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***REVIEW ARTICLE***

# Investigational New Drug Application and Approval Process

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**ABSTRACT**

The investigational new drug (IND) application is the result of a successful preclinical development program. The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials). This article will focus the approval process of investigational new drug & its approval by regulatory bodies.IND Application is the precursor of NDA Process. This article, which emphasis on easy access to understanding how this agency (USFDA) operates with respect to practical aspect of IND & its approval process. USFDA establish process albeit need to improve IND Application process.

**Key words:** Investigational New Drug, Investigator Brochure, its approval

## INTRODUCTION

The Federal Food, Drug and Cosmetic Act prohibit the shipment of a new drug into interstate commerce unless there exists for that drug an approved NDA or an effective IND application. Unlike certain European countries, such as Germany and the United Kingdom, the existence of an IND is required regardless of the proposed phase of clinical trial. Thus even phase 1 trials to be conducted in the United States on volunteer subjects require the prior submission of an IND before that trial may be undertaken. The requirements for the format and content of the IND application, as well as the requirements governing the use of the IND, are provided in Title 21 of the Code of Federal Regulations (21 CFR), Section 312[1].

IND Phase is the clinical phase where all activity is used to gather significant evidence of reasonable safety and efficacy data about the potential drug compound in humans.. IND submissions intended to support phase 2 or 3 clinical research. The clinical investigation may take as many as 12 years to complete. Finally, it will also detail the requirements for the investigator's brochure, the document that summarizes the known safety and efficacy information about the drug that will be submitted to potential investigators and to IRBs and as part of the IND document itself.

Prior to actual commencement of clinical investigation, however, a few ground rules must be established. It is covered in a straightforward format. It is a compilation & commentary of selected laws & regulation pertaining to application & approval of IND

**When do I need an IND?**

IND is required anytime ,want to conduct a clinical trial of an unapproved drug in the United States.the act defines a new drug ,in part, as 'any drug the composition of which is such that such drug is not generally safe and effective for use under the condition prescribed, recommended ,or suggested in the labeling. Because of these legal definition's, an approved drug can be considered a new drug and would require an IND to conduct a study an IND 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, and
- In combination with another drug and the combination is not approved

**When do I not need an IND?**

An IND is not required to conduct a study if the drug

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- Is not intended for human subjects, but is intended for in vitro testing or laboratory research animals(non clinical studies)and
- Is an approved drug and the study is within its approved indication for use.

**Types of INDs:**

**1 Investigator INDs:** 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 Commercial INDs:** They are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product. However, there is another class of filings broadly known as "noncommercial" INDs. The vast majority of INDs are, in fact, filed for noncommercial research. These types of INDs include "Investigator INDs," "Emergency Use INDs," and "Treatment INDs.

**3 Emergency Use IND**: This 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 Sec.312.23 or Sec.312.34. 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.

**4 Treatment IND:** Other name is Expanded Access IND, this IND may be submitted for experimental drugs showing promise in clinical testing of serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place (21 CFR 312.34).

The present format of IND was designed as IND Rewrite which is effective from June 17, 1987.

**Objectives of the IND:**

- To focus FDA's attention during early phase of clinical research on assuring the safety of human test subjects
- To provide sponsors with a greater measure of flexibility in conducting Phase 1 trials.
- To facilitate consultation between FDA & sponsors, especially after there is an indication that the new drug is safe and efficacious in humans.

**General Information Regarding INDs**

There are two IND categories:

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:

- **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 experiences with the drug in humans (often foreign use).
- **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.
- **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 fulfill 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.

An IND must also include an Investigator's Brochure which is a document intended to educate the trial investigators of the significant facts about the trial drug they need to know to conduct their clinical trial with the least hazard to the subjects or patients who will be enrolled.

If final, fully quality-assured individual study reports are not available at the time of IND submission, an integrated summary report of toxicologic findings based on the unaudited draft toxicologic reports of completed animal studies may be submitted full toxicology department individual study reports should be available to FDA, upon request, and individual study reports should be available to FDA, upon request, as final, fully quality-assured documents within 120 days of the start of the human study.

