This information should not be considered to represent advice or guidance on behalf of the U.S. Department of Health and Human Services or any agency or office thereof.

Basics of Interactions with FDA (CDER/CBER)

Refer to the **NIH OER Regulatory Knowledge Guides** for more specific guidance on the regulation of:

- Small Molecules
- Biological Products
- Cell and Gene Therapies

Context

Innovators (also called sponsors) often have a wide variety of regulatory questions related to the development of their new small molecule and biologic therapies. The U.S. Food and Drug Administration (FDA) is the federal agency that oversees this development. FDA does its best to be transparent in its regulatory practices, with a wide variety of information available on its website and through its ongoing programming. For example, you can find guidance documents, presentations, webinars, workshops, advisory committee meeting minutes, and redacted approval documentation by searching the FDA website. Despite the volumes of information already available, each sponsor will require specific input and feedback from FDA for each of its drug development programs. That's where scheduled meetings with FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) come in. This document is designed to help you understand when and how to ask for personalized feedback, what and how to prepare for, and what to expect during meetings with CBER and CDER.

Before asking FDA for a meeting, or for any official input to your drug development work, you should conduct a thorough search of online resources for relevant information. Some useful sites for you to learn more about the regulation of your drug are listed at the end of this document.
Once you have completed your online research, you will discover there are questions you cannot find specific answers to (e.g., manufacturing, impurities, potency assays) because your drug is not exactly like any other drug. When you reach that point, it is time to request a meeting with FDA to gain the additional clarity that only product reviewers can provide. FDA conducts multiple types of formal meetings; each is intended to cover specific situations and may be subject to its own procedures and processes.

- ***Type A Meetings*** help an otherwise stalled product development program proceed or address a significant safety issue. Topics can include dispute resolution, clinical holds, special protocol assessment meetings, and post-action after receiving an FDA regulatory action other than approval.
- ***Type B Meetings*** are generally milestone meetings and often include pre-Investigational New Drug application (pre-IND) meetings, pre-Emergency Use Authorization meetings, pre-New Drug Application (pre-NDA) or pre-Biologics License Application (pre-BLA) meetings; and meetings to discuss the overall development program for products granted breakthrough therapy designation.
- ***Type B End-of-Phase (EOP) Meetings*** are very specific reviews of data obtained during the most recent clinical investigations and addressing data requirements for the next stage of clinical development, or that will be expected to be addressed in a marketing application.
- ***Type C Meetings*** are a "catch-all" and can include any meeting concerning the development and review of a product that does not fall within the scope of Types A or B.

Remember to have reasonable expectations for your meeting (if granted). When communicating with FDA, the questions you submit are the focus of FDA's review. The supporting information included with the questions should outline and provide evidence to support the proposed plans. Each question should refer directly to the information provided. FDA will provide complete written feedback in advance of the meeting, allowing you to focus your actual meeting time on areas where FDA does not agree with your proposed development plan.

It's also important to understand FDA's role in the drug development process. The role of FDA is to evaluate the risk benefit profile of your product for the indication and population you intend to address. They can and will provide specific feedback about the sufficiency of your data development plan to address their concerns. However, they are not consultants and will not tell you how to conduct your studies or what to include in your plan. It is your responsibility to provide FDA with as much reasonably relevant information about your product as possible during the development campaign. When you request a meeting, the briefing packet must provide sufficient information for FDA to address your questions, and your questions should be concise. When you submit an amendment to the file, you must provide all the required information as well as information describing expansion in knowledge about the science of your drug class or disease indication.

Although both FDA and NIH support the "come early, come often" approach to streamlining the development of new therapies, the reality is there is a wealth of knowledge in the public realm, and NIH has resources available to its awardees to help them understand how to find and interpret this information.

Key Takeaways

- Thoroughly search the FDA website for public information that can help your early development work, and in establishing a data development plan to support the growth of risk benefit information about your new drug.
- Use FDA as a resource for obtaining feedback on specific questions where public information is not available and where you cannot continue your development work without their concurrence or input. It can also be helpful to ask FDA to confirm that your interpretation of the guidance is correct.

- Request a meeting with FDA when you have sufficient data from research and testing to support a substantive conversation. You will need to submit a pre-meeting package that includes your questions and summary information sufficient for reviewers to respond to your questions. FDA has draft guidance describing the information required for a meeting request.

Recommendations

Build Rapport

When requesting a meeting with CDER or CBER, sponsors (developers of new therapies) should try to anticipate future needs and address as many product development issues as are reasonable and appropriate for the meeting type. CBER and CDER prefer to provide holistic feedback on development plans that will enable you to move non-clinical, clinical, and manufacturing aspects of the development program forward to the next step in the process. Keep FDA informed of advances in your development program in an appropriate and respectful manner. If you cannot comply with FDA's feedback or data requests, justify why this is not possible (scientifically), or at what point in the development program you intend to address FDA concerns.

Understand the Q&A Process

FDA can provide specific guidance in response to your questions, but meetings are limited to one hour and all questions must be submitted in a briefing package before the meeting. When developing questions for a briefing package, carefully consider what questions you will ask and how you phrase them.

For example, rather than asking:

- What would be the best formulation for this drug? *Or*
- Does FDA think an adaptive design is a good approach for our Phase II clinical trial?

Better phrasing might be:

- Does FDA agree the use of an ointment is suitable for this clinical indication? *Or*
- We have provided an overview of our clinical testing plan and the specific protocol we intend to implement. Does FDA agree this protocol is sufficient to support the clinical outcome measures proposed and the outcomes are appropriate for the indication we are targeting?

