SPONSOR-INVESTIGATOR IND TRAINING

LEARNING SUPPLEMENT

IND/IDE Support Program

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Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Clinical Hold
An order issued by the FDA to the sponsor of an IND to delay a proposed clinical investigation or suspend an ongoing clinical investigation.

Clinical investigation
Any experiment in which a drug (including a biologic) is administered or dispensed to, or used involving, one or more human subjects. An experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

Code of Federal Regulations (CFR)
The Code of Federal Regulations (CFR) is a codification of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government. **Title 21** of the CFR is reserved for rules of the Food and Drug Administration.

- **21 CFR 312** - Title 21 Food and Drugs, Part 312 Investigational New Drug Application

Contract Research Organization (CRO)
A person or organization that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

Drug
Any article intended for the use in the diagnosis, cure, mitigation, treatment or prevention of disease…" and "…articles (other than food) intended to affect the structure or any function of the body of man or other animals." (Source section 201 (g) (1) of the FD&C Act).

Drug Biological Product
A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product (except chemically synthesized polypeptide) or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." (Source section 351 of PHSA (42 U.S.C. 262)

Essential Documents
Documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

Food and Drug Administration (FDA)
The government agency that is responsible for assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation.

Independent Ethics Committee (IEC)
A review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection. An institutional review board (IRB) is one type of IEC.

Institutional Review Board (IRB)
Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights, safety, and welfare of human research subjects.

Investigational New Drug
A new drug or biologic that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous. **IND** means an investigational new drug application.

Investigator
An individual who conducts a clinical investigation (i.e. under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Sub-investigator" includes any other individual member of that team.

Marketing Application
An application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

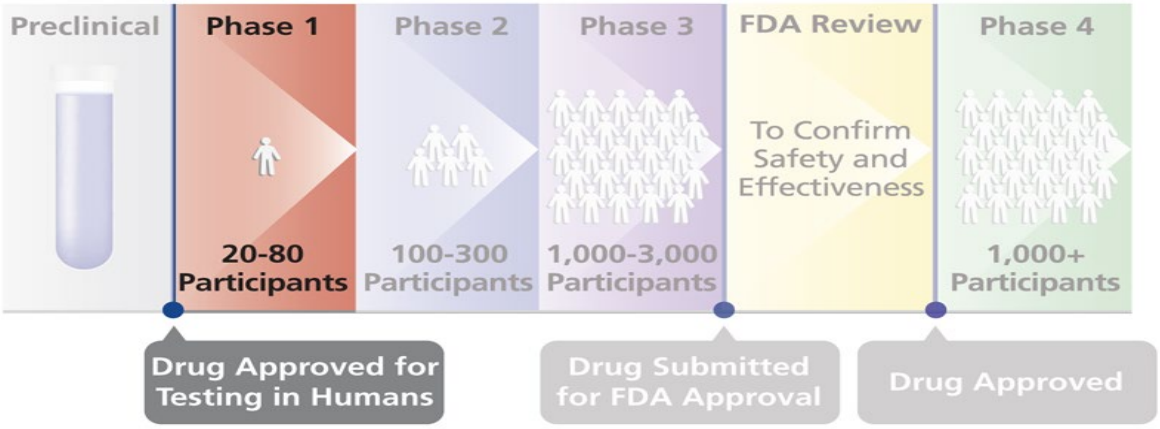
Sponsor
A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator.

- At CHOP, the sponsor is not necessarily a funding sponsor (or a pharmaceutical company). Most times the sponsor is a “regulatory sponsor” that completes and files all required documentation with the FDA and IRBs.

Sponsor-Investigator
An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor.

Trial Master File

This is the name of the collection of all essential documents and any documentation which is created during the trial that help reconstruct and evaluate the trial conduct. This may include data management, statistics, pharmacovigilance, clinical trial supplies, pharmacy, contracts, legal, and regulatory affairs.



INDs as Clinical Investigations: Clinical Trial Phases

Source: https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/568/phase-1-trial

Phase 1

- The initial introduction, or new indication, of an investigational new drug into humans
- As in all phases, safety is primary: Adverse effects are collected and reported
- "First-in-human" investigation may be conducted either in healthy volunteers, or in affected human subjects
- Dose finding/Dose escalation/Maximal tolerated dose
- PK/PD studies/Drug metabolism/Mechanism of action
- "Safety and Tolerability" clinical studies
- Early phase "pilot" studies, some without statistical power
- Data from Phase 1 inform Phase 2 study design

Phase 2

- The early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition
- These studies have therapeutic exploratory endpoints
- This phase of testing also helps determine the common short-term side effects and risks associated with the drug
- Phase 2 studies generally involve more patients than phase 1, and aim to be statistically powered
- Dose finding in Phase 2 informs the dose used in Phase 3 studies.

