

# Regulatory Strategy for Pre-IND Meetings with FDA: Why Meet and What to Ask

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## GLOSSARY

<b>Agency</b>	The Food and Drug Administration (FDA)
<b>CMC</b>	Chemistry, Manufacturing, and Controls
<b>Drug Product</b>	A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients
<b>Drug Substance</b>	An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient.
<b>Formal meeting</b>	Any Type A, B or C meeting that is requested by a Sponsor (hereafter Requester(s)) following the request procedures provided in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Sponsors of PDUFA Products" and includes meetings conducted in any format (i.e., face to face, teleconference, videoconference, or written response).
<b>IND</b>	Investigational New Drug application (also synonymous with "Notice of Claimed Investigational Exemption for a New Drug"). ( <a href="#">CDER Guidance Document on Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs</a> or <a href="#">21 CFR 314.312</a> .)
<b>PDUFA</b>	Prescription Drug User Fee Act
<b>Pre-IND</b>	Pre-Investigational New Drug Application
<b>RPM</b>	Regulatory Project Manager (at the FDA)
<b>Sponsor</b>	Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.
<b>WRO</b>	Written Response Only

## 1. INTRODUCTION

### 1.1. Background

Biologics Consulting is a full-service regulatory and product development consulting firm for biologics, pharmaceuticals and medical devices. Founded in 1993, Biologics Consulting works with companies large and small seeking to bring innovative, safe and effective products to market within the U.S. Biologics Consulting's team is comprised of subject-matter experts with decades of industry and/or FDA experience. In this paper, the authors aim to utilize their years of experience preparing meeting requests and meeting packages, participating in pre-IND meetings, and reviewing and responding to pre-IND meeting comments from the FDA to provide general recommendations for organizations looking to make the most out of their pre-IND meeting with FDA.

### 1.2. Purpose

Pre-Investigational New Drug Application (pre-IND, PIND) meetings are defined in 21 CFR 312.82 Early Consultation. According to this regulation, "Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the biologic or drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND." These meetings can serve as a valuable tool, allowing the Sponsor an opportunity to discuss challenges specific to development of their new biologic or drug product and design of their proposed nonclinical studies directly with the FDA early in the drug development process. The meeting also provides an opportunity for the Sponsor to discuss their CMC development plan to address the CMC requirements for phase 1 clinical studies.

This paper provides an overview of the current FDA guidance and recommendations for pre-IND meetings. It also discusses the benefits of having a pre-IND meeting with the FDA.

Finally, the paper provides examples of frequently asked questions (FAQ) and responses by the FDA along with general information which may be included as part of the FDA's pre-IND meeting comments.

## 2. PRE-IND MEETING DESCRIPTION

### 2.1. FDA Guidance and Observations

According to the FDA's "Guidance for Industry: Formal Meetings Between the FDA and Sponsors (March 2015, Revision 2)", pre-IND meetings are classified as Type B meetings and are subject to the timelines provided in Section 2.2. The Sponsor may request a teleconference, face-to-face meeting, or Written Response Only (WRO) and if the FDA meeting schedule permits, FDA may grant teleconferences or face-to-face meetings requested by the Sponsor.

In the current regulatory environment, pre-IND meetings are often granted as a WRO in which the Agency will provide written responses to the questions in the meeting package and reviewers' comments about the information contained within the meeting package in lieu of a meeting. Granting of a WRO will be noted in the response letter from the FDA provided to the Sponsor within 21 days of the FDA's receipt of the meeting request. In the last few years certain Offices within the FDA, such as the Office of Vaccines Research and Review (OVRR), may deny phase 3 pre-IND meeting requests, and require the Sponsor to submit a Master File (MF) instead to allow sufficient time for the review of this mature program. The need for a MF will be noted in the response letter from the FDA.

Due to the limited opportunity to interact directly with the FDA, Sponsors should ensure that their meeting request and meeting package provide information relevant to their specific product, highlighting any challenges or anticipated regulatory hurdles in a direct, succinct manner. The pre-IND meeting package should contain summaries relevant to the product and proposed clinical trial, along with sufficient supplemental material to provide

the reviewer with an understanding of the issues raised in the meeting questions. Sponsors should avoid including extraneous materials in the meeting package that are unrelated to the meeting question topics. If the volume of information provided in the meeting package is too great, the reviewing division may reschedule the meeting to allow the reviewers sufficient time to go through the information, so brevity is advised. Furthermore, in response to some recent pre-IND meeting requests, FDA has instructed the Sponsor to limit the number of questions to approximately 10 key inquiries with no subquestions. While this may pose a challenge, it encourages the Sponsors to focus on key issues, allowing the FDA reviewers to provide comments on those issues at high risk for a clinical hold.

