changes in FDA staff or organizational structure as reasons for changes in advice, but they noted that this is not typical; in fact, they stated that FDA staff usually do a good job in briefing each other during staff changes in order to foster a seamless transition. Sponsors interviewed by ERG reported no major impacts to their development programs stemming from changes in FDA advice.

Patterns by Traits of Interest

ERG found no significant patterns in changes in FDA advice by traits of interest in the sample of active commercial INDs.

Table 3-13. Data for Evaluation Metrics Related to Changes in FDA Advice from FDA (n=132) and Sponsor (n=98) Interview Respondents

Metrics	Result
Percent of interview respondents who reported no changes in FDA advice over the lifetime of their INDs	82%
Percent of interview respondents who reported no changes in FDA advice over the lifetime of their INDs: sponsors	87%
Percent of interview respondents who reported no changes in FDA advice over the lifetime of their INDs: FDA reviewers	76%

3.14 Changes in FDA Review Teams

Key Points

- The mean number of review team changes per IND in the assessment sample was 8.8 over the lifetime of the IND (from IND inception to end of assessment period), or about 1 per IND per year.
- Review team changes occurred due to retirements, resignations, position changes, and shifting INDs to rebalance workloads.
- Sponsors reported that new FDA review members appeared to be well prepared, having reviewed IND materials and debriefed with experienced team members to get up to speed.

FDA review teams consist of the RPM, medical officers, and specialists in statistics, pharmacology, toxicology, clinical pharmacology, biopharmaceutics, chemistry, biology, microbiology, and other disciplines as needed. ERG collected data on changes in FDA review teams throughout the lifetime of the 147 active commercial INDs in the sample, where lifetime is defined as the period from the inception of the IND through the end of the assessment period. For the INDs in the assessment sample, the mean IND lifetime was 6.1 years (median 4.6 years, range 0.4 to 29.0 years).

For INDs in the sample, the mean number of review team changes over an IND's lifetime was 8.8 (Table 3-14). Accounting for the lifespans of the INDs, the mean number of review team changes per IND per year was about 1. In interviews, reasons cited for changes in review teams included retirements, resignations, transfers to other divisions or other parts of FDA, promotions, reorganizations, and workload imbalances that required shifting INDs to different reviewers.

Sponsors interviewed for this assessment commented that FDA staff turnover could theoretically impact their development programs, but that this rarely happens in practice. They and FDA reviewers stated that this is because new team members typically reviewed IND materials and debriefed with experienced reviewers to get up to speed. In rare instances, sponsors reported that review team changes could potentially slow drug/biologic development or hinder communications; they stated that this is most likely to happen when the RPM and division/office director changes.

Sponsors and FDA reviewers for INDs in the sample cited a good practice to help prevent disruption due to review team changes: notify the sponsor as soon as possible so they can prepare for the change.

Patterns by Traits of Interest

ERG found no significant patterns in FDA review team changes by traits of interest in the sample of active commercial INDs.

Table 3-14. Data for Evaluation Metrics Related to Changes in FDA Review Teams

Metrics	Result
Number of FDA review team changes per IND: **Mean**	8.8
Number of FDA review team changes per IND: **Median**	7
Number of FDA review team changes per IND: **Range**	34 [0, 34]

4. Assessment Questions and Answers

4.1a What are current FDA review staff and sponsor IND communication practices?

Currently, FDA review staff and IND sponsors communicate via the formal meeting process, IRs and amendments, sponsor questions and FDA responses, and email and telephone communications (Figure 4-1).

Formal meeting process. FDA staff and sponsor representatives engage in formal meeting processes in order to discuss topics related to a stalled development program (Type A meetings), major milestones and upcoming submissions (Type B meetings), completion of a phase of clinical trials (Type B EOP meetings), and general guidance or surrogate endpoints (Type C meetings). The formal meeting process, described below based on the results of this assessment, is an effective means of addressing substantive scientific and regulatory topics that arise during the IND stage of drug/biologic development.

- ***Meeting requests.*** During the assessment period, sponsors submitted written meeting requests to FDA via the Agency's or Center's electronic gateway. Most (69%) requested face-to-face meetings, while some requested teleconferences or WROs when face-to-face meetings were unnecessary or impractical. About half of requests were for Type C meetings, and most others were for Type B or Type B (EOP) meetings; about 3% of requests were for Type A meetings. About half of meeting requests included all elements required by FDA guidance, and about one-third included all the recommended elements as well. Elements least likely to be included were meeting package date and list of requested FDA attendees (required) as well as regulatory pathway (recommended), which sponsors might not have known yet or been ready to share. Most sponsors included a suggested meeting date; about half of these dates were later than the timeframes specified in FDA guidance (Table 4-1) by a few days to two weeks.

- ***Meeting request responses.*** FDA granted nearly all (98%) meeting requests and did so within the timelines specified in FDA's guidance. The Agency occasionally denied a meeting request if the proposed topics were premature or the request was incomplete. FDA typically granted the sponsor's requested meeting type (91% of meeting request responses) and format (77% of meeting request responses).

- ***Meeting packages.*** For INDs in the assessment sample, meeting packages typically included information from meeting requests, brief background on the IND, and data to support discussion of the sponsor's questions during the meeting. FDA guidance includes a list of 15 items recommended (but not required) for inclusion in sponsor meeting packages; 35% of meeting packages in the assessment sample included all recommended items. FDA encourages sponsors to limit the number and scope of questions to a volume that can be meaningfully addressed during a standard one-hour meeting; in the assessment sample, sponsors included an average of seven questions per meeting package. Sponsors submitted most meeting packages on time or within a few days of the timeframe specified in FDA guidance.