If the integrated summary is based upon unaudited draft reports, sponsors should submit an update to their integrated summary 120 days after the start of the human study (ies).

**Exemptions**

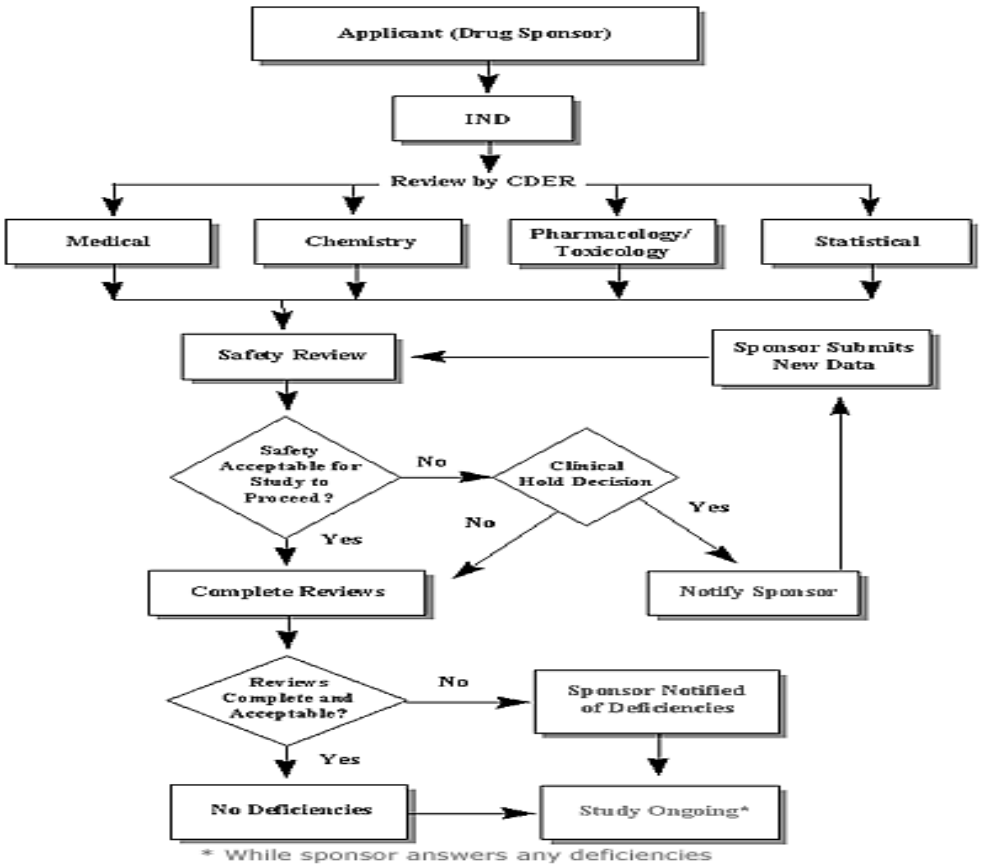
The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of an IND providing all of the following apply:

1. The investigation is neither intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor to be used to support any other significant change in the labeling for the drug,
2. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product,
3. the investigation does not involve a route of administration nor dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product, and
4. The investigation is conducted in compliance with the requirements for institutional review approval and the requirements for informed consent [3].

**Waivers**

In rare instances, the FDA may grant a waiver to the requirements for an IND on the basis of a justified request from the sponsor. Acceptable justification may include an explanation of why the sponsor's compliance is unnecessary or cannot be achieved or a description of an alternative means of satisfying the requirement. The FDA may grant such a request for a waiver if it determines that the sponsor's noncompliance would not pose a significant or unreasonable risk to the human test subjects[1] .