In addition to the 2015 “Formal Meetings” Guidance, certain divisions within the FDA, e.g. the Division of Anti-Viral Products’ (DAVP), provide information on their websites which serves as excellent resources for the format and suggested content of pre-IND meeting requests and meeting packages. Even if a Sponsor has prepared pre-IND submissions in the past, it is prudent to consult these FDA division-specific resources prior to submitting a meeting request and meeting package to ensure that the most recent recommendations from the reviewing division have been incorporated.

## 2.2. PDUFA Timelines

As noted above, the “Formal Meetings” guidance defines pre-IND meetings as Type B meetings. Timelines for these meetings are governed by the current version of the Prescription Drug User Fee Act (PDUFA). These timelines are provided in the “Formal Meetings” guidance and are also summarized below. These are general timelines; the Sponsor should check the specific review division website for any division-specific timelines. Also note that these timelines are specific to Type B meetings.

- Receipt of the Sponsor’s meeting request by the Agency initiates the submission “clock”. This may differ slightly from the date on which the meeting request was sent by the Sponsor.
- Within 21 days of receipt of the meeting request, the FDA review division should respond to the Sponsor providing notification that the meeting has either been granted or that the meeting has been denied. If the meeting has been granted, this communication will provide the meeting date and meeting type. If the reviewing division only plans to provide written comments (WRO) in lieu of a face-to-face meeting or teleconference, this will be specified in the response letter along with the date on which comments will be provided to the Sponsor.
- Meeting dates are set by the reviewing division. Meetings should be scheduled to occur within 60 days of the Agency’s receipt of the meeting request. If the Sponsor requests a date for the meeting that is more than 60 days from the date the Agency receives the request, the meeting should be scheduled to occur not more than 14 days after the requested date. When written responses will be provided in lieu of a meeting, these should be transmitted by the reviewing division within 60 days of the Agency’s receipt of the meeting request.
- The meeting package (a.k.a. background package, information package, briefing package, briefing document, etc.) must be received by the Agency at least 4 weeks prior to the formal meeting or WRO deadline, otherwise the Agency may postpone or cancel the meeting. Due to this firm submission deadline, it is advised that the Sponsor have a working draft of the meeting package before the meeting request is submitted.
- In most cases, the Agency will provide initial written comments 24 – 48 hours prior to the meeting. If the Sponsor feels these comments have sufficiently addressed all of the pre-IND questions, they may contact the Agency and cancel the meeting.
- The Agency targets to issue official minutes to all FDA attendees (with copies to appropriate files) and to the Sponsor within 30 calendar days of the formal meeting. If a WRO is provided, that serves as the final piece of communication related to the meeting.
- PDUFA VI (effective for fiscal years 2018 – 2022) pre-IND meeting timelines are shown in Table 1 derived from the PDUFA VI commitment letter.



**Table 1: PDUFA VI Pre-IND (Type B) Meeting Timelines**

Type of Meeting	FDA Response Time	Meeting Schedule	Meeting Package	FDA Meeting Minutes
	Calculated from the FDA date of receipt of the meeting request			
pre-IND (Type B)	21 days	60 days	30 days before the date of the meeting or WRO	30 days after meeting

All timeframes listed are calendar days.

As with PDUFA V (effective for fiscal years 2013 – 2017), the Agency may issue WROs for pre-IND meetings. PDUFA VI changes the deadline for Type B background packages to be due 30 calendar days before the planned meeting or written response instead of 1 calendar month under PDUFA V.

### 3. WHY MEET? BENEFITS OF PRE-IND MEETING

Although not required, the FDA recommends that Sponsors participate in pre-IND meetings prior to IND submission. Vu and Pariser (2015) evaluated new product marketing applications submitted between 2008 and 2013 and found that applications for which a pre-IND meeting were held during drug development had shorter Clinical Development Times than those that did not. Vu and Pariser's analysis further showed that small companies with limited regulatory experience gain the greatest benefit from early communications with the FDA.

Pre-IND meetings allow the Sponsor to open a direct line of communication to the FDA. Even in cases where the Sponsor has experience taking other products through the drug development process, each product presents its own challenges and regulatory expectations change over time as new technologies emerge and as a result of the development issues encountered by other products. FDA reviewers and project managers are aware of the current regulatory trends and may provide valuable input the Sponsor may not otherwise receive. While the FDA reviewers cannot share specifics about other products with Sponsors, based on their experience reviewing other products they may be able to identify potential clinical hold issues prior to IND review, allowing time for the Sponsor to resolve the issues prior to IND submission. Some of the benefits of participating in a pre-IND meeting with the FDA are discussed in the sections below.

