

Investigational New Drug Applications in FDA-Regulated Research

Introduction and Purpose

The conduct of a clinical investigation (i.e., clinical trial) under an FDA-Regulated Investigational New Drug (IND) application includes a complex set of FDA regulations, requirements, and obligations. The FDA holds the sponsor of the IND application responsible for ensuring that all of the regulations, requirements, and obligations are being met (21 CFR Part 312, Subpart D). Although sponsors of IND applications are typically pharmaceutical companies, the FDA regulations governing IND applications permit the Sponsor to be an individual, governmental agency, or academic institution (21CFR Part 312.3).

The purpose of this policy is to:

- help determine when an IND is required,
- provide guidance and resources to individuals conducting a clinical investigation, who may be sponsor-investigators, on obtaining an IND for the drug under study, and
- address the process for compassionate use (also referred to as expanded access) and emergency use of an investigational drug.

IND Definitions and Acronyms

Biologic: Also called a biological product. Defined as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product which is applicable to the prevention, treatment, or cure of a disease or condition of humans. It also includes immunoglobulin products, products containing cells or microorganisms, somatic cells, gene therapy, tissues, recombinant therapeutic proteins, and most protein products. Biologics can be composed of sugars, proteins, or nucleic acids (or complex combinations of these substances), or may be living entities such as cells or tissues. Most biologics meet the FDA's definition of drug. Investigational biologics are generally subject to the investigational drug regulations (i.e., 21 CFR 312). However, depending in part on its intended use, a biologic may be a drug or device.

Botanical: A finished, labeled product that contains vegetable matter, which may include plant materials, algae, macroscopic fungi, or combinations of these. Depending in part on its intended use, a botanical product may be a food, drug, medical device, or cosmetic.

DEA: The Drug Enforcement Administration is a United States federal law enforcement agency under the U.S. Department of Justice tasked with combating drug trafficking and distribution within the U.S. It is the lead agency for domestic enforcement of the Controlled Substances Act. The DEA has sole responsibility for coordinating and pursuing U.S. drug investigations both domestic and abroad.

Investigational New Drug Applications in FDA-Regulated Research

Drug: A drug is defined by the FDA as:

- A substance recognized by an official pharmacopeia or formulary, or
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (including supplements), or
- A substance (other than food) intended to affect the structure or any function of the body, or
- A substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).
- Schedule 1 drugs: Schedule 1 drugs have no accepted medical use in the United States, and using schedule 1 drugs can put a person at a high risk for developing a substance use disorder. The DEA has provides an official list of Schedule 1 drugs, under Part 1308, section 11, here:

https://www.deadiversion.usdoj.gov/21cfr/cfr/1308/1308_11.htm

Emergency Use: The FDA Emergency Use exemption allows the use of an Investigational Product under strict criteria on a single subject in a life-threatening situation when no standard treatment is available. Emergency use is specifically emergency clinical care and is not considered research.

Expanded Access: The FDA has several specific mechanisms and regulations that allow use of an investigational item outside of a formal clinical trial. This is called expanded access. Expanded access, also called compassionate use, is the use of an investigational drug outside of a clinical trial. Expanded access allows a patient to receive the product through expanded access when enrollment in a clinical trial is not possible. For example, a patient is not eligible for any ongoing clinical trials or there are no ongoing clinical trials. Prior IRB and FDA approval are required.

Investigational New Drug (IND): An investigational drug is an item that is not FDA approved for marketing in the United States or an item that is being evaluated for a new and not-yet-approved indication, dosage, or formulation. An IND is a request for authorization from the FDA to administer an investigational drug or biological product to humans. Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor may want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement.

IND Application: An IND application is the document submitted to the FDA for permission to conduct a clinical study using a drug or biologic that is new or not approved for a given dosage, formulation, or indication. When the FDA receives an

Investigational New Drug Applications in FDA-Regulated Research

IND application, it assigns an IND number to the specific use of the item. The FDA has 30 days to review the submission and determine if the study is safe to proceed. The IND regulations are detailed in 21 CFR 312.

