Drug Development

- Regulatory affairs: Introduction, Historical overview of Regulatory Affairs, Regulatory authorities, Role of Regulatory affairs department, Responsibility of Regulatory Affairs Professionals
- Regulatory requirements for drug approval: Drug Development Teams, Non-Clinical
- Drug Development, Pharmacology, Drug Metabolism and Toxicology, General
- considerations of Investigational New Drug (IND) Application, Investigator's Brochure (IB) and New Drug Application (NDA), Clinical research / BE studies, Clinical Research Protocols, Biostatistics in Pharmaceutical Product Development, Data Presentation for FDA Submissions, Management of Clinical Studies.

Drug Development Teams

Most pharmaceutical and biotechnology firms employ teams to guide the processes involved in taking a discovery lead through the various preclinical/nonclinical (or Safety) and clinical (or Efficacy) drug development stages for making the drug candidate into a therapeutic product.

- Drug discovery project team
- Preclinical drug development project team
- Clinical drug development project team
- Drug development logic plan

Responsibilities of Project Teams

1. Reviewing research results from experiments conducted by any of the various scientific disciplines.

2. Integrating new research results with previously generated data.

3. Planning research studies to further characterize and develop a drug candidate.

4. Preparing a detailed drug development plan, generating a timeline for completion of key research studies, and defining the critical path.

5. Monitoring the status of research studies to ensure that they are being conducted according to the timeline and critical path in the development plan.

6. Comparing research results and development status and timelines with drug candidates under development by competitors.

7. Conducting appropriate market surveys to ensure that the development of a drug candidate is economically justified and continues to meet a medical need.

8. Reporting the status of the drug development program to management and making recommendations on the continued development of the drug candidate.

Drug Discovery Project Team

- A company makes a decision to enter into a new disease area or to expand an existing therapeutic area on the basis of new research findings, an unmet medical need, or marketing surveys.

- The responsible department, commonly a group such as cardiovascular, CNS, cancer, infectious diseases, or metabolic diseases, assigns researchers to the new project—usually chemists to synthesize compounds and pharmacologists or biologists to evaluate the leads in in vitro or in vivo models of the disease or disorder.

- This small group of researchers is the first project team and is commonly called a discovery project team.

- The pharmacology results are shared with the organic or medicinal chemists, who then prepare analogues of the most active compounds to identify the pharmacophore (i.e., the chemical moiety of the compounds responsible for the biological activity) and to explore further the structural activity relationship or SAR.

Once a lead or class of leads has been identified, the discovery team commonly expands to include other scientific disciplines to more fully characterize the possibility of successfully developing the discovery leads of interest. The other disciplines include, but are not limited to:

1. **Analytical chemistry to define the physical and chemical properties** of the leads and to provide preliminary information on the solubility and stability of the potential drug substances.

2. Pharmacokinetics, which normally includes bioanalytical chemistry, to assess the absorption or delivery and disposition profiles of the leads in animal models using the route of administration projected for clinical studies and drug metabolism using in vitro systems to assess the extent of metabolism by the various drug metabolism enzymes.

3. Toxicology, possibly including safety pharmacology and genotoxicity, to evaluate the potential for the leads to cause adverse effects in in vitro or cell-based systems and in-vivo or animal models and to determine that the dose levels that cause toxicity are substantially greater than the dose levels needed to elicit the desired pharmacologic effect.

4. Biopharmaceutics to study the formulation potential of the leads and to ensure that the compounds can be effectively delivered by the proposed clinical route of administration.

- The results obtained from the preliminary or lead optimization studies conducted by these disciplines are integrated with the biological activity data obtained from the pharmacologist.

- Once the discovery project team's recommendation for preclinical development of a lead candidate is accepted by the management, this team is either disbanded or continues their efforts to discover other compounds with attributes that could identify a next-generation drug candidate.