Figure 4-1. FDA-Sponsor Communication Practices Observed for INDs in Assessment Sample (n=147) During July 31, 2018 to July 31, 2019

Meeting Process:	**Sponsor Meeting Requests** • Mean 1.7 per IND • 46% Type C 30% Type B 20% Type B (EOP) 4% Other • 69% F2F 17% T-CON 9% Other • 54% complete • Most often missing: meeting package date, list of requested FDA attendees • Characterized as straightforward • No major challenges	**FDA Meeting Request Responses** • Mean 1.6 per IND • 50% Type C 31% Type B 16% Type B (EOP) 3% Type A • 51% F2F 24% T-Con 25% Other • 83% sent on time • Characterized as straightforward, clear • No major challenges	**Sponsor Meeting Packages** • Mean 1.5 per IND • 79% submitted on time per guidance • 35% complete • Most often missing: proposed pathway • Characterized as straightforward • No major challenges • Suggestion: prepare most of meeting package before submitting request, ensure scope of questions is appropriate	**FDA Preliminary Comments** • Mean 1.0 per IND • 22% accepted as WRO by sponsors • 34% noted sponsor information insufficient to answer a question • 73% FDA raised additional issues • 64% reference guidance • 84% sent on time per guidance • Characterized as straightforward • No major challenges	**Meetings*** • Mean 1.1 per IND • 53% Type C 30% Type B 14% Type B (EOP) 3% Type A • 48% F2F 25% T-Con 27% WRO • Mean duration 47 minutes • Mean 19 (T-Con) to 21 (F2F) attendees • Characterized as effective, clear • Some challenges with equipment (T-Con) or meeting room availability (F2F)	**Meeting Minutes** • Mean 1.0 per IND • 89% sent on time • 54% reference guidance • Characterized as clear, accurate • No major challenges
IRs and Amendments, and Sponsor Questions and FDA Answers:	• Mean 4.4 IRs and 14.3 amendments per IND; mean 2.5 sponsor questions and 2.5 FDA responses per IND • Most IRs occurred after sponsor submissions and amendments to FDA • Sponsor amendments included solicited responses to IRs and unsolicited updates and additional data • Most IRs and amendments pertained to clinical topics such as clinical protocols, trials, and requirements • Characterized as smooth, straightforward, clear • Good practices included FDA providing scientific rationale for IR and a due date for sponsor response • Characterized as helpful, collaborative, usually timely • Suggestion: provide sponsor with estimate of when FDA will respond to sponsor questions					
Email and Telephone Communications:	• Nearly all sponsor communications went through RPM • Frequency varied with stage of development and proximity to major milestones and submissions • Many RPMs and sponsors preferred communicating by email, with telephone calls reserved for quick simple questions • Most pertained to questions of clarification, logistical questions, and straightforward technical/clinical questions • Characterized as clear, collaborative, effective, efficient, and usually timely • Good practices included establishing up front the RPM's preferred modes and frequency of communications					

*For CBER INDs, assessment period extended to August 31, 2019 to capture more meetings in CBER.

Table 4-1. PDUFA VI Meeting Management Procedural Goals*

Meeting Type	FDA Response to Meeting Request	Sponsor Meeting Package to FDA	FDA Preliminary Comments to Sponsor**	Sponsor Response to FDA Preliminary Comments**	Scheduled Meeting Date	Meeting Minutes from FDA to Sponsor*
A	14 days	With meeting request	At least 2 days before meeting	Within 3 days of prelim comments	Within 30 days of meeting request	By 30 days after meeting
B	21 days	At least 30 days before meeting	At least 2 days before meeting	Within 3 days of prelim comments	Within 60 days of meeting request	By 30 days after meeting
B (EOP)	14 days	At least 50 days before meeting	At least 5 days before meeting	Within 3 days of prelim comments	Within 70 days of meeting request	By 30 days after meeting
C	21 days	At least 47 days before meeting	At least 5 days before meeting	Within 3 days of prelim comments	Within 75 days of meeting request	By 30 days after meeting

**From FDA Guidance: U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2017). Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA. Products Guidance for Industry.*
***Face-to-face meetings and teleconferences only.*

- ***Preliminary comments.*** FDA typically submitted its preliminary comments within the timelines specified in guidance. FDA reviewers and sponsors believed that the Agency's preliminary comments were effective in answering sponsor questions. In fact, in about 22% of cases sponsors cancelled scheduled meetings because FDA's preliminary comments fully answered their questions. In some cases, sponsors responded by identifying a subset of questions that they would like to focus on during the meeting. Sponsors sometimes raised new questions, which FDA staff accommodated when feasible; FDA staff were sometimes unable to prepare answers for additional new questions asked just before the meeting took place. Most (97%) of preliminary comments were prepared using FDA's standard template.

- ***Meetings.*** The meetings themselves were an effective forum for discussing sponsor questions and FDA answers in order to achieve resolution or a shared understanding of the issues. FDA staff typically included the RPM, reviewers, team leads, and often a review division director. Sponsor staff often included one or more senior managers (directors, vice presidents, chief executives), consultants, and researchers. Face-to-face meetings often included more attendees (mean, 21) than did teleconference (mean, 19), and often ran longer as well. Most meetings were scheduled for 60 minutes, with some being scheduled for longer or shorter durations; the mean actual meeting duration was 47 minutes.