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

Supplement: A product (other than tobacco) that is intended to supplement the diet and that bears or contains one or more of the following dietary ingredients: (a) a vitamin; (b) a mineral; (c) an herb or other botanical; (d) an amino acid; (e) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (f) a concentrate, metabolite, constituent, extract, or combination of these ingredients. Depending on the use of supplements in research, they can be an investigational product requiring an IND.

CFR: Code of Federal Regulations
CRSO: Clinical Research Support Office
FDA: United States Food and Drug Administration
IRB: Institutional Review Board
SOP: Standard Operating Procedure

IND Support

The IND Specialist with the University of Utah Clinical Research Support Office (CRSO) assists sponsor-investigators with all aspects of the IND process documented in this SOP. Sponsor-investigators within departments that do not provide IND services should contact the CRSO IND Specialist. Some departments may offer qualified IND support. In such cases, sponsor-investigators are welcome to utilize their department resources. However, sponsor-investigators and department-specific IND representatives are still welcome to collaborate with the CRSO IND specialist if they have questions or require additional support. The CRSO IND Specialist may be contacted by emailing Jonna.Montgomery@hsc.utah.edu.

IND Guidance

1. IND Requirements

- 1.1 U.S. regulations require that an IND be in effect prior to the clinical study of an investigational drug.
- 1.2 Investigational use can mean a product not approved by FDA for any use, or it could also mean the use of an approved product in a way that is beyond its approved labeling (e.g., use, route of administration, etc.).

Investigational New Drug Applications in FDA-Regulated Research

1.3 When the principal intent of the investigational use of a drug is to develop information about the product's safety or efficacy, submission of an IND may be required.

1.3.1 Investigations into Schedule 1 drugs must also obtain approval from the DEA.

1.4 The clinical investigation of a marketed drug is exempt from the IND submission requirement if **all** the following conditions are met:

- It is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in the labeling for the drug.
- It is not intended to support a significant change in the advertising for the product.
- It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. Usually, the FDA determines that these changes do change risk and an IND will be required.
- It is conducted in compliance with the requirements for IRB review and informed consent.
- It is conducted in compliance with the requirements concerning the promotion and sale of drugs.
- It does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

1.5 If an investigator believes that a study does not require an IND, but the IRB disagrees, then the sponsor investigator may be requested to submit an IND application (or Pre IND Meeting Request) to the FDA to determine if an IND is required.

1.5.1 It is the responsibility of the sponsor-investigator to explain why a study meets or is exempt from IND regulations. Investigators who are unsure if their study meets reporting criteria may seek advice from the University of Utah IND specialist (see "IND Support", above).

2. Pre-IND Meeting

2.1 Once a sponsor investigator has determined that their study requires an IND, they can request a pre-IND meeting with the FDA.

2.2 Although a pre-IND meeting is not required, it provides an opportunity to achieve the following tasks before submission of the IND:

- Confirm the requirement for an IND
- Ensure that studies are designed to provide useful information

Investigational New Drug Applications in FDA-Regulated Research

- Minimize the potential for clinical hold
- Minimize costs and time to study approvals
- Allow early interactions with the FDA

2.3 To schedule a meeting, a Pre-IND Meeting Request and a Background Package must be submitted to the FDA. The contents of the package vary depending on the study and the investigational product but must include the study protocol and information about the investigational product.

2.4 Pre-IND meetings are usually scheduled within 60 days of the receipt of the request.

3. Initial IND Submission

3.1 It is the responsibility of the sponsor-investigator to have the IND application prepared and submitted to the FDA.

3.2 The content of each IND differs depending on the investigational product and the study. A complete protocol, informed consent, and information about the investigational product are required for an IND submission.

3.3 The FDA has 30 calendar days from receipt of the initial IND package to review the submission. During the review, the FDA may request additional information and the sponsor-investigator needs to reply to all requests for information. During the 30-day review, the investigator may not begin the clinical study under submission.

3.4 After 30 calendar days from initial submission, the sponsor-investigator may begin the study, unless the FDA notifies the site that the study is on clinical hold or notifies the site earlier that the IND may begin.

3.5 IRB Requirements:

3.5.1 The sponsor-investigator is responsible for ensuring that an IRB reviews and approves the study prior to beginning the study.

3.5.2 The University of Utah IRB may require that proof of IND submission or waivers be submitted with the initial submission.