INTRODUCTION

- Creation of a new drug involves :-

1. Drug discovery (Research) :- Identification of a potential therapeutic target - --Selection of a single molecule for testing in humans.
2. Drug development (Development) :- Preclinical studies that support initial clinical trials through approval of the drug by regulatory authorities.
3. Commercialization (Marketing) :- Product ----Therapeutic application---- Sales

INTRODUCTION

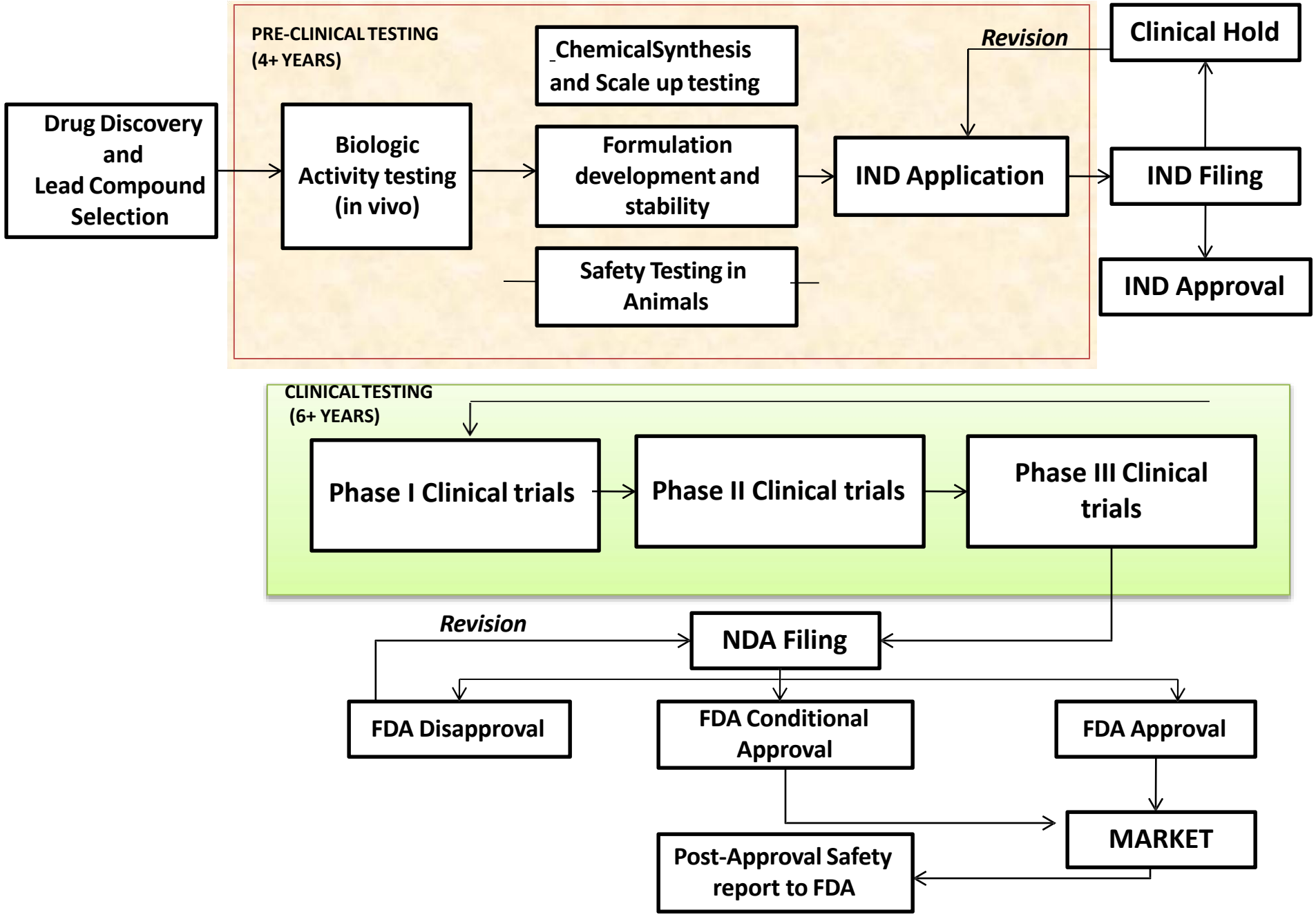
- In ancient time most of the drug used in the treatment of disease were derived from naturally occurring substances of plant origin, e.g. Opium from poppy, Quinine from cinchona, digitalis from foxglove .
- Presently, the majority of new therapeutics agent are synthetic in nature
- Drug discovery and development is complex, time-consuming, costly process which carries commercial risk.
- Drug discovery and development is broadly divide into three main components- drug discovery,

Drug discovery

- Typically, researchers discover new drugs through New insight into a disease process that allow researcher to design product to stop or reverse the effects of the disease.
- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases.
- Existing treatments that have unanticipated effects. New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.
- At this stage in the process, thousands of compounds may be potential candidates for development as a medical treatment.
- After early testing, however, only a small number of compounds look promising and call for further study.