The second set of questions will elicit a more complete response from FDA. When the answer is yes, you will know that the proposed plan is acceptable. When the answer is no, FDA will provide details about why it is not acceptable and may also provide recommendations to the proposed plan.

Below are more examples of questions an innovator might ask for different meeting types:

- Type A – Does FDA agree that the information provided is sufficient to lift the clinical hold and continue process development?
- Type B (Pre-IND) – Does FDA agree that the sponsor-conducted non-clinical studies are sufficient to enable the proposed clinical development program?
- Type B (EOP 1) – Does FDA agree that the proposed Phase 2 protocol (which includes subject inclusion/exclusion criteria, type of control group/placebo arm, statistical analysis plan, and endpoint selection) is sufficient to move to Phase 2?

- Type B (EOP 2) – Does FDA agree that the clinical trial design (which employs clinical trial simulation and quantitative modeling of drug and placebo group responses) is sufficient to complete dose-response estimation?
- Type B (EOP 2) – Does FDA agree that the chemistry manufacturing control (CMC) readiness concerning adequate critical quality attributes and the qualified potency assay is sufficient to proceed to Phase 3?
- Type B (Pre-NDA) – Does FDA agree that the clinical pharmacology information in the lethal dose labeling, in conjunction with the pharmacokinetic data for the sponsor's product, is sufficient to fulfill the clinical pharmacology requirements for the New Drug Applications?
- Type B (Pre-BLA) – Does FDA agree that a control strategy based on the outlined drug substance (DS) and drug product (DP) quality attributes will be sufficient to support the identity, potency, purity, quality, and stability review of the DS and the sponsor's DP?
- Type C – Does FDA agree to using a biomarker as a surrogate endpoint in the proposed clinical study?
- Type C – Does FDA agree that the CMC issues have been resolved?

When questions are clear and specific, FDA reviewers are more likely to provide meaningful and helpful recommendations, such as to either agree or disagree with a proposed plan. Here are some common examples of FDA feedback:

- The proposed information appears to be *adequate or reasonable*, but FDA will assess the acceptability of the data during the IND submission package.
- FDA *agrees with the approach* presented; however, the final determination on the acceptability occurs during review of the formal submission.
- FDA *does not agree* with the proposed methods or specifications and considers the information exploratory; additional information or data is required to demonstrate that the product meets the acceptability criteria. (FDA would follow with information about the type of data they would want submitted.)

Utilize FDA Feedback

Pre-IND consultation with FDA may be useful in establishing and refining a drug development strategy by discussing additional, expedited, and alternate methods to engage FDA's resources and programs for development. These can include orphan drug designation, fast track designation, accelerated approval, the animal efficacy rule, and breakthrough therapy.

Meeting with FDA provides you with advice specific to your product. Interacting with FDA at appropriate points throughout your development program can streamline your path to market approval. It can also provide significant strategic value for future programs and investments by:

- Identifying and avoiding unnecessary studies
- Ensuring that necessary studies are designed to provide required information
- Minimizing the potential for a clinical hold
- Clearly defining the endpoints and goals of the development program
- De-risking development pathways and confirming development plans
- Answering questions and facilitating discussions with investors, board members, or strategic partners

Regulatory Resources

Innovators should use the extensive sources of product development information that are publicly available before seeking a meeting. In addition, FDA develops and maintains web pages, portals, and databases and participates in interactive media to advise on matters outside of established guidance, policy, or practices.

- General guidance documents and FDA resources
  - Draft Guidance for Formal Meetings Between FDA and Sponsors or Applicants of PDUFA Products – recommendations on formal meetings relating to the development and review of drug or biological products
  - Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff – recommendations for innovators on conducting timely, transparent, and effective communications with FDA
  - CGMP for Phase 1 Investigational Drugs – guidelines for using current good manufacturing practices in early stages of clinical development
  - Drug Development Process: Clinical Research – overview for innovators as they develop a clinical research plan
  - Small Business and Industry Assistance: Frequently Asked Questions on the Pre-Investigational New Drug (IND) Meeting – resources for innovators planning an IND meeting with FDA
  - Expedited Programs for Serious Conditions - Drugs and Biologics – descriptions of the programs' sponsors may utilize to gain access to additional FDA resources throughout a drug development campaign
- For CBER regulated biological products
  - OTP Learn – a list of courses available through FDA's Office of Tissues and Advanced Therapies
  - Workshops, Meetings, and Conferences (Biologics) – resources including minutes, transcripts, summaries and/or presentations
  - Industry (Biologics) – descriptions of CBER's policies, procedures, and review resources
  - CBER Approved Biologics Database: Biological Approvals by Year – a database of the biologics approved by regulating authorities
  - Biologics Procedures (SOPPs) – an overview of CBER's standard operating procedures and policies
    - SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products – CBER guidelines for scheduling and conducting regulatory meetings
- For CDER regulated small molecules
  - CDER Learn – a list of free education CDER educational opportunities
  - Oncology Center of Excellence – conducts expedited review of medical products for oncologic and hematologic malignancies
  - Project Catalyst – a regulatory platform of guidance on anticancer therapy development
  - CDER SBIA Learn – a repository of online training for industry and small businesses
  - CDER SBIA YouTube Learning Library – an online database of recorded presentations

Drugs@FDA – a searchable database of drug products approved by FDA since 1939

- NIH network
  - Work with program officers to obtain feedback within NIH
  - NIH awardees can request a meeting with the NIH Small business Education and Entrepreneurial Development (SEED) Innovator Support Team to ask questions about this process and request they review the draft cover letter and overall approach. However, the SEED office does not review or comment upon the scientific validity or data elements of the submission.