3.5.3 The University of Utah Pre-IND Audit must be completed prior to IRB approval.

3.5.3.1 The IRB Pre-IND Audit process is initiated automatically following IRB submission. During the pre-review period the sponsor-investigator will be contacted with details on how to initiate and complete the audit.

3.5.3.2 As part of the audit, the sponsor-investigator will be required to

Investigational New Drug Applications in FDA-Regulated Research

complete the Pre-IND Checklist, which the IRB has made available here:

<https://irb.utah.edu/guidelines/fda-requirements/prep-initiated-studies.php>

3.5.4 For additional investigator responsibilities, please see the University of Utah UUSOP-4, located at:

<https://qualitycompliance.research.utah.edu/clinical-research-sops.php>.

4. IND Amendment Requirements

Common reasons for an IND amendment include:

4.1 Protocol Amendment: An amendment to the IND is required in the event of one of the following protocol-related events:

4.1.1 Reporting a new protocol to an existing IND.

4.1.1.1 A sponsor-investigator with an existing IND may want to conduct an additional study (e.g., different population, study procedures, additional phase) for the same indication and drug without amending the original investigation. Rather than submit another IND, the sponsor-investigator can add the new study protocol onto the existing IND.

4.1.2 Any changes to the existing clinical protocol.

4.1.3 Addition of a new investigator.

4.1.4 Additional of new site(s).

4.2 Informational Amendment: An informational amendment is required when there is:

4.2.1 Any information not reportable in a protocol amendment, safety report, or annual report

4.2.2 Responses to FDA requests for additional study or investigational product information.

5. IND Safety Reports

5.1 The sponsor must notify the FDA and all participating investigators of any serious adverse experience associated with the use of the drug or participation in the study that is unexpected in a written IND safety report. This reporting is in addition to FDA reporting requirements (e.g., SUSAR).

5.2 Reportable (serious, related and unexpected) Serious Adverse Events must be

Investigational New Drug Applications in FDA-Regulated Research

submitted to the FDA as soon as possible, no later than 15 days after sponsor notification, and must also be summarized on the Annual Report.

5.2.1 Unexpected fatal or life-threatening adverse reactions (related to study drug) must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

5.3 Follow-up Reporting: Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.

5.4 Non-serious adverse events must be summarized in the Annual Report.

6. IND Annual Reports

6.1 Annual reporting is due within 60 days of the anniversary date that the IND went into effect.

6.1.1 The annual report must include a current study summary (e.g., current protocol, enrollment, safety information), including a summary of all adverse events occurring during the reporting period.

6.1.2 Annual reports must be submitted even if the study has not yet opened.

7. IND Final Study Report

7.1 A complete report of study results is submitted when all study activity is complete and the IND will be closed.

8. IND Submission Documentation

8.1 The complete submission packet for all IND submissions, FDA responses, and pertinent correspondence in support of the IND should be retained for the duration of the study, and for a period of time following the completion of the study, in accordance with University of Utah Clinical Research SOP-06, "Study Records Management".

8.2 For studies utilizing the services provided by the University of Utah CRSO IND Specialist, all FDA submission documents, responses, and correspondence for the IND will be retained by the IND Specialist and will not be filed in the regulatory/essential documents record for the study.

8.2.1 The study team is welcome to include a Note-to-File within the main regulatory/essential documents file indicating that the IND and FDA documents are stored by the CRSO IND Specialist in accordance with this SOP.

Investigational New Drug Applications in FDA-Regulated Research

8.2.2 Requests to review IND submission materials made by the study team and/or appropriate compliance entities will be accommodated by the CRSO IND Specialist.

References

- 21 CFR Part 312: Investigational New Drug Application
- 21 CFR Part 312, Subpart D: Responsibilities of Sponsors and Investigators
- 21CFR Part 312.3: Definitions and Interpretations
- University of Utah Clinical Research SOP-06, Study Records Management:
https://qualitycompliance.research.utah.edu/resources/documents/uusop/uusop-06_study_records_management_17aug2020.pdf

Document Approval



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DATE

Revision History

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Printed or photocopied versions are considered unofficial copies unless it is the original signed document.