#### 3.1. Reduce Time to Market

Obtaining pre-IND input from the FDA may shorten the time to market by:

##### 1. Speeding development

- Identifying and avoiding unnecessary development studies.
- Using FDA feedback to ensure that necessary nonclinical studies are designed to provide safety and toxicology information to enable clinical studies.
- Minimizing potential for clinical hold due to insufficient information in the design of the clinical and nonclinical protocols, and in the product manufacturing and control of product safety, identity, purity, potency, and strength.
- Focusing on objectives that must be met for approval and potentially limiting extra work should save the Sponsor both time and money. Obtaining assistance from the FDA with the design of CMC comparability studies will help minimize the chances that the Sponsor does extra clinical or nonclinical work that is unnecessary.
- Clearly defining clinical endpoints and goals of the development program will help the Sponsor plan their clinical trials and analyze their data.

## 2. Obtaining FDA's unpublished regulatory insight

- While the Sponsor's proposed development strategy may seem the most expeditious to the Sponsor, often the FDA has worked with similar product types and/or with the Sponsor's proposed indication and is aware of what may or may not have worked in the past.
- The Sponsor benefits from FDA reviewers' experience and knowledge of existing regulations and potential new guidances as well as recent regulatory trends. Keep in mind that the reviewers have knowledge of failures and successes experienced by other Sponsors with similar products and/or indications.
- For new product types, obtaining FDA "buy in" at an early stage will provide the Sponsor with some level of assurance that following the proposed strategy and maintaining open communications with the FDA throughout product development will improve the chances of successfully developing the product.
- Discussing the early stages of Chemistry, Manufacturing, and Controls (CMC) development, i.e. before the manufacturing process has undergone full development and scale up may accelerate development. The FDA reviewers may have knowledge about similar products produced using similar manufacturing processes. The reviewers are familiar with the analytical methods being used to characterize similar products and may have suggestions for how to solve specific challenges the Sponsor may face with their product. The Sponsor still has an opportunity to make changes, refine the manufacturing process and perform further characterization while there is still time before key pivotal IND studies. Otherwise, they may have to address some of these issues with full comparability studies, additional nonclinical studies, or additional clinical studies.

## 3. Personal Factor

- A pre-IND meeting provides an opportunity for early interactions/negotiations with FDA. This is an opportunity for the FDA reviewers to gain an understanding of the Sponsor's product and knowledge base as they share results of the work that has been conducted. Well focused questions will produce actionable answers from the FDA.
- Reading the meeting guidances and CBER SOPPs or CDER MAPPs related to meetings and then following those guidances will assure the FDA that the Sponsor understands FDA's expectations and is serious about developing the product.
- Showing respect to your reviewers will help build a solid relationship. The Sponsor should involve the Agency when issues arise, then they should try to comply with the FDA's suggestions and/or provide justification when the Sponsor can't or won't be able to meet those requests. In return, the reviewers will be open with the Sponsor and will try to help as the FDA wants the Sponsor to succeed in bringing new biologics and drugs to the market. However, if the Sponsor takes advantage of the reviewers, for example by wasting their time with questions to which the answers may be easily found, by not following the FDA's recommendations without a good justification, and/or by failing to have good science behind the filing, the FDA review of the IND is likely to be very challenging and is may result in multiple cycles of review. The Sponsor should build an early bridge with FDA and should also be cautious to maintain a solid bridge throughout product development.

### 3.2. Accelerate Drug Development Activities

Pre-IND consultation with the FDA may be useful to the drug development process in the following situations:

- When the product is intended to treat a serious or life-threatening disease.
- When there is a novel indication: the FDA can work with the Sponsor to determine unique needs for this indication. Sponsors should talk to the FDA as development progresses so FDA can guide the Sponsor as new data becomes available. The FDA may also provide advice regarding the potential for the Sponsor to request an accelerated review.
- When there are no current guidance documents for novel indications.

- When the Sponsor is new to drug development.
- When there are known concerns, for example:
  - Questions about the origin of the cell line from which the drug substance is produced. Depending on the cell line and its history, this can be a hot topic for reviewers. Unless it can be tied to an ATCC line, FDA may ask the Sponsor to show requisite information linking the cells used to prepare the original cell line to the cell line being used to manufacture the Sponsor's current product. The FDA will also be concerned about the cell line's exposure to materials of animal origin, as well as adventitious agent contamination.
  - When there are manufacturing differences between toxicology lot production and the cGMP process used to manufacture clinical trial material. These should be discussed to assure acceptability of the toxicology studies. Documentation of further CMC characterization may be needed.
  - In instances where pharmacologic or toxicologic safety signals of concern exist and need to be addressed. The Sponsor may utilize the pre-IND meeting to work with the FDA and determine what additional toxicology studies will be needed prior to phase 1. The FDA can help the Sponsor understand unexpected results and may be helpful in suggesting additional signals to monitor that have been problematic to other Sponsors.
  - When the Sponsor plans to approach FDA with a late phase product that has already undergone phase 1 & 2 studies overseas and now wants to develop the product for commercialization in the US. In this case more detailed information and data will be expected by FDA than would normally be needed for early phase products. This may include more extensive CMC characterization, product specifications and the ability to demonstrate a good understanding of the product and the manufacturing process.