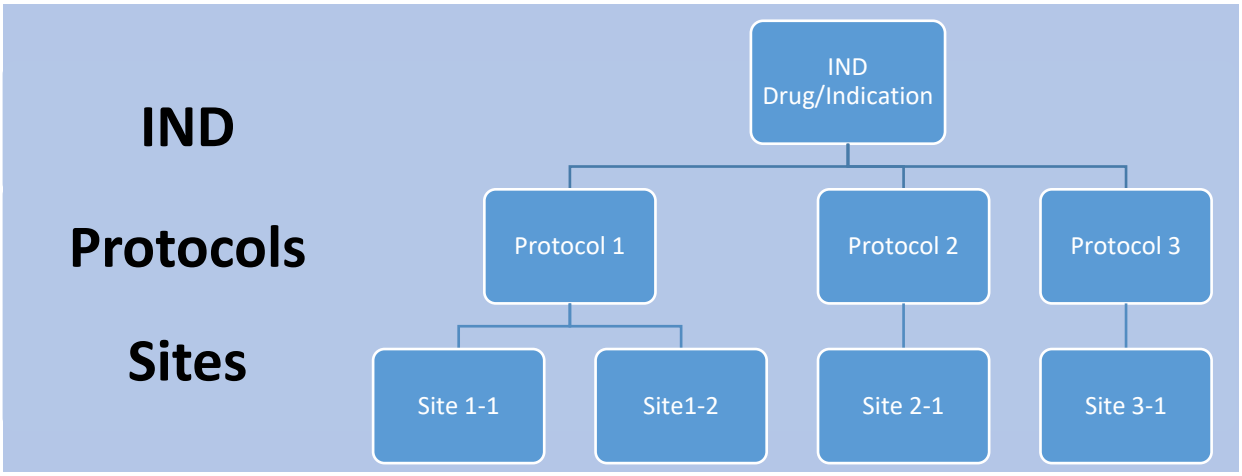
Phase 3

- Gathers data primarily about effectiveness, as well as safety, that is needed to evaluate the overall benefit-risk relationship of the drug
- Provide an adequate basis for extrapolating the results to the general population and transmitting that information to the FDA-approved drug label
- Conducted at multiple sites
- Frequently randomized, placebo-controlled, blinded studies that are "pivotal" for drug development

Phase 4

- Post-marketing surveillance

IND Submissions: Protocols, Amendments, Safety Reporting, Annual Reports and Clinical Holds



Protocol Requirements

A protocol is required to contain the following, with the specific elements and details of the protocol reflecting the distinctions depending on the phase of study:

- A statement of the objectives and purpose of the study.
- The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.
- A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.
- The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.
- A description of the observations and measurements to be made to fulfill the objectives of the study.
- A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk
- Plans for monitoring data and safety, and reporting safety findings.

Protocol Amendments

Once an IND application is in effect, the sponsor of the application may amend the application as needed to ensure that the clinical investigations are conducted according to protocols included in the IND application. Sponsors are expected to submit protocol amendments for new protocols or changes to existing protocols **before** implementation of the respective changes. New studies may begin when the sponsor has submitted the change to FDA for its review **and** the new protocol or changes to the existing protocol have been approved by the Institutional Review Board (IRB) with the responsibility for review and approval of the studies. If the IND application sponsor desires FDA to comment on a submission, they should submit a request for such comment and the specific questions that FDA's response should address.

When several submissions with minor amendments are expected within a short period, sponsors are encouraged, to the extent feasible, to include all amendments in a single submission.

Any specific technical information referenced in an IND application amendment as already submitted to FDA in the original IND application is expected to be identified by name, reference number, volume, page number, and date of submission. The general types of protocol amendments are shown below.

- New protocol
- New investigator (or change of investigator (PI) at current investigational site)
- Changes in previously submitted protocols

New Protocol

Identified on FDA Submission as – **Protocol Amendment: New Protocol**

If a sponsor (or sponsor-investigator) intends to conduct a study that is not covered by a protocol already contained in their IND application, the sponsor is expected to submit to FDA a protocol amendment containing a copy of the new protocol and a brief description of the most clinically significant differences between it and the previous protocols..

Such study may begin provided two conditions are met (in either order):

- The sponsor (or sponsor-investigator) has submitted the protocol to FDA for its review; and
- The protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56.