- ***Meeting minutes.*** FDA's minutes accurately summarized key topics (paths forward, action items, decisions) discussed during the meeting. About half of meeting minutes also addressed issues not originally raised by sponsors in their meeting packages; these were usually considerations that FDA believed that sponsors should address in their development programs, such as aspects of clinical trial protocols for safety and efficacy. In many cases, FDA raised these topics during the meetings and documented them in minutes; in some cases, there was no verbal discussion because FDA added the topics as post-meeting comments or because the minutes were WROs. FDA staff used established templates for meeting minutes, included regulatory and advisory language to distinguish between requirements and recommendations, and often included references to published FDA guidance to help answer sponsor questions. FDA submitted meeting minutes on time, within the 30 days specified by guidance.

In this assessment, the mean number of formal meetings was 1.1 per IND per year. As expected, this number was statistically significantly higher for INDs with BTD, where FDA commits to a greater degree of communication.

IRs and amendments. FDA reviewers sent IRs to sponsors to request clarification of data already submitted for the IND or more data. In about a quarter of cases, FDA included a due date for response (mean 7 days). Sponsors responded with amendments containing answers and additional data. They also submitted unsolicited amendments to provide additional information that FDA did not request, such as updates and additional protocols. Most IRs and amendments pertained to clinical topics, such as clinical trials and protocols. During the one-year assessment period, the mean number of IRs per IND was 4.4, and the mean number of amendments per IND was 14.3; these numbers were statistically significantly higher for INDs with BTD and for INDs in Phase 1.

Sponsors also submitted questions and requests for comments on submissions to FDA, which Agency reviewers answered. During the one-year assessment period, the mean number of sponsor questions (and FDA responses) per IND was 2.5.

Email and telephone communication. RPMs and the IND sponsor's authorized representative often communicate via email and telephone calls. Many RPMs and sponsors preferred email, which provided documentation of the interaction for reference; many IND sponsors asked about the RPMs' communication preferences early in the relationship. These rapid communications were an effective way of addressing logistical and relatively straightforward questions and issues. These communications were most frequent around the time of major development milestones and before major sponsor submissions to FDA. RPMs occasionally facilitated teleconferences that included other reviewers during those periods. The OND Meeting Support Team was helpful in assisting with meeting scheduling and logistics.

4.1b To what extent do current IND communications incorporate recommended practices, guidances, and standard operating procedures?

FDA offers recommended practices, guidances, and standard operating procedures relevant to IND communications:

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

- Guidance for industry and review staff: *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*
- Guidance for review staff and industry: *Good Review Management Principles and Practices for PDUFA Products*
- CBER SOPP 8101.1: *Regulatory Meetings With Sponsors and Applicants for Drugs and Biological Products*
- PDUFA VI timeline goals for various elements of the formal meeting process (Table 4-1).

In general, most types of FDA-sponsor communications conformed to PDUFA VI goals, guidances, and recommended practices. However, there was considerable variability, as shown in Table 4-2 (required practices) and Table 4-3 (recommended practices).

Table 4-2. Conformance of Communication Practices for INDs in Sample (n=147) with Requirements in PDUFA VI Goals and FDA Guidance

Communication Type	Percent That Conformed to Required Timeline	Percent That Contained All Required Elements	Notes
Meeting Requests (n=249)	*	• 54% included all required items (Table 3-4)	• Elements most often missing: date for meeting package submission, list of requested FDA attendees
Meeting Request Responses (n=237)	• 82% on time responses	• 100% of denied requests were given a reason	• Reasons for denial: discussion of the meeting topics was premature, or the meeting request was incomplete
Meeting Packages (n=216)	• 79% submitted on time (Table 3-6)	*	• Mean number of days late: Type B (EOP), 5; Type B, 8; Type C, 19
Preliminary Comments (n=154)	• 84% submitted on time (Table 3-7)	*	• Reasons for delays: late or incomplete meeting packages, heavy FDA workload, unexpected FDA closings (e.g., due to weather)
Meeting Minutes (n=152)	• 89% issued on time (Table 3-9)	*	• Reasons for delays: changed to Type C WROs that FDA issued within 46 to 87 days of the cancelled meeting date

* No requirements.

Table 4-3. Conformance of Communication Practices for INDs in Sample (n=147) with Recommendations in PDUFA VI Goals and FDA Guidance

Communication Type	Percent That Conformed to Recommended Timeline	Percent That Contained All Recommended Elements	Notes
Meeting Requests (n=249)	• 29% included all recommended items • 57% suggested meeting dates within timelines in guidance	• 29% included all recommended items • 90% of requested FDA meeting attendees aligned with question disciplines	• Elements most often missing: regulatory pathway, list of requested FDA attendees by discipline, specialty items
Meeting Request Responses (n=237)	• 83% submitted on time	• 69% granted meeting date requests (Table 3-5)	• Reasons for denying requested date: outside guidance timeline, FDA staff or meeting room schedule conflicts
Meeting Packages (n=216)	*	• 35% included all recommended items (Table 3-6)	• Commonly missing elements: proposed regulatory pathway, specialty items
Preliminary Comments (n=154)	• 98% submitted within internal goals	*	• Reasons for delays: late or incomplete meeting packages, heavy FDA workload, unexpected FDA closings (e.g., due to weather)
Meeting Minutes (n=152)	*	• 100% used template (Table 3-9) • 100% presented the same key topics (paths forward, action items, decisions) as observed during meetings (Table 3-9) • 70% included a list of agreements/decisions by discipline (Table 3-9) • 55% addressed issues not identified by sponsors in meeting packages	*(None)*
Point of Contact	Nearly all sponsors communicated with the RPM nearly all the time. In rare instances, sponsors directly contacted FDA reviewers or division directors in hopes of accelerating IND progress or because they felt that the RPM did not respond promptly. This occurred with a small number of experienced sponsors who had established relationships with FDA staff.		