### 3.3. Define Drug Development Strategy

Pre-IND consultation with the FDA may be helpful in establishing and refining a drug development strategy by:

- Discussing nonclinical studies, such as pharmacology, immunogenicity and toxicology, that will be needed to support the initiation of clinical trials
- Discussing additional, expedited, and alternate methods to engage FDA's resources and programs for development including:
  - Orphan Drug Designation
  - Fast Track Designation
  - Accelerated Approval
  - Animal Efficacy Rule
  - Breakthrough Therapy
- Discussing potential safety issues affecting the CMC Product Development Plan:
  - Physical, chemical, and/or biological characteristics of the product
  - Manufacturers
  - Cell substrate selection and documentation for biologics
  - Removal of toxic reagents
  - Suitability and traceability of the starting materials including ancillary materials
  - Quality controls (e.g., identity, assay, purity, impurities profile)
  - New molecular entities (NME)
  - Manufacturing feasibility – biologics, drugs
  - Novel manufacturing platforms
  - Viral clearance – biologics
  - Formulation
  - Specifications
  - Stability
  - Novel excipients
  - Adjuvants



Per FDA guidance for pre-IND meetings, the discussion of safety issues for conventional synthetic drugs is typically brief. For certain types of drugs, such as biotechnological drugs, biological drugs, natural products, complex dosage forms, and drug-device combinations, it may be appropriate to discuss the CMC information in more detail. Examples provided by the FDA guidance (May 2001) where detailed discussion may be appropriate include, but are not limited to:

- Drugs from human sources (e.g., appropriate donor screening procedures for tissues, blood, or other fluids); removal or inactivation of adventitious agents (e.g., viruses, bacteria, fungi, mycoplasma)
- Drugs from animal sources (e.g., removal or inactivation of adventitious agents, transmissible spongiform encephalopathy (TSE)-free certification)
- Biotechnology drugs, particularly rDNA proteins from cell line sources (e.g., adequacy of characterization of cell banks, potential contamination of cell lines, removal or inactivation of adventitious agents, potential antigenicity of the product, and genetic stability)
- Botanical drugs (e.g., raw material source, absence of adulteration)
- Reagents from animal or cell line sources (same considerations as for drugs derived from animal cell or cell line sources)
- Novel excipients
- Novel dosage forms (e.g., characteristics, potential for overly rapid release of dose, if applicable)
- Drug-device delivery systems (e.g., demonstration of device and its characteristics, potential for overly rapid release of dose, particle size distribution considerations, where applicable)

### 3.4. Getting the Most from a Pre-IND Meeting

Prior to submitting the request, the Sponsor should check with the reviewing division's website to be sure they address any specific requirements and guidances as there may be nuances within different groups at the FDA. As pointed out above, the Sponsor should check the CBER SOPPs or CDER MAPPs related to meetings to understand what the FDA will do once they receive the meeting request and package. For some meeting types, FDA offices now limit the number of meeting questions and/or limit the meeting time. While writing the meeting package, consider that FDA does not get much time to review the information provided so it benefits the Sponsor to focus the pre-IND meeting package on key issues which are not already addressed by current guidance documents or information available on the FDA's website.

#### 3.4.1. Face-to-Face Meetings, or Teleconferences

The FDA will provide preliminary responses to the questions outlined in the meeting package prior to the meeting. Upon receipt of these preliminary written responses, usually a day or two prior to the scheduled meeting, the Sponsor should hold an internal meeting with the planned meeting participants and support staff to review and discuss FDA's comments. This team should determine which responses are clear and require no further clarification prior to implementation versus those responses that need further discussion. If possible, on the same day the comments are received from FDA, the Sponsor should clarify to the FDA Regulatory Project Manager (RPM) those questions that will require further discussion and those questions that have been sufficiently answered. If the Sponsor believes that all responses from the FDA are sufficient, the Sponsor may cancel the meeting by alerting the FDA RPM via email that all comments by FDA are clear and the meeting is no longer needed.

Once the Sponsor has narrowed the questions for discussion during the meeting, they should hold a preparatory session to go through the FDA comments with the Sponsor's meeting participants to develop a strategy for the discussions. For those unfamiliar with FDA meetings or for products with specific regulatory challenges, it is recommended that the Sponsor include someone experienced with FDA interactions to help prepare the Sponsor's representatives for the meeting. During this meeting, the Sponsor should identify who will serve as their main representative and which subject matter experts or other representatives will speak about each point. During the preparatory meeting the Sponsor should have someone play "devil's advocate" to explore what would be done if the FDA says no to the Sponsor's proposals or suggests an alternative

response to FDA preliminary responses that in effect requires the Sponsor do something that will be costly or require more time than the Sponsor plans to spend. Commitments made by the Sponsor during the meeting will be recorded in the meeting minutes so Sponsors should be cautious about making commitments. It is acceptable to tell FDA during the meeting that the Sponsor will consider FDA's advice.

