Succeeding with the FDA: Answers to Seven Common Questions About IND Submissions

Submission of an Investigational New Drug Application (IND) is a milestone in new drug development, marking the transition from bench research to clinical studies in human participants. Successful IND submission requires careful planning and strict compliance with regulatory requirements, which can be especially challenging for first-time applicants. In this article, we offer answers to seven questions we commonly receive about developing a timely and well-structured IND submission.

1 What is the structure of the Common Technical Document?

The Common Technical Document (CTD) consists of five modules:

- *Module 1* – Region-specific administrative and prescribing information, as required by the regulatory authority to which the IND is being submitted
- *Module 2* – Summaries and overview of quality, non-clinical data, and clinical data sections of the CTD
- *Module 3* – Information related to the quality of the pharmaceutical drug substance and drug product, including information on manufacturing
- *Module 4* – Nonclinical study reports, including toxicology, pharmacology and pharmacokinetics evaluations. Some studies require full data sets in Standard for Exchange of Nonclinical Data (SEND) format
- *Module 5* – Clinical Study Data including Clinical Study Reports for completed studies, Protocols, 1572, and CV for investigators and supporting clinical publications

The U.S. Food and Drug Administration (FDA) requires applicants, except academic institutions, to provide IND submissions in the electronic CTD (eCTD) format through the Electronic Submissions Gateway (ESG). FDA guidance on providing submissions using eCTD specifications can be found here.

2 What is the purpose and value of a pre-IND meeting?

Sponsors who wish to seek advice from the FDA prior to submitting an IND can request a pre-IND meeting. Timing of this meeting will vary depending on the development program, but typically applicants schedule it three to nine months before planned IND submission.

The purpose of this meeting is to gain agency feedback on the proposed development strategy to minimize the likelihood of a clinical hold. Typically, the FDA will respond to a pre-IND meeting request within 21 days of receiving the request and the meeting will be scheduled within 60 days. Sponsors will be required to submit a briefing document with their specific questions for the agency 30 days prior to the meeting. In some cases, the FDA may provide a written response in lieu of a meeting.

Topics sponsor may request feedback on during the pre-IND meeting include:

- Potential issues with the drug substance, drug product, or formulation intended for human use
- Acceptability of the clinical trial design
- Adequacy of preclinical studies including toxicology studies
- Potential pharmacokinetics concerns and dosing limitations
- Questions regarding clinical safety monitoring

The FDA will provide any final comments within 30 calendar days following the meeting.

3 Can foreign data be included in the IND?

Generally, the FDA will accept foreign studies in support of an IND or marketing application provided that those studies are well-designed and follow Good Clinical Practice (GCP), including:

- Use of qualified investigators
- Review by an independent ethics committee
- Appropriate monitoring
- Proper informed consent
- Use of the appropriate drug product

Importantly, the data will need to be deemed applicable to the U.S. population and U.S. medical practice. For instance, if the foreign study uses concomitant medications or comparators, those medicines need to be approved in the US for the same use. In addition, the FDA should be able to validate the foreign study through onsite inspection, if needed.

4 For combination products, which FDA medical product center will review the application?

Combination products are assigned to an FDA center for premarket review and regulation based on a determination of the primary mode of action (PMOA) of the product. The PMOA is defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product." If a combination product is drug led, as with metered dose inhalers or autoinjectors, the Center for Drug Evaluation and Research (CDER) will have primary jurisdiction. Biologic-led products would be reviewed by the Center for Biologics Evaluation and Research (CBER). For device led combination products, such as stents, the FDA center responsible for review will be the Center for Devices and Radiological Health (CDRH).

5 What are the requirements for manufacturing in the IND?

The FDA takes a stage-appropriate approach to the application of Good Manufacturing Practice (GMP) regulations. In INDs for Phase 1 studies, the agency's emphasis is on Chemistry, Manufacturing and Controls (CMC) information that ensures product safety for participants in the proposed clinical trial. This includes assurance of proper identification, quality, purity, and strength of the investigational drug substance and drug product, as supported by:

- Well-defined, written procedures, methods, and specifications
- Adequately controlled equipment and manufacturing conditions
- Accurate and consistent data from manufacturing, including analytical methods, release testing, and stability testing
- Proof of compatibility with intravenous bags and tubing, for parenteral products

Moreover, sponsors will need to demonstrate that the stability of the drug will remain consistent throughout the duration of the trial.

For an IND supporting a First In Human study, emphasis will include qualifying the drug product used in nonclinical toxicology studies in support of the clinical drug product.

6 What is the regulatory timeline for U.S. IND submissions?

Below is a sample timeline for IND submissions.

To streamline the submission process, sponsors should implement a methodical and systematic approach to documenting their discovery and development efforts from day one. We recommend beginning with the end (IND submission) in mind and documenting each of the milestones required on the application as they are completed, rather than trying to compile all the necessary documents at once during IND development.