* No recommendations.

4.2 How do communication practices vary by IND characteristics such as sponsor size, special designations, review division, meeting type, and IND phase?

In general, FDA-sponsor IND communication practices were consistent across sponsor sizes, FDA review offices and divisions, and meeting types. Communication practices were similar, but more frequent, for INDs with BTD and for INDs in Phase 1 trials. This finding was consistent with expectations given that BTD explicitly provides for more frequent communications and more frequent communications are often needed during the early stages of drug/biologic development.

Sponsor Size. Based on this assessment, communication practices (including frequency of communications) did not vary significantly by sponsor size. Anecdotally, many FDA reviewers interviewed for this assessment stated that communications tended to be more frequent with small sponsors and those without previous regulatory experience. It is possible that statistically significant differences exist but could not be detected with the sample size used for this assessment.

Special Designations. Designations such as BTD and RMAT give sponsors opportunities for increased communication with FDA. In fact, for the INDs in this assessment FDA-sponsor communications of all types were more frequent for INDs with BTD than for INDs without BTD; some types of communications were also more frequent for INDs with RMAT designation than for INDs without RMAT (Table 4-4). Communications were more *frequent*, but communication *practices* were the same as those for INDs without special designations.

FDA Review Office or Division. In general, FDA-sponsor communication practices during the IND stage of development did not vary by FDA review office or division, with one exception: in this assessment, INDs in CBER's OBRR were associated with fewer sponsor meeting requests, FDA meeting request responses, and sponsor meeting packages than in the sample as a whole.

Meeting Type. In general, IND-stage communication practices did not vary by meeting type. However, meeting types varied widely in how frequently they were requested. In particular, Type C meetings were most common (46% of requests, 53% of meetings held in assessment sample), followed by Type B meetings (30% of requests, 30% of meetings held in assessment sample) and Type B (EOP) meetings (21% of requests, 14% of meetings held in assessment sample). Type A meetings were uncommon (3% of meetings in sample).

IND Phase. In general, FDA-sponsor communication practices did not vary by IND phase (i.e., phase of clinical trials being conducted for the IND). FDA issued more IRs for INDs in Phase 1 than in other phases, but otherwise communication practices were consistent.

Table 4-4. Frequency of Communications for INDs with BTD (n=13) or RMAT (n=6) Compared to all INDs in Sample (n=147) for One-Year Assessment Period (July 31, 2018 to July 31, 2019)

Communication Type	Mean Number of Communications					
	INDs with BTD	All INDs	Difference Statistically Significant	INDs with RMAT	All INDs	Difference Statistically Significant
Sponsor Meeting Requests	2.7	1.7	Yes	1.3	1.7	No
FDA Meeting Request Responses	2.7	1.6	Yes	1.3	1.6	No
Sponsor Meeting Packages	2.2	1.5	Yes	1.3	1.5	No
FDA Preliminary Comments	2.5	1.0	Yes	0.8	1.0	No
Meetings	2.0	1.1	Yes	1.1	1.1	No
Meeting Minutes	2.0	1.0	Yes	1.1	1.0	No
FDA IRs	26.5	2.7	Yes	0.5	2.7	No
Sponsor Amendments	12.8	8.3	Yes	6.2	8.3	No
Sponsor Questions / FDA Answers	9.9	0.7	Yes	0.8	0.7	No

4.3 How do FDA review staff and sponsors characterize IND communications during drug/biologic development?

FDA review staff and sponsors characterized their communications during the IND stage of drug/biologic development as clear, effective, efficient, collaborative, and timely. This was true across all types of communications: the formal meeting process, IRs and amendments, sponsor questions and FDA answers, and email and telephone communications. FDA reviewers and sponsors observed that the frequency and modes of communication varied throughout the lifecycle of the IND, and that this was appropriate and purposeful based on the stage of development of the drug/biologic. Sponsors described communications with FDA as very important in enabling them to improve or make decisions about their development programs—in order to make progress as efficiently and confidently as possible.

RPMs. FDA reviewers and sponsors affirmed that the Agency's model of having IND-related communications flow through the FDA RPM is effective and desirable. This model provides for consistency in information-sharing as well as efficiency in communication management. Sponsors especially praised RPMs for their collaborative approach and responsiveness.

For the INDs in the sample for this assessment, a few sponsors noted instances where the FDA was less responsive than typical. Sponsors attributed these outliers to heavy workloads, or occasionally to the RPM's personality or the sponsor's lack of knowledge about the RPM's preferred communication methods. In some cases, sponsors also expressed frustration with not knowing when to expect responses to their questions submitted via email or telephone calls with the RPM. FDA reviewers sometimes noted delays in sponsor responses as well – and frustration with the rare instances when sponsors communicated directly with reviewers or division directors instead of the RPM.

Distinction Between Requirements and Advice. Sponsors characterized FDA's verbal and written communications as being very clear in distinguishing between regulatory/statutory requirements and FDA advice or recommendations. This was consistent across all types of communications (FDA preliminary comments, verbal statements in meetings, meeting minutes, and email and telephone communication).

Guidances. FDA review staff and sponsors characterized FDA's published guidances as clear and useful. Some sponsors suggested adding or clarifying timelines for FDA responses to sponsor questions (during communications outside the formal meeting process). In addition, sponsors sometimes wished that FDA reviewers would provide development program-specific advice instead of directing them to guidance; FDA reviewers sometimes felt that the requests for advice were premature (due to lack of sufficient data on which to base advice), so directing the sponsors to guidance was more appropriate. These comments were not a reflection on FDA's guidance; rather, they reflected the challenge of balancing an understandable desire for early feedback (sponsors) with an equally understandable desire to provide advice that is scientifically sound (FDA reviewers).