Some FDA divisions record "live minutes" during either face-to-face meetings or teleconferences. In this case, the minutes are typed in real time and are shown on a screen during the meeting. This is beneficial because the official minutes are finalized quickly and the Sponsor can see and advise regarding the wording within those minutes. However, if the FDA and/or the Sponsor spend time wordsmithing the minutes, this takes time away from the pre-IND discussions.

Remember that communication is important in any meeting with the FDA, particularly the pre-IND meeting since it is often the Sponsor's first interaction with the reviewing division. During the teleconference or face-to-face meeting, be sure to:

- Only ask specific, well-phrased follow up questions to the FDA preliminary responses to the meeting package. Questions should be phrased in a targeted manner, not open-ended, e.g., "in our clinical study, we plan to have stopping rules for X by doing Y. Does the FDA agree with this plan?" rather than "Does the FDA have suggestions about what we should incorporate as stopping rules?"
- Prioritize the discussion of questions for which discussion and agreement is needed in order for the IND to proceed, and leave the "nice to have" discussions for the end if there is time.
- Stay focused on the agenda. The Sponsor shouldn't allow one topic or one meeting participant to dominate the meeting. The Sponsor has limited time and should be sure to discuss all the items for which answers are needed.
- Don't hide concerns either before or during the meeting. Problems are likely to come out during IND review and it is better to flag potential problems early in the process to get friendly feedback from the FDA rather than waiting until the IND review period.
- Don't present data during the meeting that was not included in the meeting package. The FDA's standard reply to new questions or information is that they are unable to answer the question now but that the information should be included for review in the Sponsor's IND.
- When presenting data already in the package, make sure it is clear and consistent with the Sponsor's argument. Scientific, data-driven arguments are most effective, as the FDA will review the data again when the IND is submitted.

In addition to the above, be sure to:

- Agree with FDA on timing for the pre-IND meeting and required attendees. This information should be included in both the meeting request and meeting package (see the "Formal Meetings" guidance from the FDA).
- Prepare a well-organized first draft of the meeting package before submitting the meeting request. FDA invites staff to the meetings based on the questions within the request so if the Sponsor changes the questions significantly between the request and the package FDA may not have the best person at the meeting to contribute to a meaningful discussion.
- In the meeting package, include strategic questions about IND enabling issues. These should be questions which are not easily answered in the FDA guidances or from previous submissions of related products by the Sponsor. Remember that the Sponsor may revise questions slightly between the meeting request and the meeting package. Do not add questions at this time as it may result in a delay of the scheduled meeting to accommodate appropriate FDA reviewer schedule. Please note that questions may not be changed between submission of the meeting package and the meeting.
- For face-to-face meetings, provide completed foreign visitor forms to the FDA RPM one month in advance of the meeting and follow up with your RPM to confirm receipt and ensure that those non-US participants will be granted clearance on meeting day.

- Provide an updated list of meeting participants via email to the RPM 2 weeks before the FDA meeting.
- Have a Sponsor representative designated to take Sponsor minutes. While the FDA RPM will record the official minutes, we suggest having someone from the Sponsor's side who will not speak or participate in the meeting who just records the minutes from the Sponsor's perspective.

### 3.4.2. Written Responses Only

When WRO will be provided, the meeting package provides the main conduit to provide information to the FDA. Recommendations above concerning the content of the meeting package apply for this situation as well.

In the event that the written response provided by the FDA does not fully address the Sponsor's questions, follow up may be requested via written communication to the FDA RPM.

### 3.5. Pre-IND Meeting Minutes

It is up to the Sponsor to decide if they would like to provide the FDA with the Sponsor's version of the meeting minutes. The Sponsor should ask the FDA if they would like a copy; some divisions do not want Sponsor minutes as they rely solely on the formal FDA minutes. Other divisions accept them, but whether or not the Sponsor meeting minutes are sent to FDA, the Sponsor has a copy of what they heard at the meeting.

FDA issues meeting minutes within 30 days of the meeting. If the FDA includes anything of concern to the Sponsor in the minutes, the Sponsor can send a response to attempt to have the FDA clarify and/or change their comment. However, once the FDA has issued the final minutes the Sponsor must comply or else provide a compelling reason (or reasons) why the FDA's suggestion has not been or cannot be implemented. See Section 5 on Strategic Decision Making below.