- Development Once researchers identify a promising compound for development, they conduct experiments to gather information on: How it is absorbed, distributed, metabolized, and excreted.
- Its potential benefits and mechanisms of action. The best dosage The best way to give the drug (such as by mouth or injection).
- Side effects or adverse events that can often be referred to as toxicity. How it affects different groups of people (such as by gender, race, or ethnicity) differently. How it interacts with other drugs and treatments. Its effectiveness as compared with similar drugs.

The new drug approval process



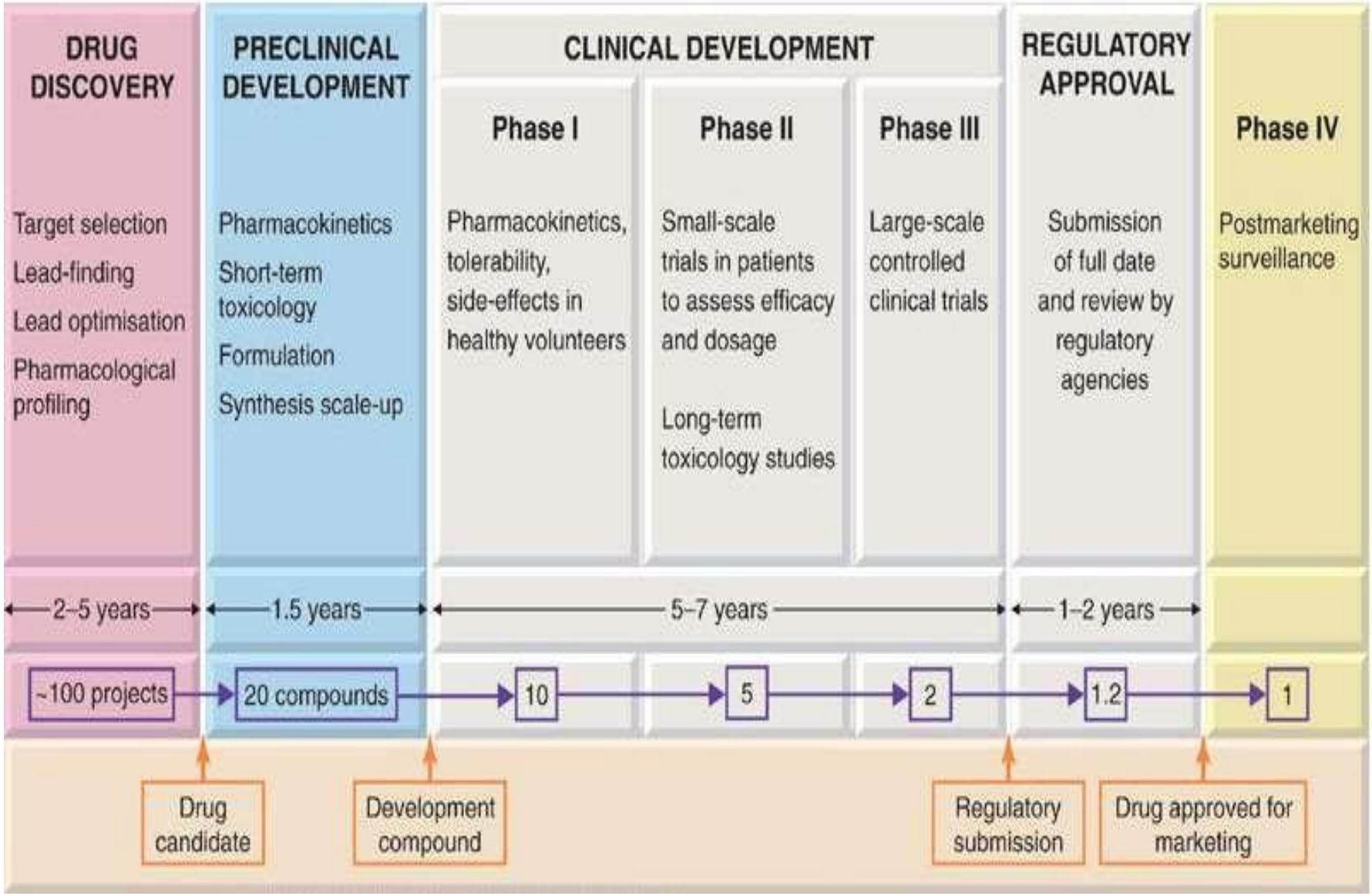
Drug Development

- Once a new chemical entity is discovered it has to be subjected to the development process
- Chemical synthetic activity is mostly carried out in R&D divisions of p'ceutical lab by synthetic chemistry.