Following IND submission, the FDA will review the application within 30 days. At the end of this review cycle, the agency will either issue a Study May Proceed letter or inform the applicant that the study is on clinical hold. Then, within 30 days, the FDA will provide a written explanation of the basis for the hold and the sponsor will need to address the cited deficiencies and submit a response to the issues identified in the clinical hold letter in separate submission. Once this submission has been received, the FDA will have 30 days to review it and determine whether the hold can be lifted.

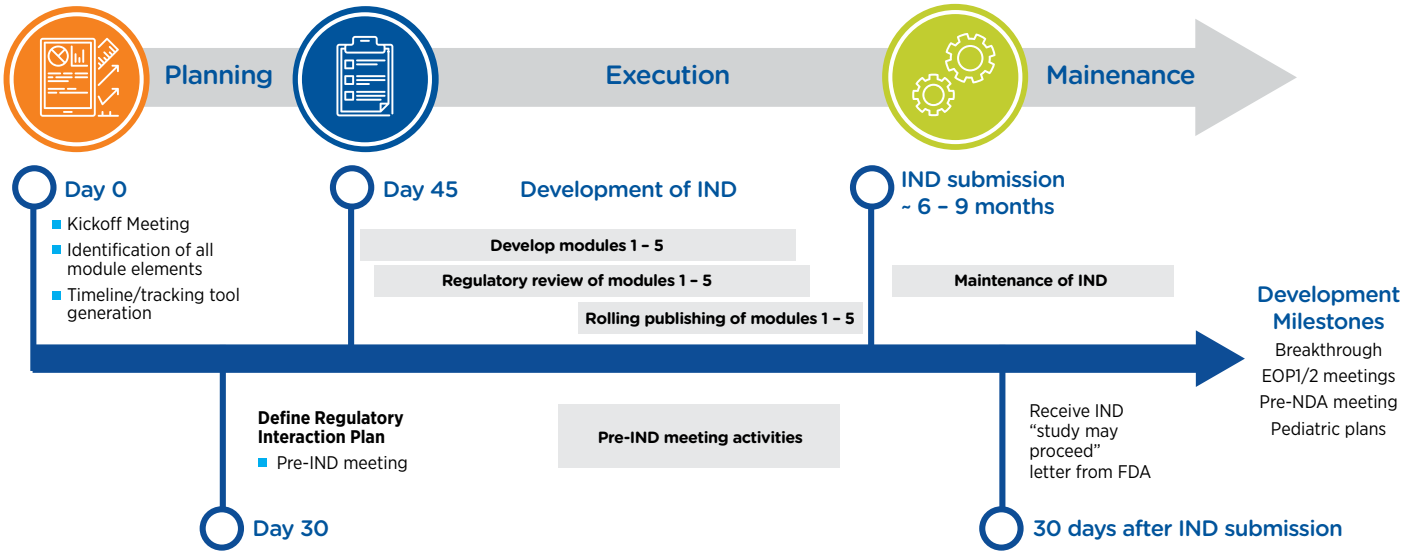

Figure 1. Example regulatory timeline

7 Is there a way to expedite regulatory review or approval?

The FDA currently provides four designations and one approval pathway to expedite development, as shown in the figure below. Each of these approaches has its own qualification criteria, associated benefits, and timing.

	Orphan Designation	Fast Track	Breakthrough Therapy	Priority Review	Accelerated Approval
Classification	**Designation**	**Designation**	**Designation**	**Designation**	**Approval Pathway**
Qualification	Prevalence of disease in less than 200,000 in the U.S.	Serious condition and nonclinical or clinical data support potential to address an unmet need	Preliminary clinical evidence drug may have substantial improvement on clinically significant endpoint over available therapies	Serious condition and significant improvement in safety or efficacy or supplement to report on pediatrics	Serious condition and meaningful advantage over available therapies based on surrogate endpoint likely to predict effect on confirmatory endpoint
Benefits	▪ Tax incentives ▪ Marketing application filing fee waived	Increased interaction and rolling review of NDS/BLA	Intense interaction with senior staff and rolling review of NDA/BLA	Two month filing period and six month review vs. 10 month standard review	Earlier approval – with commitment to provide confirmatory data to support full approval
When to apply	When data supports – can be before IND	With IND or any time after	Usually with Phase 2 or later data	At marketing application	N/A

Figure 2. Options for expediting drug development[2]

Getting support for your IND submission

Premier Consulting is a strategic product development and global regulatory consulting company dedicated to helping biotech innovators transform their life-changing ideas and breakthrough science into new medical treatments. Our end-to-end solutions in strategy, regulatory, nonclinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.

To learn more about how Premier Consulting can help increase the chance of IND success, contact us.

References

1. U.S. Food and Drug Administration. Frequently Asked Questions About Combination Products. Available at https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products#review.

2. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. Available at https://www.fda.gov/media/86377/download.

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Premier Consulting is a strategic product development and global regulatory consulting company dedicated to helping biotech innovators transform their life-changing ideas and breakthrough science into new medical treatments.

Our end-to-end solutions in strategy, regulatory, nonclinical, clinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.

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