New Investigator

Identified on FDA Submission as – **Protocol Amendment: New Investigator**

A sponsor of an IND application is expected to submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol. The amendment should include the investigator's name, the qualifications to conduct the investigation, and any reference to the previously submitted protocol, if relevant. FDA should be notified within 30 days of the investigator being added.

Such study may begin provided two conditions are met (in either order):

- The sponsor (or sponsor-investigator) has submitted the protocol to FDA for its review; and
- The protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56.

A protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under 312.315 or 312.320.

Note: The FDA provides the following definition of Investigator: *Investigator* means an individual who actually conducts a clinical investigation (*i.e.*, under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312#p-312.3(Investigator)
Therefore, a change to a "subinvestigator does not required a Protocol Amendment – New Investigator submission to the FDA.

Changes in Previously Submitted Protocols

A sponsor of an IND application is expected to submit a protocol amendment in cases when there are changes in the existing protocol that significantly affect safety of subjects, scope of the investigation, or scientific quality of the study. Such amendment should contain a brief description of the change and reference (date and number) to the submission that contained the original protocol.
For example, changes requiring an amendment to an IND application may include:

- Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of a protocol (such as the addition or elimination of a control group).
- Addition of a new test or procedure intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or elimination of a test intended to monitor safety.

A protocol change can be implemented provided two conditions are met (in either order):

- The sponsor has submitted the change to FDA for its review; and
- The change has been approved by the IRB with responsibility for review and approval of the study.

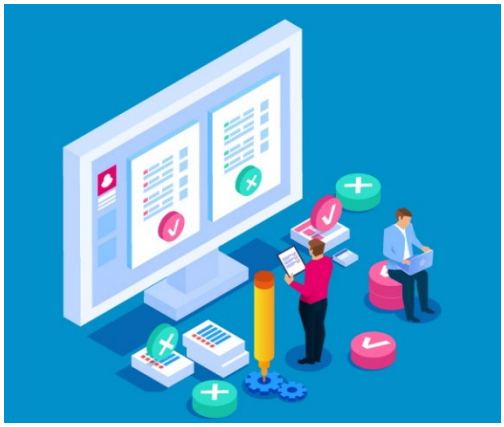
A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided that the FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 56.104(c).

Protocol Amendment Checklist

Use the following checklist to ensure appropriate updates to the trial are made before implementing a protocol amendment:

1. Update version and date of protocol and file tracked changes in the Trial Master File/Regulatory Binder
2. Update the Informed Consent Form (if applicable)
3. FDA Reporting
4. IRB Reporting
5. Other regulatory reporting
6. Obtain or update certification/accreditation, quality control, or validation for new procedures, reading centers, or laboratories
7. Generate or update procedures (Standard Operating Procedures (SOPs)) and processes

8. If applicable, update Chemistry, Manufacturing, and Controls
9. Inform the pharmacy (document the communication)
10. Train study team members
11. Obtain additional personnel qualifications (if new procedures)
12. Update recruitment material
13. Update Data Collection Tools to reflect protocol changes
14. Update tools for safety reporting
15. Update study monitoring plan or other appendices to the protocol
16. Update subject eligibility checklist or study visit checklists
17. Obtain or update existing contracts and/or budgets



Information Amendments

Information amendment is any amendment to an IND application with information essential to the investigational product that is not within the scope of protocol amendments, safety reports, or annual reports. For example, information amendments to IND applications may include new toxicology, chemistry, or other technical information or a report regarding discontinuance of a clinical or non-clinical investigation. Information amendments to an IND application should be submitted as necessary but, to the extent feasible, not more than every 30 days.

Any information amendment submitted under an IND application is required to bear prominent identification of its contents (e.g., “Information Amendment: Chemistry, Manufacturing, and Control”, or “Information Amendment: Pharmacology-Toxicology”, or “Information Amendment: Clinical”), and to contain the following:

- A statement of the nature and purpose of the amendment,
- An organized submission of the data in a format appropriate for scientific review, and
- A request for FDA’s comment, if the sponsor desires FDA to comment on the information amendment.

Safety Reporting

An IND safety report must document potential serious risks, from clinical trials or any other source. Any information that suggests increased risk requires prompt reporting to the FDA and Investigators.