**IND Chart**




**Application:**

**1 Criteria for application:**

A clinical study is required for an IND if it is intended to support a:

- New indication
- Change in the approved route of administration or dosage level
- Change in the approved patient population (e.g. pediatric) or a population at greater or increase of risk (elderly, HIV positive, immunocompromised)
- Significant change in the promotion of an approved drug[5]

**2 Application submissions:**

Most INDs are paper submissions. While only 12% of INDs are submitted electronically, 28% of IND Amendments are submitted electronically a result of maintaining a growing number of INDs submitted electronically to date[1].

**3 Additional regulations:**

- Experimental drugs under an IND must be labeled, "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

**4 Noteworthy examples:**

The FDA closed its medical marijuana IND program (the Compassionate Investigational New Drug program) in 1991, facing an influx of AIDS patients seeking access to the drug. Seven patients continue to receive cannabis from the government under the program.

**5 Resources for IND Applications**

The following resources have been gathered to provide the legal requirements of an IND application, assistance from CDER to help meet those requirements, and internal IND review principles, policies and procedures.

**Pre-IND Consultation Program**: CDER offers a Pre-Investigational New Drug Application (IND) Consultation Program to foster early communications between sponsors and new drug review divisions in order to provide guidance on the data necessary to warrant IND submission. The review divisions are organized generally along therapeutic class and can each be contacted using the designated Pre-IND Consultation List.

**Guidance Documents for INDs:**Guidance documents to help prepare INDs include:

- Guidance for Industry: CGMP's for Phase 1 Investigational Drugs
- Guidance for Industry: Exploratory IND Studies
- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs Including Well Characterized, Therapeutic, Biotechnology-Derived Products.
- Q & A - Content and Format of INDs for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products. This guidance is intended to clarify when sponsors should submit final, quality-assured toxicology reports and/or update the Agency on any changes in findings since submission of non-quality-assured reports or reports based on non-quality-assured data.
- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. This guidance should be useful for applicants planning to conduct bioavailability (BA) and bioequivalence (BE) studies during the IND period for an NDA, BE studies intended for submission in an ANDA, and BE studies conducted in the post approval period for certain changes in both NDAs and ANDAs.
- IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer.
- **Drug Master Files:** A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.
- **Immunotoxicology Evaluation of Investigational New Drugs:** This guidance makes recommendations to sponsors of investigational new drugs (INDs) on
  1. The parameters that should be routinely assessed in toxicology studies to determine effects of a drug on immune function
  2. When additional immunotoxicity studies should be conducted, and
  3. When additional mechanistic information could help characterize the significance of a given drug's effect on the immune system.

**Laws, Regulations, Policies and Procedures**

| | |
|---|---|
| 21CFR Part 312 | Investigational New Drug Application |
| 21CFR Part 314 | INDA and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval) |
| 21CFR Part 316 | Orphan Drugs |
| 21CFR Part 58 | Good Lab Practice for Nonclinical Laboratory [Animal] Studies |
| 21CFR Part 50 | Protection of Human Subjects |
| 21CFR Part 56 | Institutional Review Boards |
| 21CFR Part 201 | Drug Labeling |
| 21CFR Part 54 | Financial Disclosure by Clinical Investigators |

***Code of Federal Regulations* (CFR):** The following regulations apply to the IND application process:[2]

**Requirement for an IND:**

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical

investigation with an investigational new drug that is subject to 312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to 312.2(a) until the investigation is subject to an IND which is in effect in accordance with 312.40.

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under 50.24 of this chapter. 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 [2].

**Phases of Clinical Investigations**

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the phases are conducted sequentially, they may overlap. These three phases of an investigation are a follows:

**1 Phase 1 Clinical Trial**

Perform initial human testing in a small group of healthy volunteers.In Phase 1 trials the candidate drug is tested in people for the first time. These studies are usually conducted with about 20 to 100 healthy volunteers. The main goal of a Phase 1 trial is to discover if the drug is safe in humans. Researchers look at the pharmacokinetics of a drug: How is it absorbed? How is it metabolized and eliminated from the body? They also study the drug's pharmacodynamics: Does it cause side effects? Does it produce desired effects? These closely monitored trials are designed to help researchers determine what the safe dosing range is and if it should move on to further development.