Communication Infrastructure. Some FDA reviewers and sponsors reported that technical issues with FDA's teleconference system sometimes disrupted meetings held by teleconference, resulting in an inability to hear all meeting participants, less meeting time, and challenges in fully discussing all planned topics. Some also noted that insufficient availability of FDA meeting rooms posed a challenge in scheduling meetings in a timely manner.

Accuracy and consistency. FDA reviewers and sponsors characterized FDA documentation (e.g., meeting minutes) as accurate, reflecting their understanding of conversations. Importantly, sponsors characterized FDA's communications as consistent across staff and throughout the lifetime of the IND. For example, sponsors observed that FDA's advice remained consistent even when the review team experienced staffing changes; sponsors attributed this consistency to FDA staff being diligent in briefing each other and reviewing IND documentation when they joined the review team. FDA's advice sometimes changed upon receipt of new data or additional information, which FDA reviewers and sponsors deemed to be appropriate and expected.

4.4 What practices help optimize IND communications, what challenges hinder optimum communications, and what steps can FDA take to improve communications moving forward?

Good practices for fostering transparency and predictability for FDA review staff and sponsors included the following:

- ***Proactive and courtesy communications,*** such as sponsors providing courtesy copies of submissions and amendments, sponsors notifying the RPM of upcoming large submissions to the IND, FDA RPMs providing estimates for when they will respond to sponsor questions, and FDA RPMs providing due dates for sponsor responses to IRs. In cases where these practices were implemented, FDA reviewers and sponsors noted that these practices helped them plan their time effectively.
- ***Early submission*** of meeting packages and preliminary comments. In cases where these materials were transmitted as early as possible, FDA reviewers and sponsors felt that this makes it easier for them to review and respond to the materials in a timely manner.
- ***Use of templates and conformance with guidances*** to maintain consistency in written materials, making it as easy as possible to scan for, locate, and consider pieces of information.

IND sponsors and FDA reviewers interviewed for this assessment reported some challenges:

- ***Short time between FDA preliminary comments and sponsor responses and meetings.*** For some sponsors, receiving preliminary comments 48 hours before a meeting made it difficult to respond to FDA's comments and plan travel to FDA. For FDA reviewers, receiving additional data or questions from the sponsor within 48 hours of a meeting did not provide enough time to review materials, especially when the meeting package already contained numerous or complex questions or questions that were premature based on stage of development. On the other hand, both agreed that moving timelines earlier could make it difficult for sponsors and FDA review teams to meet deadlines.
- ***Balancing sponsors' desire for early feedback and FDA's need for adequate data as a basis for scientifically sound advice.*** For sponsors, early feedback from FDA is extremely useful in shaping development programs in ways that optimize the likelihood of forward progress. During the assessment period, frustration sometimes ensued when sponsors hoped to receive early feedback and FDA reviewers instead directed sponsors to guidance because existing data were an insufficient basis for advice. Neither sponsors nor FDA reviewers felt that there was an easy solution to this dilemma.
- ***Technical problems*** with the teleconference system in meetings. These problems sometimes disrupted meetings and prevented attendees from hearing each other, especially when one or more attendees participated via external cell phones.
- ***Uncertainty about when FDA would provide feedback*** about sponsor questions or submissions (occasional).
- ***Lack of responsiveness on the part of the RPM or the sponsor representative*** (uncommon).

Although they generally characterized their communications very favorably, IND sponsors and FDA reviewers interviewed for this assessment offered some suggestions for further enhancing these communications:

- ***Provide guidelines for how quickly FDA should respond*** to questions and submissions from sponsors submitted via email or telephone calls with the RPM.
- ***Recommend that sponsors prepare the meeting package (to the point of near completeness) early,*** before submitting a meeting request.
- ***Provide guidelines to sponsors on the appropriate number and scope/complexity of questions*** for meetings to ensure that it is feasible to fully address the questions during the meeting.
- ***Continue FDA's focus on hiring and retaining talented review staff*** and rebalancing workloads and resources as necessary.

5. Findings and Recommendations

Based on data collected during this assessment of current IND communication practices, ERG developed a set of findings and recommendations (Table 5-1) organized in two categories: overarching (related to IND communications overall) and specific (related to particular aspects of communication or portions of the IND drug development process).

Table 5-1. Findings and Recommendations

Type	No.	Finding	Recommendation(s)
Overarching	O1	During the IND stage of drug/biologic development, communications between IND sponsors and FDA reviewers are typically clear, effective, efficient, collaborative, and timely.	No action needed.
	O2	RPMs are effective in their role as the point of contact who coordinates all other communication activities with and for IND sponsors.	No action needed.
	O3	FDA staff usually complete work for IND meetings within specified timelines, but heavy workloads and regular staff turnover can make this challenging.	Continue FDA's efforts to hire and retain talented and qualified reviewers. Continue to rebalance workloads judiciously to ensure efficient use of resources.
	O4	Technical problems with FDA's teleconference systems sometimes cause disruptions in meetings with sponsors (and internal meetings as well).	Consider (1) capacity and technical testing for the current teleconference system, including with the use of external cell phones; (2) providing more handheld microphones for main conference rooms; and (3) providing a brief quick-reference guide for troubleshooting the system during meetings.
	O5	Proactive and courtesy communications facilitate transparency and predictability (FDA).	Add recommendations for these types of communications to guidelines or guidance: courtesy copies of submissions or amendments (sponsors), notification of upcoming responses or submissions (sponsors), estimates of when FDA will respond to sponsor questions (FDA), and due dates for sponsor responses to IRs (FDA).
	O6	FDA advice to sponsors remains consistent and stable throughout the IND's lifetime, except when new data warrants changes in advice. This is true even when there is turnover in FDA's review team.	No action needed.