Documenting Relevant Information

The sponsor must review all information relevant to the safety of the drug and received from foreign or domestic sources, including:

- Information derived from any clinical or epidemiological investigations,
- Animal or in vitro studies,
- Reports in the scientific literature,
- Unpublished scientific papers,
- Reports from foreign regulatory authorities, and
- Reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

Any information that suggests increased risk requires prompt reporting to the FDA and Investigators

A) Findings from other studies
- The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

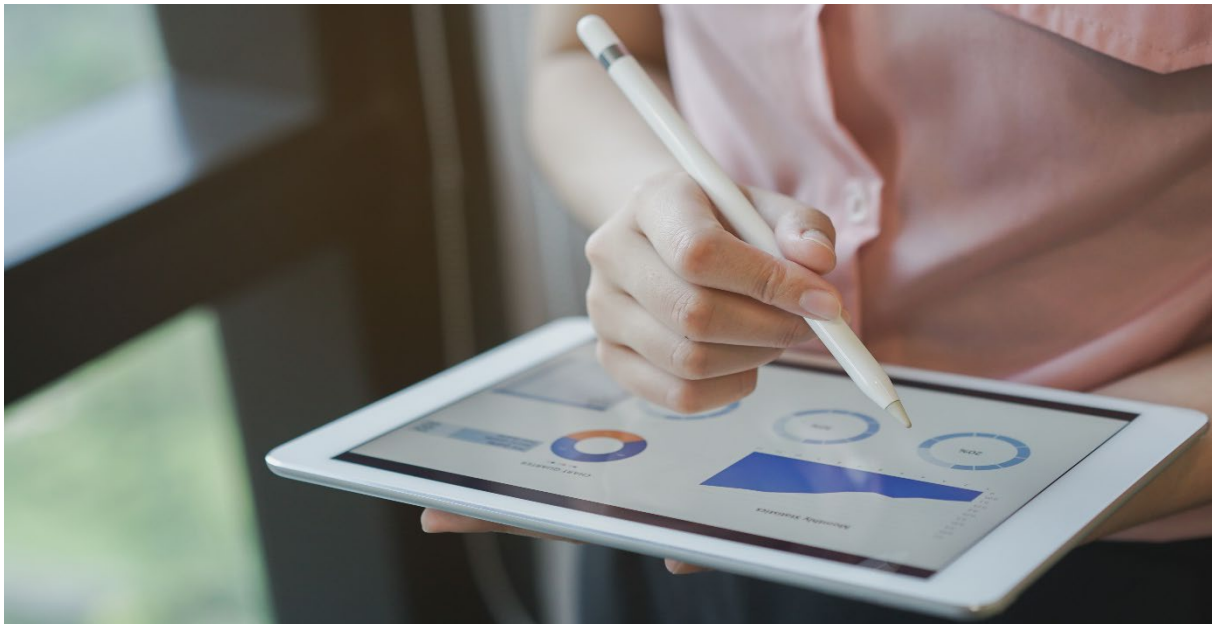
B) Findings from animal or in vitro testing
- The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.

- Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation

C) Investigations of marketed drugs
- A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post-marketing safety reporting requirements (e.g., 310.305, 314.80, and 600.80).

D) Reporting study endpoints
- Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.



Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
Suspected Adverse Reaction	When there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event
Life-threatening adverse event or Life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It is not an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
Serious adverse event* or serious suspected adverse reaction	An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: • Death, • a life-threatening adverse event, • inpatient hospitalization or prolongation of existing hospitalization, • a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, • or a congenital anomaly/birth defect. • Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Unexpected adverse event or unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if: • It is not listed in the study documents (protocol, IB, consent, etc) or is not listed at the specificity or severity (or frequency) that has been observed. • "Unexpected," also refers to adverse events or suspected adverse reactions that are mentioned in the investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

A) Unexpected fatal or life-threatening suspected adverse reaction reports

- The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

B) Serious and unexpected suspected adverse reaction (SUSAR)

- The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
    - **A single occurrence** of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
    - **One or more occurrences** of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
    - **An aggregate analysis of specific events** observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

C) Increased rate of occurrence of serious suspected adverse reactions

- The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

Submission Timeline

The safety report must be submitted as soon as possible, but in no case later than 15 calendar days (7 for life threatening) after the sponsor determines that the information qualifies for reporting. The sponsor must notify:

- The FDA
- All participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND)

Relevant follow-up information to an IND safety report must be submitted as soon as the information is available.

Type of Event	Types of Safety Reports	FDA Reporting Timeframe
Unexpected fatal or life threatening adverse event or adverse reaction associated with the study drug	Telephone/Fax	No later than 7 days of receipt of information
Serious and Unexpected adverse events or adverse reactions	Written	No later than 15 days of receipt of information*
New/additional information relevant to the initial report is received (ex: new test results, change in clinical course, additional procedures, etc).	Follow-Up	In a timely manner

IND Annual Reporting

Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year. 21 CFR 312.22. The reports should include information obtained during the previous year's clinical and nonclinical investigations, including:

- **Study Status/Overview**
  - Title, protocol number, purpose, patient population, status of the study is completed.
  - A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.
  - A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

- **Study Results/Key Findings**
  - If the study has been completed, or if interim results are known, a brief description of any available study results.
  - A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.

