INVESTIGATIONAL USE OF DRUGS

An investigational drug is a chemical or biological substance that has been tested in the laboratory and approved by the US Food and Drug Administration (FDA) for testing in people during clinical trials.

An investigational drug may be approved by the FDA for use in one disease or condition but still be considered investigational in other diseases or conditions.

Investigational drugs can include both prescription and non-prescription medications, but some fall into the category of high-alert medications and have a narrow therapeutic index that requires careful testing to determine the most effective and safe doses.

There are three **IND types:**

1. **An Investigator IND** is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
2. **Emergency Use IND** allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
3. **Treatment IND** is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:

1. Commercial
2. Research (non-commercial)

The IND application must contain information in three broad areas:

1. **Animal Pharmacology and Toxicology Studies** - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).

2. **Manufacturing Information** - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
3. **Clinical Protocols and Investigator Information** - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfil their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Importance of INDA

- An INDA is required any time to conduct a clinical trial of an unapproved drug.
- An INDA would be required to conduct a clinical trial if the drug is
    - A new chemical entity, not approved for the indication under investigation in a new dosage form.
    - Being administered at a new dosage level.
- In combination with another drug and the combination is not approved.
- All clinical studies where a new drug is administered to human subjects, regardless of whether the drug will be commercially developed, require an INDA.

An INDA is not required to conduct a study if the drug:

- Is intended for human subjects, but is intended for in vivo testing or lab research animals (non-clinical studies).
- It is an approved drug and the study is within its approved indication for use.

INVESTIGATIONAL USE OF MARKETED DRUGS, BIOLOGICS AND MEDICAL DEVICES

"Investigational use" suggests the use of an approved product in the context of a clinical study.

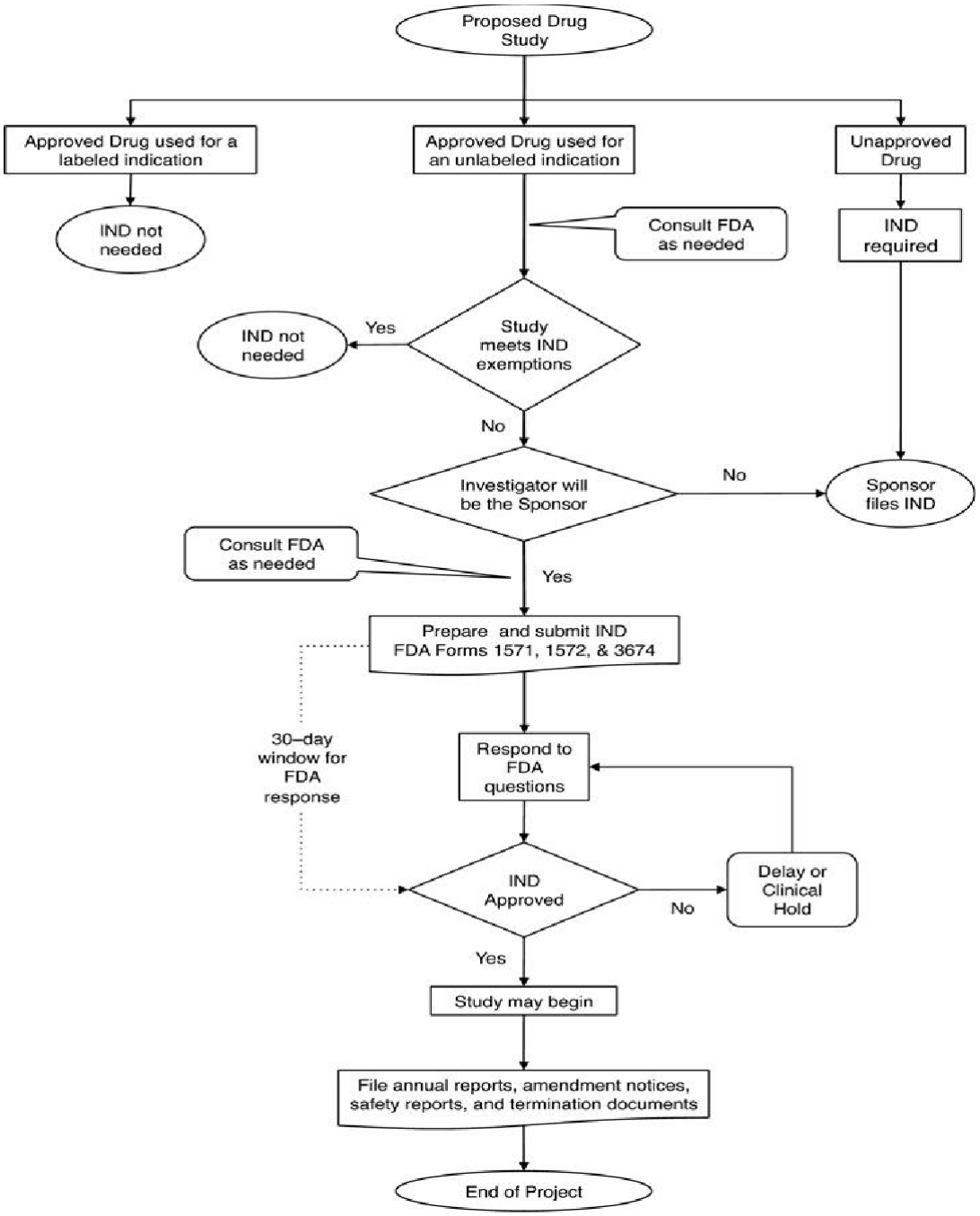
When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND may be required. Once the INDA is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials.