## 4. WHAT TO ASK? FREQUENT PRE-IND QUESTIONS

During pre-IND interactions with the FDA, Sponsors tend to ask lots of questions. The FDA answers some questions while others receive a "generic" response (i.e. "The plan presented appears to be sufficient however a final determination of the appropriateness of the plan will be a review issue.").

Sponsors should ask for agreement of the content to be provided in the IND, especially if there are potential limitations of the information available at the time of the planned IND submission. Refer to FDA guidance for phase 1 trials to understand what is expected. The sections below provide suggestions about some general areas of inquiry for pre-IND interactions with the FDA.

### 4.1. CMC

Most often Sponsors request agreement from the FDA for proposed quality characterization and testing for in-process and release samples. Safety is a major focus on CMC for phase 1 to ensure reagent and process impurities are well detected and controlled, and to provide tentative specifications for identity, quality, purity, strength and potency. Frequent areas of inquiry include:

- **Drug Substance and Drug Product Specifications:** The FDA will usually provide input about the Sponsor's specifications and will note that these should continue to be revised as clinical product development proceeds. For example, for a phase 1 product, the FDA may accept specifications for analytical tests, other than detection of impurities, which have been set as "report result." However, the FDA will expect to see a more defined specification as the product moves into later clinical development phases. If the Sponsor defines an acceptance range, they should make sure it is also phase-appropriate. For example, a potency range of 50 – 150% reference standard may be fine for a product intended for phase 1 studies but is unlikely to be acceptable for later phase products.

- Analytical Methods: The Sponsor should expect to receive input about potency assays, requests for additional testing methods, and suggestions of other methods appropriate for the proposed clinical phase. For later phase products, the Sponsor also may want to ask about the status of the method validation for their test methods and the adequacy of any orthogonal testing methods in use. In some cases, Sponsors ask for input from the FDA regarding their potency testing method(s) during the pre-IND meeting.
- Another frequently asked question on analytical methods is the level of method validation required for a phase 1 product. Typically, FDA will respond that methods used to release product should be qualified/verified such that test methods are suitable for their intended purpose (i.e., disposition of product)
- Certificates of Analysis (CoA): Often the CoA for Clinical Trial Material is not quite ready at the time of IND submission, but the Sponsor seeks approval to submit the final CoA after the IND is in effect but before the clinical trial is initiated.

The Sponsor should also expect unsolicited responses about cell line histories, analytical methods development, method validation, process validation, drug substance and drug product stability, as well as other CMC related topics.

The following bullets reflect typical FDA CMC comments for biologics:

- Your proposed potency assay will need to be fully developed and able to demonstrate accurate quantitation of that which you propose to measure, prior to initiating late-phase clinical trials.
- Data supporting the clearance of the (various process impurities) from the drug substance (DS) should be provided in the IND.
- The development and qualification of a working cell bank (WCB) is encouraged to avoid depletion of the master cell bank (MCB). Should you consider developing and qualifying a WCB, both MCB and WCB should be tested for: (i) absence of bacteriophage and fungal/yeast contamination; (ii) viability (recovery of viable cells from frozen vials); (iii) vector integrity; (iv) insertions and deletions; (v) plasmid copy number; (vi) integrity of the protein coding sequence; and (vii) protein production levels. Acceptance criteria for these tests should be established. Refer to ICH Q5B and Q5D for guidance. [For an E. coli-derived product]
- End of production cells (EPC) should be characterized in order to determine the following attributes as appropriate: (i) microbial purity; (ii) plasmid copy number and stability (e.g., % cell retaining the expression vector); (iii) viability; (iv) integrity of the protein coding sequence; and (v) protein production levels. In addition, fermentation data regarding the number of cell population doublings should be provided. Refer to ICH Q5B and Q5D for guidance. [For an E. coli-derived product]
- In-process controls should be developed in phase 1 & 2 and in place for phase 3 studies. In-process controls for fermentation and harvesting should include but not be limited to tests for cell growth/viability and bioburden after each relevant chromatographic/processing step. In-process controls for the purification process should include step yield calculations along with tests for protein recovery and purity at relevant purification steps.
- A meaningful comparability study could be conducted using release, stability and characterization test methods. In addition, for each analytical method, the materials should be tested, side-by-side, under nearly identical experimental conditions. The test results should be tabulated for direct comparison or graphically (e.g., electropherogram, chromatogram) presented.
- We recommend that you develop a two-tiered system for your reference standard (RS). The two-tiered system should consist of a primary and a secondary RS of which, the secondary RS is calibrated against the primary RS that is representative of production and clinical material (see ICH Q6B). Please note that the qualification protocol for new RS should consist of release and additional characterization tests. We expect tighter acceptance criteria for the qualification of a new RS, when compared to those of release tests, in order to prevent a drift in product quality. We advise you to submit detailed descriptions of primary and secondary RS qualification protocols for review. The long-term stability of the primary RS should be considered when evaluating storage temperatures. The primary RS should be stored under conditions that prevent degradation to the greatest extent possible.