- **Study Subjects**
  - The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.
  - A list of subjects who died during participation in the investigation, with the cause of death for each subject.
  - A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

- **Safety Reporting**
  - A summary of all IND safety reports submitted during the past year.
  - A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

- **Summary of Changes**
  - A summary of any significant manufacturing or microbiological changes made during the past year.
  - If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.
  - A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

- **Next Steps**
  - A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under 312.23(a)(3)(iv).
  - If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.

Clinical Holds for IND Submissions

Clinical Hold: [21 CFR 312.42(a)]

- Full Clinical Hold – a delay or suspension of all clinical study under an IND
- Partial Clinical Hold – a delay or suspension of only part of the clinical study under an IND (e.g., a specific protocol or part of a protocol is allowed to proceed

FDA Clinical Hold Explanations

- Study is not designed to be adequate and well controlled
- The protocol is clearly deficient in design to meet its stated objectives
- Unreasonable risk, and significant risk of illness/injury
- Unjustified reproductive or developmental toxicity
- Prior studies strongly suggest lack of effectiveness
- Another drug under investigation has demonstrated better benefit: risk balance
- The commissioner determines it is not in the public interest

FDA Specific Examples of Clinical Holds

A) Product Quality

- Impurity profile presents health hazard
- Chemical stability is inadequate

B) Pharmacology and Toxicology

- Studies are not sufficient
- Studies are poor quality (non GLP)

C) Clinical

- Prior toxicities are not addressed
- High potential for unpredictable acute reaction without consideration of staggered administration

Response to Clinical Holds

- FDA Guidance Final Guidance October 2000
  Submitting and Reviewing Complete Responses to Clinical Holds

- FDA Regulations
  21 CFR 312.42

Clinical Trial Management Resources

ORC resources and policies: Located in the CHOP policy library

- Clinical Research Essential Documents Policy
- Essential Documents Checklist
- Children's Hospital of Philadelphia Policies and Procedures
    - Research Institute Manual
        - Office of Research Compliance (ORC)

Center for Childhood Cancer Research (CCCR) (Oncology only)

- Clinical Trials Management System: OnCore
- Investigator Study Files: @CHOP

Clinical Research Support Office (CRSO)

- Recruitment Enhancement Core (Recruitment Resources)
- Clinical Research Staff

Additional Regulatory Guidelines for Sponsors and Investigators

Sponsor Regulatory Obligations

IND Sponsorship Requirements

A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under 21 CFR 312.50. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written determination 30 days after FDA receives the IND or earlier.

Informing Investigators

Before the investigation begins, the sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in 312.23(a)(5).

The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use.

Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with 312.32.

Sponsor Recordkeeping

Receipt, shipment, or other disposition of the investigational drug
A sponsor shall maintain adequate records showing the **receipt, shipment, or other disposition of the investigational drug**. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

Financial Interest
A sponsor shall maintain complete and accurate records showing any **financial interest** in 54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.

Record Retention
A sponsor shall **retain the records** and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

Sample Retention
A sponsor shall **retain reserve samples** of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, 320.38 or 320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in 320.38.

Inspection of Records

FDA inspection
A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part.

Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

ORC inspection
The Office Research Compliance (ORC) at CHOP has the right to inspect sponsor records upon request.

Inspection of controlled substances
If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

Drug Control
A sponsor shall ship investigational new drugs only to investigators participating in the investigation (21 CFR 312.53 (b)). CHOP policy mandates use of the CHOP Investigational Drug Service for INDs.

Guidelines for disposal of unused investigational drug (312.59):

- The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated.
- The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug.
- The sponsor shall maintain written records of any disposition of the drug in accordance with 312.57. (312.59)

Investigator Regulatory Obligations

An investigator is responsible for ensuring that a study:

- Is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; (312.60)
- Is conducted in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects; (312.56)
- Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part; (312.56).

Assurance of IRB review (Sec. 312.66)
An investigator must assure that an IRB will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator must also assure that he or she will:

- Promptly report to the IRB all changes in the research activity
- Report all unanticipated problems involving risk to human subjects or others
- Make no changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Investigator Recordkeeping

Disposition of drug
An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59.

Case histories
An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Record retention

An investigator shall retain records required to be maintained under for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated.