Type	No.	Finding	Recommendation(s)
Specific	S1	Submitting meeting packages (sponsors) and preliminary comments (FDA) as early as possible helps the parties prepare effectively for meetings.	No action needed. Both parties attempt to do so to the extent feasible.
	S2	Sponsor meeting requests and meeting packages vary widely in completeness. In some cases, this is due to the stage of drug/biologic development.	Draft and pilot templates for meeting requests and meeting packages to make it easy to include more items or to be explicit why the items are not included (e.g., not applicable, or not yet available).
	S3	IND sponsors occasionally submit more questions (or more complex questions) than can be fully addressed during a meeting. They occasionally ask questions that are premature for the drug or biologic's phase of development.	Add guidelines on (1) the number and scope of questions that are appropriate for a single meeting package, and (2) exceptional circumstances when the sponsor should consider two meeting requests or FDA should consider a longer meeting.
	S4	The OND Meeting Team is helpful in managing meeting logistics, offloading burden from RPMs and making it easier for sponsors to arrive at meeting rooms on time.	Consider expanding OND Meeting Team to cover OPQ-led CMC-specific IND meetings and pre-NDA and pre-BLA meetings requested under the NDA or BLA.

OPQ = Office of Pharmaceutical Quality. CMC = Chemistry, Manufacturing, and Controls. NDA = New Drug Application. BLA = Biologics License Application.

Appendix A. Acronyms and Glossary

Acronym	Term
BLA	Biologics License Application
BTD	Breakthrough Therapy Designation
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CMC	Chemistry, Manufacturing, and Controls
DAAAP	Division of Anesthesia, Analgesia, and Addiction Products
DAIP	Division of Anti-Infective Products
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DAVP	Division of Anti-Viral Products
DBRUP	Division of Bone, Reproductive, and Urologic Products
DCRP	Division of Cardiovascular and Renal Products
DDDP	Division of Dermatology and Dental Products
DGIEP	Division of Gastroenterology and Inborn Errors Products
DHP	Division of Hematology Products
DMEP	Division of Metabolism and Endocrinology Products
DMIP	Division of Medical Imaging Products
DNDP	Division of Non-prescription Drug Products
DNP	Division of Neurology Products
DPARP	Division of Pulmonary, Allergy, Rheumatology Products
DPMH	Division of Pediatrics and Maternal Health

DPP	Division of Psychiatry Products
DOP1	Division of Oncology Products I
DOP2	Division of Oncology Products II
DTOP	Division of Transplant and Ophthalmology Products
EOP	End Of Phase
ERG	Eastern Research Group, Inc.
EDR	Electronic Document Room
FDA	Food and Drug Administration
F2F	Face-to-face meeting
IND	Investigational New Drug
IR	Information Request
MAPP	Manual of Policies and Procedures
NDA	New Drug Application
NME	New Molecular Entity
OAP	Office of Antimicrobial Products
OB	Office of Biostatistics
OBRR	Office of Blood Research and Review
OCBQ	Office of Compliance and Biologics Quality
ODE	Office of Drug Evaluation
ODEI	Office of Drug Evaluation I
ODEII	Office of Drug Evaluation II
ODEIII	Office of Drug Evaluation III
ODEIV	Office of Drug Evaluation IV
OHOP	Office of Hematology and Oncology Products

OND	Office of New Drugs
OMB	Office of Management and Budget
OPQ	Office of Pharmaceutical Quality
OPSA	Office of Program and Strategic Analysis
OSE	Office of Surveillance and Epidemiology
OTAT	Office of Tissues and Advanced Therapies
OVRR	Office of Vaccines Research and Review
PETT	Program Evaluation Tracking Tool
PDUFA	Prescription Drug User Fee Act
PRA	Paperwork Reduction Act
RMAT	Regenerative Medicine Advanced Therapy
RPM	Regulatory Project Manager
SOPP	Standard Operating Procedure and Policy
T-CON	Teleconference meeting
WRO	Written Response Only
V-CON	Videoconference meeting

Glossary

30-Day Safety Review: Period when FDA reviewers assess a new IND protocol for safety before the clinical trial can proceed. If this review raises safety concerns, the IND can be placed on Clinical Hold until the issues are resolved. FDA may issue non-hold comments in the "Study May Proceed" letter.

Advisory Language: Language used to denote that FDA's feedback is advice or a recommendation, not a regulatory or statutory requirement. Advisory language includes words such as "should", "recommend", and "advise".

Biologic: A type of drug isolated from natural sources (e.g., human, non-human, microorganism). Biologics include vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

Breakthrough Therapy Designation (BTD): Designation intended to expedite development and review of drugs or biologics for serious or life-threatening conditions. The criteria for Breakthrough Therapy Designation include preliminary clinical evidence that the drug/biologic might confer substantial improvement on at least one clinically significant endpoint compared to available therapy. A Breakthrough Therapy Designation provides the sponsor with all Fast Track designation program features, more intensive FDA guidance on an efficient drug development program, an organizational commitment involving senior managers, and eligibility for Rolling Review and Priority review.

Center for Biologics Evaluation and Research (CBER): FDA organization that regulates biological products for human use (e.g., blood-derived products, vaccines, allergenics, tissues, and cellular and gene therapies) and ensures that these products are safe, effective, and available to those who need them.

Center for Drug Evaluation and Research (CDER): FDA organization that regulates over-the-counter and prescription drugs for human use and ensures that these products are safe, effective, and available to those who need them.