- SEC-HPLC should be validated for its ability to detect and accurately measure aggregates. This can be done by generating aggregates under stress conditions and comparing the results of SEC-HPLC aggregate testing with those obtained with orthogonal test methods, including but not limited to analytical ultracentrifugation (AUC), field flow fractionation (FFF) or light scattering techniques (MALLS or DLS).
- Although most of the proposed release test methods for drug substance (DS) and drug product (DP) are acceptable, provisional acceptance criteria should be provided in the IND with upper and lower limits for all DS/DP release tests, where applicable.
- Visible and/or sub-visible particle formation can represent a significant degradation pathway for biotechnology products and impact product quality and safety. We recommend that in addition to <USP 788> particulate testing, sub-visible particles of 2 to 10 µm in size be characterized at release and at regular intervals in the DP stability program including under accelerated and/or stressed conditions. While your product should comply with compendial limits for particles greater in size than 10 µm and 25 µm during development, it is not necessary to establish acceptance criteria at this time for smaller sub-visible particles. As part of this evaluation, you should use orthogonal techniques to characterize the type of particulates. We recommend that testing for subvisible particulates be performed at least on an annual basis in the DP stability program. We would further expect that for Phase 3, sufficient data will be available to set a meaningful specification for 2 – 10 µm sub-visible particles.
- We note that you test for sub-visible particles. Please comment on testing for visible particles and the release specifications for visible particles.
- Please provide data supporting the stability and biocompatibility of the product with the delivery materials.

#### 4.2. Nonclinical

The Sponsor should seek agreement from the FDA that the material tested in the toxicology studies is produced in a similar manner that the GMP clinical trial material will be manufactured. The Sponsor should also seek agreement that the animal model(s) used for the toxicology study are relevant and the study design is acceptable.

#### 4.3. Clinical

The Sponsor should seek agreement from the FDA that the proposed Clinical Study synopsis is acceptable. If there are areas of clarification that need to be discussed, the issues should be raised – for example, clinical design including endpoints, inclusion and exclusion criteria, primary and secondary endpoints, starting dose, dose escalating rules, safety stopping rules are key points to gain clarification for preparation of the Clinical Protocol to be submitted to the IND.

### 5. STRATEGIC DECISION MAKING

#### 5.1. Pre-IND Risk Assessment of Potential Clinical Hold for IND Initial Study

Assure the Clinical Protocol follows all the ICH guidances for good clinical practice (ICH E6 (R2)) and assess the clinical design to assure safety of clinical subjects.

From “Review of Chemistry, Manufacturing, and Controls (CMC) of an Investigational New Drug Application (IND)”, Presentation at US FDA Regulatory Education for Industry Conference, Fall Conference, September 27, 2017, by Maria Cecilia Tami (OBP, OPQ) and Balajee Shanmugam (ONDP, OPQ), examples of clinical hold CMC issues are presented below:

- Proposed clinical lot has not been manufactured
- Insufficient characterization of cell banks
- Insufficient data to support viral clearance
- Insufficient data to support comparability between toxicology and proposed clinical lots
- Inadequate specifications for release and stability testing
- Lack of information for raw materials of animal origin



- Insufficient data to support product stability for the duration of the clinical studies
- Lack of evidence for final drug product sterility
- High levels of process-related impurities
- Endotoxin at higher doses > 5 EU per kg per hour
- Product lacks potency assay
- Product lacks adequate characterization

## 5.2. To Comply or Not to Comply with FDA Requests/Comments

Following a formal meeting, the FDA RPM will provide meeting minutes which serve as the official record of the meeting. Written comments from the FDA, in lieu of the meeting, also serve as official correspondence and the Sponsor is expected to comply with the recommendations included in these comments. In some cases, Sponsors may disagree with a statement or statements that appear in the meeting minutes / written comments, or the Sponsor may have reason to believe that a specific request cannot reasonably be met. In these instances, the Sponsor may submit a response to the FDA communicating their interpretation of the discussion or providing justification for why the FDA's recommendation cannot be followed. While the FDA may not change the minutes, such communication may provide an opportunity to continue discussions with the FDA about other approaches which may be employed to alleviate FDA's concern.

For items that present significant challenges to the Sponsor, a risk analysis of compliance vs. noncompliance should be performed. The Sponsor should decide if there is justifiable reason why they are unable to comply with the FDA's recommendations as presented in the official minutes. Science and data-based arguments are optimal. The FDA is highly unlikely to waive a requirement because of cost or impact on time-to-market.