**2 Phase 2 Clinical Trials**

Test in a small group of patients.

In Phase 2 trials researchers evaluate the candidate drug's effectiveness in about 100 to 500 patients with the disease or condition under study, and examine the possible short-term side effects (adverse events) and risks associated with the drug. They also strive to answer these questions: Is the drug working by the expected mechanism? Does it improve the condition in question? Researchers also analyze optimal dose strength and schedules for using the drug. If the drug continues to show promise, they prepare for the much larger Phase 3 trials.

**3 Phase 3 Clinical Trials**

Test in a large group of patients to show safety and efficacy.

In Phase 3 trials researchers study the drug candidate in a larger number (about 1,000-5,000) of patients to generate statistically significant data about safety, efficacy and the overall benefit-risk relationship of the drug. This phase of research is key in determining whether the drug is safe and effective. It also provides the basis for labeling instructions to help ensure proper use of the drug (e.g., information on potential interactions with other medicines).

Phase 3 trials are both the costliest and longest trials. Hundreds of sites around the United States and the world participate in the study to get a large and diverse group of patients. Coordinating all the sites and the data coming from them is a monumental task.

During the Phase 3 trial (and even in Phases 1 and 2), researchers are also conducting many other critical studies, including plans for full scale production and preparation of the complex applicationrequired for FDA.

(**Table 1**) provides information regarding the differences between the phases of investigation with respect to the size and scope of the particular phase [1].

**Table 1: Phases of Clinical Investigation**

| | | |
|---|---|---|
| 1 | Drug Name® | |
| 2 | IND table of contents | |
| Item | Title | Volume/ page |
| 3 | Introductory statement & General Investigational Plan... | |
| | Introductory Statement… | |
| | Summary of Previous Human Experience with the Drug… | |
| | If the Drug Has Been Withdrawn from Investigation / Marketing… | |
| | General Investigational Plan… | |
| 5 | Investigator's Brochure… | |
| 6 | Protocol… | |
| 7 | Chemistry, Manufacturing & Control Information… | |
| | Drug substance…… | |
| | Drug Product…….. | |
| | Placebo (if applicable)… | |
| | Labeling…….. | |
| | Environmental Analysis… | |

| | |
|---|---|
| 8 | Pharmacology & Toxicology Information… |
| 9 | Previous Human Experience with the Investigational Drug…….. Summary of Previous Human Experience… If the Drug is a Combination of Drug Previously Investigated / Marketed…… If the Drug has been Marketed Outside the United States… …… |
| 10 | Additional Information (as applicable for radioactive drugs or drugs with dependence or abuse potential)……. |

It consists of four subsections:

| Phase | Number of patients | Length | Purpose | Percent of drugs successfully tested* |
|---|---|---|---|---|
| 1 | 20–200 | Several months | Mainly safety | 70% |
| 2 | Up to several hundred | Several months | Some short-term safety, dosage and effectiveness | 33% |
| 3 | Several hundred to several thousand | 1 to 4 years | Safety, dosage and Effectiveness | 25–30% |

*For example, of 100 drugs for which IND applications are submitted to the FDA, about 70 will successfully complete phase 1 trials and go on to phase 2; about 33 of the original 100 will complete phase 2 and go to phase 3; and 25 to 30 percent of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).

**Format & Content of an IND**

Following sections are contained in an IND:

**1 Cover Sheet (form FDA 1571):**

The form is provided for basic information like name of drug, submission date, sponsor identification, phase of proposed clinical investigation, sponsor commitments, identification of clinical monitor and safety evaluator, information regarding transfer of responsibilities to a contract research organization.

**Table 2 of Contents:**

The sections of the IND are numbered in accordance with 21 CFR 312.23, specifying IND format and content.