Center for Devices and Radiological Health (CDRH): FDA organization that regulates medical devices and radiation-emitting products and ensures that these products are high-quality, safe, and accessible.

[PDUFA VI] Commitment Letter: Document that summarizes the performance goals and procedures agreed to for the sixth authorization of PDUFA. ERG's Program evaluation metrics, protocols, and instruments are based on this document.

Discipline: A scientific review team responsible for specific aspects of an application. For the purpose of this assessment, ERG recognizes eight disciplines in CDER and seven disciplines in CBER:

CDER

- Clinical
- Nonclinical
- Product Quality
- Clinical Pharmacology

CBER

- Clinical
- CMC
- Non-clinical
- Pharm/Tox

- Statistics
- Office of Surveillance and Epidemiology
- Clinical Microbiology
- Other
- Human Pharmacokinetics
- Bioavailability
- Other

Document Archiving and Regulatory Reporting Tracking System (DARRTS): CDER's internal database for storing and managing official IND, NDA, and BLA records. DARRTS serves as a source of application history and regulatory information for ERG's Program evaluation.

Drug: A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. When used broadly, this term includes biologics. When used more specifically (as in this report), the term refers to non-biologic substances.

Eastern Research Group, Inc. (ERG): Independent contractor enlisted to design and conduct the PDUFA VI assessment of IND communication practices.

Electronic Document Room (EDR): Internal database for storing and managing sponsor submitted IND, NDA, and BLA records. EDR serves as a source of application history and regulatory information for ERG's Program evaluation.

Evaluation Metrics: For this assessment, measurements used to evaluate current communication practices under PDUFA VI.

[The United States] Food and Drug Administration (FDA): Agency within the Department of Health and Human Services that is responsible for:

- Protecting the public health by assuring the safety, efficacy and security of products that the Agency regulates.
- Advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.
- Regulating the manufacturing, marketing and distribution of tobacco products.
- Ensuring the nation's counterterrorism capability by the security of the food supply and by fostering development of medical products to respond to public health threats.

Information Request (IR): FDA communication to a sponsor to request data, analysis, or clarification needed to allow completion of a review. For the purpose of the PDUFA VI IND communications assessment, ERG counted IRs issued between July 31, 2018 and July 31, 2019.

Investigational New Drug (IND): Current federal law requires that a new drug be the subject of an approved marketing application before it is transported or distributed across state lines. The IND is the means through which the sponsor obtains an exemption from this requirement in order to ship the investigational drug to clinical investigators in many states. The data gathered during the animal studies and human clinical trials of an IND become part of the New Drug Application.

Office of Management and Budget (OMB): Federal government agency that evaluates, formulates, and coordinates management procedures and program objectives within and among departments and agencies of the Executive Branch. It also controls the administration of the federal budget, while providing the president with recommendations regarding budget proposals and relevant legislative enactments.

Office of New Drugs (OND): Office within FDA's CDER responsible for providing regulatory oversight for investigational studies during drug development and making decisions regarding marketing approval for new drugs, including decisions related to changes to already marketed products. Its reviewing offices include Office of Drug Evaluation I/II/III/IV, Office of Antimicrobial Products, and Office of Hematology and Oncology Products.

Office of Pharmaceutical Quality (OPQ): Office at FDA within CDER responsible for product quality functions, including review, inspection, and research. After being launched in January 2015, OPQ has assumed responsibility for pre-approval and surveillance inspection activities from the Office of Compliance.

Office of Surveillance and Epidemiology (OSE): Office at FDA within CDER responsible for maintaining a system of post-marketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug development process. OSE staff identify drug safety concerns and recommend actions to improve product safety and protect the public health. Other activities include updating drug labeling, providing information to the community, implementing or revising a risk management program, and reevaluating approval or marketing decisions.

Prescription Drug User Fee Act (PDUFA): Enacted in 1992, law that provided added funds through user fees that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. In exchange, FDA agreed to review performance goals, such as completing application reviews for NDAs and BLAs in a predictable timeframe. PDUFA has been reauthorized every five years since its passage, with the most recent reauthorization being PDUFA VI (for FYs 2018-2023).

Interview: For this assessment, face-to-face or telephone interview that ERG conducted with sponsor representatives or FDA reviewers. The purpose of the interview was to gather sponsor and FDA review team opinions and experiences (including good practices, challenges, and suggestions) with IND communication practices.

Program Evaluation Tracking Tool (PETT): A tool used by ERG to consolidate and monitor quantitative, qualitative, observational, and calculated data on IND attributes and characteristics. The PETT stores and houses primary data collected by ERG as well as additional data drawn from internal FDA databases.

Regulatory Project Manager (RPM): The FDA staff member responsible for coordinating communication between FDA and the sponsor and serving on the review team as one of the regulatory leaders.

Regulatory/Statutory Language: Language used to denote that FDA's feedback is a regulatory requirement, not just a suggestion. This language includes words such as "must" and "require".

Sponsor: Individual or entity who takes responsibility for an IND.