During this time, FDA has an opportunity to review the INDA for safety to assure that research subjects will not be subjected to unreasonable risk.

IND application process for a sponsor-investigator

An initial part of the regulatory process involved for investigational drugs is notifying the FDA that a pharmaceuticalwill be used in an experimental way. This notification is called an Investigational New Drug (IND) application

- The IND application provides the FDA with the data necessary to decide whether the new drug and the proposed clinical trial pose a reasonable risk to the human subjects participating in the study.
- INDA is reviewed to ensure the protection of rights and safety of the human subjects and that the investigational plan is sound and allows evaluation of safety and effectiveness of approval.
- The Appendix I of Schedule Y of Drugs and Cosmetics Rules specifies the data required to be submitted along with the application to conduct clinical trial
- For drug trials conducted by the pharmaceutical industry or other commercial sponsors, individuals highly trained and expert in meeting the regulations address the regulatory requirements.



Contents of INDA [US FDA Requirements]

- Name, address, and telephone number of the sponsor of the drug.
- Name and titles of the person responsible for monitoring the conduct and progress of the investigation.
- Name and titles of the persons responsible for the review and evaluation of information relevant to safety of the drug.
- Name and address of any CRO involved in the study.

- Identification of phase or phases of clinical investigation to be conducted.
- Introductory statement and general investigational plan.
- Description of the investigational plan.
- Brief summary of previous human experience with the drug, including the reasons if the drug has been withdrawn from any other investigation and/ or marketing.
- Chemistry, manufacturing and control information.
- Pharmacologic and toxicology information.
- If the new drug is the combination of previously investigated components, a complete preclinical and clinical summary of these components when administered singly and any data or expectations relating to the effect when combined.
- Clinical protocol of each planned study.
- Commitment that an Institutional Review Board has approved the clinical study and will continue to review and monitor the investigation
- Investigator Brochure.
- Commitment not to begin clinical investigation until the INDA is approved
- Signature of the sponsor or authorized representative, and the date of signed application.

REFERENCES

1. https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
2. https://www.ismp.org/resources/investigational-drugs-product-related-issues-pose-significant-challenges-part-i#:~:text=An%20investigational%20drug%20is%20a,in%20people%20during%20clinical%20trials.
3. Holbein ME. Understanding FDA regulatory requirements for investigational new drug applications for sponsor-investigators. *J Investig Med*. 2009;57(6):688-694. doi:10.2310/JIM.0b013e3181afdb26