If no application is to be filed or if the application is not approved for such indication, the investigator shall retain records until 2 years after the investigation is discontinued and FDA is notified.

CHOP record retention policy provides specific institutional standards for record retention based on the type of record.

Drug Control

Control of the investigational drug (312.61)
An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

Handling of controlled substances (312.69)
If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution

Appendix 1: Chemistry, Manufacturing, and Controls (CMC) & Current Good Manufacturing Practices (cGMP)

Chemistry, Manufacturing, and Controls (CMC)

A section in the IND application describing the **composition, manufacture, and control of the drug substance and the drug product**, as appropriate for the particular investigations covered by the IND. The CMC section includes investigational drug information such as:

- Drug Master File (DMF)
- Certificate of Analysis (COA)
- Package Insert
- Dietary Supplement
- Compounded product
- Placebo

What to Consider when Developing the CMC Section

A) Amount of Information

Sufficient information is required to be submitted to assure the proper **identification, quality, purity, and strength** of the investigational drug, the amount of information needed to make that assurance will vary with:

- The phase of the investigation
- The proposed duration of the investigation
- The dosage form, and
- The amount of information otherwise available.

FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on **the identification and control of the raw materials and the new drug substance**. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

The amount of information to be submitted depends upon the **scope of the proposed clinical investigation**.

- For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

B) Information Amendment Submission

A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:

- New toxicology, chemistry, or other technical information; or
- A report regarding the discontinuance of a clinical investigation

Content/Format

An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), and to contain the following:

A) A statement of the nature and purpose of the amendment.
B) An organized submission of the data in a format appropriate for scientific review.
C) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

When to Submit

Information amendments should be submitted as necessary but, to the extent feasible, not more than every 30 days.

Chemistry, Manufacturing and Control Amendments

As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the **chemistry, manufacturing, and control** (CMC) processes with information appropriate to the expanded scope of the investigation.

FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

Pharmacology and Toxicology Amendments

The sponsor is required to submit information amendments, as appropriate, with additional information pertinent to drug safety. (IND Application 312.23) Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.

The kind, duration, and scope of animal and other required tests vary with the duration and nature of the proposed clinical investigations.

- Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection.

C) Stability Data

- Stability data is required for all phases to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation
- Emphasis for Phase 1 submissions should generally be placed on the identification and control of the raw materials and the new drug substance
- Sufficient information to assess whether batches can be adequately produced and consistently supplied.

D) Drug Substance (i.e. active ingredient)

- A description of the drug substance, including its physical, chemical, or biological characteristics;
- The name and address of its manufacturer;
- The general method of preparation of the drug substance;
- The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance;
- Information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies.
- Reference to the current edition of the United States Pharmacopeia--National Formulary may satisfy relevant requirements in this paragraph.

E) Drug Product (i.e. final product)

- A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage;
- The name and address of the drug product manufacturer;
- A brief general description of the manufacturing and packaging procedure as appropriate for the product;
- The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product;
- Information sufficient to assure the product's stability during the planned clinical studies.
- Description of plan for disposal of any unused portion of the drug

Reference to the current edition of the United States Pharmacopeia--National Formulary may satisfy certain requirements in this paragraph.

F) Placebo Product

A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

G) Labeling

A copy of all labels and labeling to be provided to each investigator.

- The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6)

H) Environmental analysis requirements:

A claim for categorical exclusion under 25.30 or 25.31 or an environmental assessment under 25.40.

Additional CMC Considerations for Drugs not Marketed in the US

A) Investigated Under Cross-Referenced

- Letter of Cross-Reference
- Letter of Authorization

B) Approved and Marketed ex US

- Components and composition of the drug
- Name of manufacturer or supplier of the drug
- English version of the labeling
- Certificate of analysis (COA)

Current Good Manufacturing Practices (cGMPs)

cGMP refers to the Current Good Manufacturing Practice regulations enforced by the FDA. cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting, and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.

The cGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "C" in cGMP stands for "current," requiring companies to use technologies and systems that are up to date in order to comply with the regulations. Systems and equipment that may have been "top-of-

the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

It is important to note that cGMPs are minimum requirements. Many pharmaceutical manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards.