**3 Introductory Statement & General Investigational Plan:**

| | 1st subsection (introductory statement) | 2nd subsection | 3rd subsection | 4th subsection |
|---|---|---|---|---|
| Content | • Name of drug<br>• P'cological Class<br>• Structural formula<br>• Route of administration<br>• Broad objectives<br>• Planned duration of the proposed clinical investigation | Brief summary of any previous human experience with the drug, including investigational or marketing experience in other countries | It is a statement as to whether or not the drug has been withdrawn from investigation or marketing in any country for any reason of safety or efficacy | Brief description of overall investigational plan for drug during the following year like:<br><br>Indications to be studied, kinds of clinical trials to be conducted in first |

**4 Investigator's Brochure:**

**Definition:** It is a body of information characterizing the drug product that is given by a sponsor to each participating clinical investigation.

The Investigator's Brochure is a constantly evolving document that grows as the knowledge gained form research with the investigational drug grows. While a drug is under an accepted IND, application, the Brochure serves as the approved labeling for the substance. As such, it must contain summaries of each and every study conducted with the investigational drug, and often contains text on similar drugs of the same class, if such information is useful and/or necessary for an investigator.

**Importance of Investigator's Brochure:**

- It provides the clinical investigator with all the known information and research on the drug under study
- It serves as the approved labeling for the investigational drug; and,
- It contains the basic summaries of all research done to date on the investigational drug for filing the IND/NDA.

Investigator's Brochure has to be honest, accurate, up-to-date, and complete, as well as clear, concise,

and easy-to-read.

| **Drug Name®** | **Investigator's Brochure**<br>**Table of contents** |
|---|---|
| Introduction…….. | |
| Chemistry……. | |
| Physical Properties…… | |
| How Supplied…….. | |
| Pharmacology……. | |
| Specific Effect Studies… | |
| General Studies……. | |
| Toxicology…….. | |
| Acute Toxicity……. | |
| Multidose Toxicity……. | |
| Special Toxicity Studies… | |
| Reproductive Studies…… | |
| Mutagenicity Studies……. | |
| Pharmacokinetics…… | |
| Preclinical……. | |
| Clinical…….. | |
| Clinical Trial…….. | |
| Phase 1…… | |
| Phase 2/3… ……. | |
| Safety/Efficacy Overview | |
| Safety…….. | |
| Efficacy…….. | |
| Possible Risks and Side Effects… | |
| References…….. | |

**5 Protocols:**

- Phase 1 protocols are may be less detailed and more flexible than those for Phase 2 or Phase 3.
- Phase 1 protocol provides an outline of investigation by specifying information as estimated number of test subjects, inclusion/exclusion criteria and dosing plan
- It is specific in safety and monitoring of vital sign and clinical laboratory evaluations.
- Phase 2 and Phase 3 protocols are detailed, describing all aspects of the studies, such that any deviation in a design if required, it can be established in the protocol from the beginning.

All protocols are required to contain the following elements:

- Statement of the objectives and purpose of the study
- Patient inclusion/exclusion criteria
- Estimate of number of patients to be studied
- Description of study design
- Dosing information including planned maximum dosage and duration of individual patient exposure to the Drug
- Description of the observations and measurements planned to fulfill the study objectives
- Description of the clinical procedures, laboratory tests, or other methods employed to monitor the effects of the drug in the subjects and to minimize risk
- Statement of commitment to obtain IRB approval before initiating the clinical investigation
- Form FDA 1572 which provides for such critical information as name and address and a statement of qualifications of each investigator, name of each sub investigator, name and address of the research facilities to be used and the name and address of each reviewing IRB (international regulatory board)

**6 Chemistry, Manufacturing & Control Information:**

- **Drug Substance**:
  Information regarding the physical, chemical or biological characteristics of the drug substance, along with the name and address of the manufacturer.
  Description of the general method of preparation, identification of the analytical methods and acceptable limits used to assure the identity, purity and strength of the drug substance.

Stability data must be sufficient to support the stability of drug substance throughout the preclinical and proposed clinical studies.