## 5.3. Plan to Answer all FDA pre-IND Comments in the IND Submission

In Module 1 of the IND, the Sponsor should include a pre-IND response document with the questions from the meeting package, FDA's responses from the FDA meeting minutes or written responses, followed by the Sponsor's response and a link (or links) to where the relevant information addressing the comment may be found within the IND. This confirms to FDA that their comments were taken seriously and allows them to easily find the information they requested.

For the following actual example of FDA comments, the Sponsor should include a brief response which includes links to the requested information within their electronic IND.

- Please submit the following information to your IND:
  - Full sequence of the recombinant [product designation] for the final drug product (FDP) clinical lot that will be used for the Phase 1 trial.
  - Summaries of analytical methods used in Master Cell Bank, the Master Virus Seed, Drug Substance, and Drug Product. Please include Certificates of Analysis for all serum, cell culture media, media supplements, and any raw materials of human or animal origin. Please also identify where in the manufacturing process these materials were used.

## 5.4. Track Timing and Commitments to Meet FDA Expectations During Clinical Development and for the BLA/NDA Submission

Once the Sponsor has received formal written Pre-IND responses and/or meeting minutes from the FDA, the FDA will expect all commitments agreed upon during the meeting to be met. In some cases, the FDA comments will indicate when they expect specific additional tasks to be performed as in the example below related to an End-of-Phase 2/pre-IND meeting.

- Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an

outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

Other comments will include specific recommendations with no specific product development deadlines, as in the example below.

- Implement an identity test in [drug product] release specifications for both drug substance and drug product and set appropriate acceptance criteria accordingly.

The Sponsor's periodic review of the project status and timelines should include a review of the progress made toward addressing each of these commitments.

To address certain specific comments which do not need to be completely resolved by the time of IND submission, it may be useful to provide periodic updates to determine if the Agency is in agreement with the Sponsor's approach to addressing the issue. Following IND submission, this information may be submitted as amendments to the IND, though it should be noted that the Agency is not under obligation to review these amendments within a specified timeframe although they do target 60 days. It may be useful to obtain Agency input regarding unforeseen issues that arise during product development while attempting to comply with the FDA's recommendations. Information such as stability data, manufacturing process updates, and a summary of nonclinical studies completed and/or initiated within the past year may also be provided as part of the IND annual report, which must be submitted each year within 60 days of the anniversary date on which the application was allowed to proceed.

To ensure that all pre-IND comments have been or are in the process of being addressed, and that those with submission deadlines are met in a timely manner, the Sponsor should work with their team of subject matter experts, clinical team, and regulatory experts. The team should devise plans for how best to approach a resolution for each comment and determine the best mechanism for submitting the required information to the FDA. A project manager familiar with FDA interactions can be useful to oversee the program, help maintain product development timelines, and facilitate communications with the FDA.

## 6. SUMMARY AND CONCLUSIONS

Pre-IND meetings present an opportunity for Sponsors to receive direct feedback on their product from the FDA early in the development process and are likely to result in a shorter time to getting the investigational product into clinical studies in the US. The Sponsor is advised to make the most of the limited time they have by asking targeted, well-phrased questions, the answers to which will help them make key decisions about their biologic or drug development program for CMC, nonclinical and clinical studies.

Sponsors are strongly advised to follow the "Formal Meetings" guidance document from the FDA. Sponsors should also review the division-specific pre-IND information provided on each web page.

Sponsors who are not familiar with the pre-IND process should consider working with a consultant and/or non-FDA Regulatory Project Manager who can help them with preparation and submission of the meeting request, meeting package, and meeting preparation.

## 7. REFERENCES

### 7.1. FDA Resources

- 21 CFR 312.82: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=312.82>
- CBER SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Sponsors (Version #5, effective date: October 15, 2012): <https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/proceduressopps/>

- [ucm079448.htm](https://www.fda.gov/ucm079448.htm)
- CDER Small Business and Industry Assistance: Frequently Asked Questions on the Pre-Investigational New Drug (IND) Meeting:  
<https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069906.htm>
- Division of Anti-Viral Products' (DAVP) Pre-IND Letter of Instruction:  
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/ucm077776.htm#CMC>
- Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Sponsors (March 2015, Revision 2): <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm437431.pdf>
- Guidance for Industry, IND Meetings for Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Information, May 2001
- Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology Products, November, 1995.
- Guidance for Industry: INDs for Phase 2 and Phase 3 Studies CMC Information, May 2003.
- Guidance for Industry: CGMP for Phase 1 Investigational Drugs, July 2008
- Prescription Drug User Fee Act (PDUFA) VI commitment letter:  
<https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>

## 7.2. Other References

- Vu HH, Pariser AR. Pre-Investigational New Drug Meetings with the FDA: Evaluation of Meeting Content and Characteristics of Applications for New Drug and Biologic Products. *Therapeutic Innovation & Regulatory Science*. 2015;49(3):434-442.