All guidelines follow a few basic principles:

- **Hygiene.** Pharmaceutical manufacturing facility must maintain a clean and hygienic manufacturing area.
- **Controlled environmental conditions** in order to prevent cross contamination of drug product from other drug or extraneous particulate matter which may render the drug product unsafe for human consumption.
- **Manufacturing processes are clearly defined and controlled.** All critical processes are validated to ensure consistency and compliance with specifications.
- **Manufacturing processes are controlled**, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.
- **Clear Instructions.** Procedures are written in clear and unambiguous language. (Good Documentation Practices)
- **Operators are trained** to carry out and document procedures.
- **Quality Record-keeping**
    - Records are made, manually or by instruments, during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented.
    - Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.
- **Distribution** of the drugs minimizes any risk to their quality.
- **A system for recall.** A system for recall is available for recalling any batch of drug from sale or supply.
- **Plan to address complaints.** Complaints about marketed drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.
- **Safeguarding patient health.** Practices are recommended with the goal of safeguarding the health of patients as well as producing good quality medicine, medical devices, or active pharmaceutical products. In the United States, a drug may be deemed "adulterated" if it has passed all of the specifications tests but is found to be manufactured in a facility or condition which violates or does not comply with current good manufacturing guideline. Therefore, complying with cGMP is mandatory in pharmaceutical manufacturing.

FDA Guidance – Questions and Answers on Current Good Manufacturing Practices for Drugs
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/questions-and-answers-current-good-manufacturing-practices-drugs

FDA Guidance for Industry cGMP for Phase 1 Investigational Drugs
https://www.fda.gov/media/70975/download

Appendix 2: Pre-IND Meetings

Pre-IND Requirements

- Drug is reasonably safe for initial use in humans
- Compound exhibits pharmacological activity that justifies commercial development

General Recommendations for Pre-IND Data/Study Preparation

- Compile existing nonclinical data from past in vitro laboratory or animal studies on the compound;
- Compile data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population; or
- Undertake new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

Toxic and Pharmacologic Effects (Animal Testing)

A) At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors:

- Develop a pharmacological profile of the drug;
- Determine the acute toxicity of the drug in at least two species of animals, and
- Conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

B) Genotoxicity considerations:

- Drug absorption and metabolism
- Toxicity of the drug's metabolites
- Speed with which the drug and its metabolites are excreted from the body.

Pre-IND Meeting Frequently Asked Questions: ***(See below for responses)***

1. In the process of drug development, when can a pre-IND meeting be useful?
2. Can pre-IND meetings be helpful in developing a strategy for drug development?
3. What information should be included in the meeting request?
4. What is the purpose of the pre-IND meeting packet?
5. What do you include in a pre-IND meeting packet?
6. Is communication important in a pre-IND meeting?
7. Are there recurrent problems at pre-IND meetings?
8. What are some helpful tips for the pre-IND meeting discourse?

1. In the process of drug development, when can a pre-IND meeting be useful?

- When the product is intended to treat a serious or life-threatening disease
- When there is a novel indication
- When there are no current guidance documents
- When there are sponsors new to drug development
- When there are questions from the sponsor
- When there are pharmacologic or toxicologic signals of concern
- When the drug is a new molecular entity

2. Can pre-IND meetings be helpful in developing a strategy for drug development?

Yes. The following can be helpful in developing a strategy:

A) Identifying studies that will support the initiation of clinical trials

B) Discussing available methods to enhance development, for example:

- Orphan Drug Designation
- Fast Track Designation
- Accelerated Approval
- Animal Efficacy Rule

C) Discussing the differences between submitting a 505(b)(1) or 505(b)(2) application

3. What information should be included in the meeting request?

Sponsors should review the guidance Formal Meetings with Sponsors and Applicants for PDUFA Products for information on formal meetings with sponsors and applicants. Adequate information in the meeting request is a very important part of having a successful outcome of a pre-IND meeting and should include the following information:

A) Meeting objective

B) Proposed agenda, including estimated times needed for each agenda item

C) Listing of specific questions categorized and grouped by discipline.
For example, chemistry, manufacturing, and controls (CMC), pharmacology/toxicology, clinical pharmacology and biopharmaceutics, and clinical investigations:

- List of sponsor participants
- List of requested participants from CDER
- Quantitative composition (all ingredients by percent composition) of the drug proposed for use in the study to be discussed
- Proposed indication
- Dosing regimen, including concentration, amount dosed, and frequency and duration of dosing if known
- Proposed meeting date (propose 6-8 weeks in the future)
- When the background packet will be available (at least 4 weeks before the proposed meeting date)

4. What is the purpose of the pre-IND meeting packet?

- Provides the historical background information on the chemical development concept
- Provides information on the active ingredient
- Provides an initial clinical and preclinical development strategy
- Provides future development strategy including product scale-up and final formulation, and animal and clinical studies proposed in support of an NDA
- Provides FDA with a clear and concise overview of the planned development program
- Allows FDA the opportunity to comment on a proposed program of development