- **Drug Product:**
  Qualitative & Quantitative compositions are required; information regarding the manufacturing facility, manufacturing and packaging procedure description, identification of analytical methods, acceptable limits used to assure identity, purity, and strength of components and finished products. Stability data to support duration of proposed clinical studies.
  Same information may be submitted for placebo where applicable.
- **Labeling:**
  A copy of all labels and labeling to be provided to each clinical investigations must be submitted
- **Environmental Analysis:**
  Unless, if IND falls as per 21 CFR 25.24 defined exclusion, an environmental analysis must be submitted this includes: identification and quantities of any chemical substances emitted during the manufacture of the product, use of resources and energy, mitigation measures etc.

**7 Previous Human Experiences with the Investigational Drug:**
Such findings if available must be submitted whether drug is marketed in U.S. or other foreign country.

**Pharmacology and toxicology information**: 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.

**(i) Pharmacology and drug disposition**: A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

**(ii) Toxicology**: An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, sub acute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity

**8 Additional Information:** In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i)Drug dependence and abuse potential: If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii)Radioactive drugs: If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii)Pediatric studies: Plans for assessing pediatric safety and effectiveness.

(iv)Other information: A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

**Reports:**

**IND Safety Reports:**

If a sponsor notify any unexpected fatal / life threatening experience associated with the use of the drug requires to notify the FDA by telephone no later than 3 working days after receipt of the information, followed by a written report within 10 days.

**IND Annual Reports:**

Annual report comprising the annual progress made by sponsor to FDA with in 60 days of the effective date of the IND which includes following seven sections:

| | |
|---|---|
| 1. individual study information | Brief summary of status of each study in progress and each study completed during previous year.<br>E.g. title of study, patient population, initially planned no. of patients, actual entered into study, no. of them dropped out of study due to any reason |
| 2. summary | Most freq. & serious adverse experiences by body system |

| | |
|---|---|
| information | Tabulation of all safety reports |
| | Preclinical work in progress & completed |
| | Summary of significant manufacturing / microbiological changes made during past year |
| 3. Updated Investigational Plan | Focusing the plan for forthcoming year |
| 4. Updated Investigator's Brochure | Any updating made in Brochure |
| 5. Phase I Modification | Any modification not reported in previous year |
| 6. Foreign Marketing Development | Approval, Market withdrawn etc., in foreign |
| 7. Outstanding Business (optional) | List of all issues of IND waited for FDA approval (this section is optional) |

**Withdrawal of an IND:**

- At any time a sponsor may withdraw an effective IND without prejudice.
- If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with 312.59.
- If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.
- Requirements for use of an IND in a Clinical Study & Clinical Holds: IND will be placed in clinical study legally only when investigations of IND are to be conducted in compliance with the regulations governing institutional review boards (21 CFR 56) and informed consents (21 CFR 50) .An IND goes into effect 30 days after the FDA receives it, unless FDA notify sponsor that application has been put on clinical hold .If the FDA concludes that a deficiency exists in an IND, but it will not pose an immediate and serious risk to subjects, FDA will resolve the matter with sponsor before issuing a clinical hold order. Resumption of the affected investigations will be authorized by the FDA when the sponsor has satisfactorily corrected the deficiency.

**Inactive Status:**

- On sponsor's request FDA may place an IND on inactive status if no subjects have entered clinical studies for at least two years or if the IND has been on clinical hold for at least one year
- After remaining on inactive status for five years, the FDA may terminate an IND.

**Emergency use of an investigational new drug (IND):**

- Need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in accordance with 312.23 or 312.34. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to FDA by telephone or other rapid communication means.

## CONCLUSION

Describe in some detail the requirements of an IND application. Emphasis has been placed on the different requirements for the study of a drug in a phase 1 situation compared with a more advanced stage of drug research, that is, phases 2 and 3. Information relating to the submission of IND protocol and information amendments and IND annual reports has also been included. Finally, the newest guidance relating to the writing and content for an IB based on the International Conference on Harmonization has also been provided in detail. 30 days after an IND is submitted to the FDA, if the sponsor has not heard anything from the FDA it can be assumed that the drug is not on a clinical hold and clinical trials may be started. The Investigator's Brochure, which will be used during that important first clinical study and in every clinical study thereafter, acts as the approved labeling for the drug while it is under an IND

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