Appendix B. Evaluation Metrics

Metrics		Result
General Meeting Information		
GMI1	Number of meeting requests per IND: **Mean**	1.7
	Number of meeting requests per IND: **Median**	1
	Number of meeting requests per IND: **Range**	6 [0, 6]
GMI2	Number of meeting packages per IND: **Mean**	1.5
	Number of meeting packages per IND: **Median**	1
	Number of meeting packages per IND: **Range**	5 [0, 5]
GMI3	Number of meeting granted per IND: **Mean**	1.6
	Number of meeting granted per IND: **Median**	1
	Number of meeting granted per IND: **Range**	6 [0, 6]
GMI4	Percent of INDs with an initial comprehensive multidisciplinary BTD/RMAT meeting	1%
GMI5	Meeting Format: **Face-to-Face**	48%
	Meeting Format: **Teleconference**	25%
	Meeting Format: **Videoconference**	0%
	Meeting Format: **Written Response Only**	27%
GMI6	Meeting Duration: **Mean**	47 minutes
	Meeting Duration: **Median**	50 minutes
	Meeting Duration: **Range**	72 minutes [13, 85]
GMI7	Meeting attendees: sponsor role (distribution)	See Figure 3-10
GMI8	Meeting attendees: FDA role (distribution)	See Figure 3-9
GMI9	Percent of meetings where a topic is:	See Section 3-7
GMI10	Percent of meetings related to BTD/RMAT designation	17%
GMI11	Percent of written communications where FDA staff used statutory/regulatory or advisory language	88%
GMI12	Of written communications where FDA staff used statutory/regulatory or advisory language, percent where they used appropriate language	100%

Metrics		Result
Meeting Requests		
MRD1	Of meeting requests received, percent with meeting type adjusted by FDA	9%
MRD2	Of meeting requests received, percent with meeting request granted	98%
MRD3	Percent of suggested meeting dates within timelines suggested in guidance	57%
MRD4	Percent of suggested meeting dates granted	72%
MRD5	Number of questions per meeting request: **Mean**	7
	Number of questions per meeting request: **Median**	6
	Number of questions per meeting request: **Range**	30 [1, 31]
CMR1	Percent of meeting requests that are complete	54%
CMR2	Percent of meeting requests with all recommended items included	29%
CMR3	Percent of meeting requests for: **Face-to-face**	69%
	Percent of meeting requests for: **Teleconference**	17%
	Percent of meeting requests for: **Videoconference**	0%
	Percent of meeting requests for: **Written response only (WRO)** ‡	9%
CMR4	Percent of meeting requests that include pediatric study plans	22%
CMR5	Percent of meeting requests that include human factors engineering plan	9%
CMR6	Percent of meeting requests that align questions with review disciplines requested to attend	90%
CMR7	Percent of meeting request response letters sent on time	82%
CMR8	Percent of meeting dates scheduled on time	44%
CMR9	Percent of meeting dates granted within 14 days of requested meeting dates, when requested dates are outside guidance timelines	80%
Meeting Packages		
CMP1	Percent of meeting packages with all recommended items included	35%

Metrics		Result
QMP1	Percent of meeting packages where inadequate sponsor information precludes an answer from FDA in preliminary comments or WROs	34%
QMP2	Percent of meeting packages submitted on time	79%
QMP3	Percent of FDA responses that direct sponsors to a published guidance	64%
Preliminary Comments		
QPMR1	Percent of preliminary comments resulting in withdrawal or cancellation of meeting	22%
QPMR2	Percent of preliminary comments that address issues not identified by sponsors	73%
QPMR3	Percent of preliminary comments sent on time	84%
QPMR-N	Percent of preliminary comments prepared with a template	97%
QPMR4	Percent of preliminary comments where FDA staff used statutory/regulatory or advisory language	98%
QPMR5	Percent of preliminary comments where FDA staff used statutory/regulatory or advisory language, percent where they used appropriate language	100%
QPMR6	Percent of preliminary comments that direct sponsors to a published guidance	64%
Meeting Minutes (including WROs)		
QMM1	Percent of meeting minutes sent on time	89%
QMM2	Percent of meeting minutes that include a list of agreements/decisions by discipline	70%
QMM3	Percent of meeting minutes that present the same key topics (paths forward, action items, decisions) as observed during the meeting	100%
QMM4	Percent of meeting minutes that contain statutory/regulatory or advisory language, excluding WROs	95%
QMM5	Of meeting minutes that contain statutory/regulatory or advisory language, percent that use appropriate language	100%
QMM6	Percent of meeting minutes that direct sponsors to a published guidance	54%

Metrics		Result
QMM7	Percent of meeting minutes that address issues not identified by sponsors	55%
Use of Templates		
CTU1	Percent of meeting minutes prepared with a template	100%
CTU2	Percent of meeting preliminary comments prepared with a template	97%
Other Communications		
FSE1	Number of sponsor questions per IND: **Mean**	2.5
	Number of sponsor questions per IND: **Median**	0
	Number of sponsor questions per IND: **Range**	98 [0, 98]
FSE2	Number of FDA responses per IND: **Mean**	2.5
	Number of FDA responses per IND: **Median**	0
	Number of FDA responses per IND: **Range**	98 [0, 98]
FSE3	Number of FDA IRs per IND: **Mean**	4.4
	Number of FDA IRs per IND: **Median**	1
	Number of FDA IRs per IND: **Range**	74 [0, 74]
FSE4	Number of sponsor amendments per IND: **Mean**	14.3
	Number of sponsor amendments per IND: **Median**	10.5
	Number of sponsor amendments per IND: **Range**	71 [0, 71]
FDA Transitions/Changes		
CRTM1	Number of FDA review team changes per IND: **Mean**	8.8
	Number of FDA review team changes per IND: **Median**	7
	Number of FDA review team changes per IND: **Range**	34 [0, 34]
CAS1	Percent of survey respondents who reported no changes in FDA advice over the lifetime of their INDs	82%
	Percent of survey respondents who reported no changes in FDA advice over the lifetime of their INDs: **Sponsors**	87%
	Percent of survey respondents who reported no changes in FDA advice over the lifetime of their INDs: **FDA reviewers**	76%