5. What do you include in a pre-IND meeting packet?

- Overall program synopsis
- Whether the animal efficacy rule is being considered
- Clinical study synopsis to obtain FDA input on inclusion, exclusion, and endpoints
- Results for in vitro and early in vivo toxicology
- Rationale for safety, based on toxicological profile and safety margin using dose regimen and exposure
- Brief description of the manufacturing scheme for the active pharmaceutical ingredient (API) and formulation for clinical study
- Brief assay descriptions
- Full description of the development plan
- Copy of the meeting request with updates to reflect the most current information

6. Is communication important in a pre-IND meeting?

Yes, be sure to:

- Ask specific, well-phrased questions
- Prioritize questions
- Stay focused on the agenda
- Don't hide concerns
- Don't present data not included in the meeting packet
- Obtain clear and concise information through clear questions and listening

7. Are there recurrent problems at pre-IND meetings?

Yes, the following have been identified in pre-IND meetings:

- Inadequate CMC information
- Insufficient pre-clinical support
- Unacceptable clinical trial design
- Noncompliance with Good Clinical Practices (GCPs)
- Lack of information on selection of dosage

8. What are some helpful tips for the pre-IND meeting discourse?

- Make the best use of allotted time
- Agree with FDA on timing and required attendees
- Identify questions to ask FDA
- Make sure that a pre-IND meeting is necessary; answers to your questions may be available in the guidances
- Make sure that issues support good use of industry and FDA time
- Present data clearly and consistently

Pre-IND Meeting References

- Additional information (regulations, guidances, and websites)
- FDA Pre-IND Consultation Contacts
- FDA Pre-IND FAQs
- FDA Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants
- 21 CFR 312.47 (meetings)
- 21 CFF 312.82 (early consultation)
- Guidance for Industry- M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals – January 2010 (PDF - 325KB)
- E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry
- CDER Small Business and Industry Assistance webpage

Appendix 3: Investigator's Brochure

The Investigator's Brochure Includes Physical, Chemical, and Pharmaceutical Properties/Formulations:

- Description of investigational product substance(s)
- Chemical and structural formulation
- Summary of relevant physical properties
- Summary of relevant chemical properties
- Summary of relevant pharmaceutical properties
- Description of the formulation(s) to be used and justification if clinically relevant
- Description of excipients to be used and justification if clinically relevant
- Instructions for storage of the dosage form(s)
- Instructions for handling of the dosage form(s)
- Any structural similarities to other known compounds should be mentioned

Appendix 4: Additional Resources

FDA Forms and Guidance Links	
Form FDA 1571	Form FDA 1571 Form FDA 1571 Instructions
IND Content and Format	21 CFR 312.23 IND Content and format, 21 CFR 312 IND Regulations, FDA Guidance: Content & format of IND for Phase 1 IND Applications Prepared and Submitted by S-I
Form FDA 1572	Statement of Investigator- Form FDA 1572 Form FDA 1572 Instructions FAQs Statement of Investigator (Form FDA 1572) (Revision 1) FAQs Statement of Investigator (Form FDA 1572)
Form FDA 3674	Form FDA 3674 FDA website: FDAAA Certification Instructions: Form FDA 3674
Form FDA 3926	Form FDA 3926 Form FDA 3926 Instructions
CMC	CMC Information – FDA Website FDA Guidance on Environmental Assessment cGMP (Current Good Manufacturing Practices for Phase 1) CDERLearn CMC Perspective of the IND course
Pharm/Tox	Pharmacology and Toxicology Information Current Good Manufacturing Practice (cGMP) Regulations Pharmacology/Toxicology Review M3(R2) Nonclinical Safety Studies
Clinical Protocol Applicable Clinical SOPs	Clinical Protocols ICH E6(R2) Good Clinical Practice: Section 6 Statistical Principles, Providing Evidence of Effectiveness

For Additional CHOP IND Guidance, click here: Getting Started with INDs-IDEs

References

- FDA Presentations (2009 and 2011)
- CFR - Code of Federal Regulations: 21 CFR 312
    - Title 21 Food and Drugs
    - Chapter 1 FDA DHHS Subchapter D
    - Subchapter D Drugs for Human Use
    - Part 312 Investigational New Drug Application

Gregory M Podsakoff, M.D.

Digitally signed by Gregory M Podsakoff, M.D.
DN: cn=Gregory M Podsakoff, M.D., o=Children's Hospital of Philadelphia, ou=IND-IDE Support Program, CRSO, email=podsakoff@chop.edu, c=US
Date: 2023.10.26 15:57:38 -04'00'