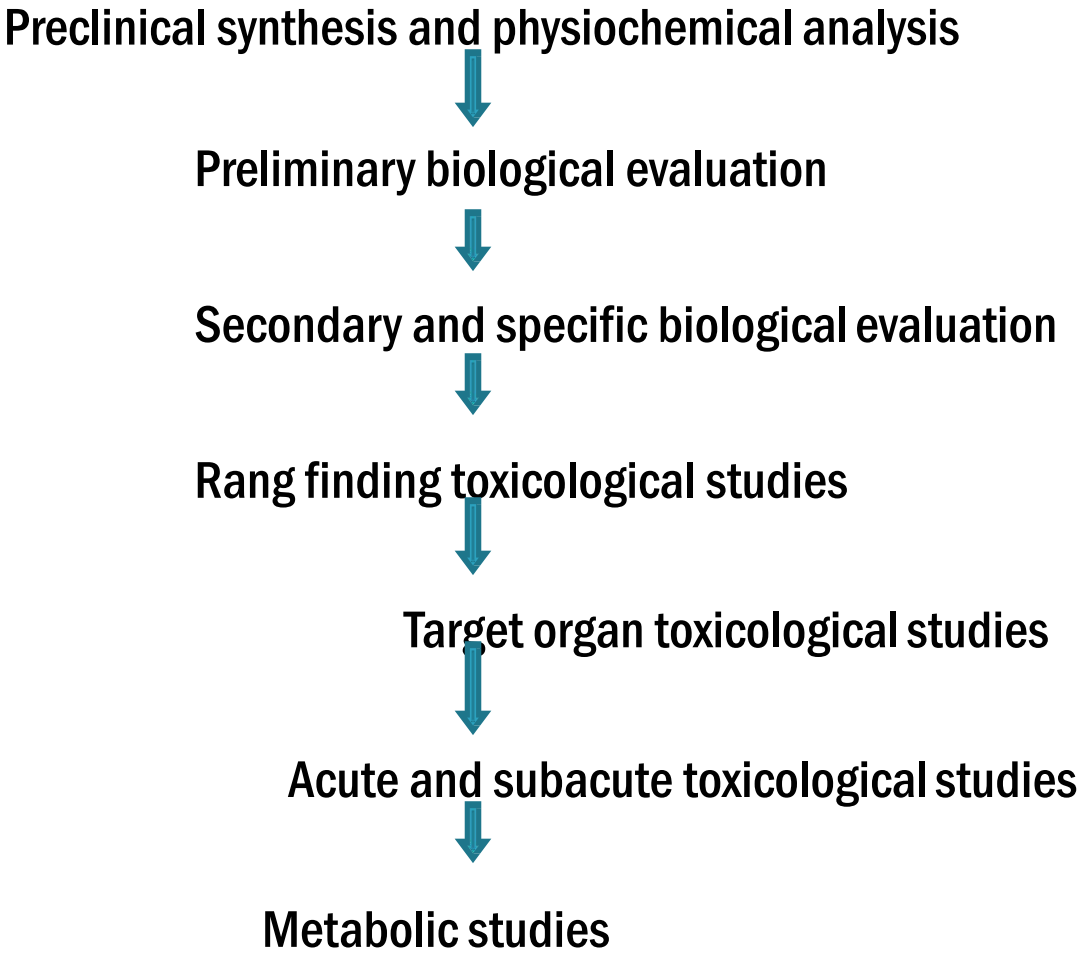
- After synthesis the structure of new compound and its purity is determine and confirmed by analytical chemist.

- It can be divided into –
- preclinical pharmacology
- clinical pharmacology

Drug Discovery & Development



Steps Involved in Drug Development



synthesis and quality control of bulk materials

Phase 1 clinical evaluation

Final formulation and final physiochemical analysis

Phase 2 clinical evaluation

Phase 3 clinical evaluation

Phase 4 clinical evaluation

TYPES OF APPLICATIONS

- Investigational New Drug Application
- New Drug Application
- Abbreviated New Drug Application
- Biologic License Application
- Over-the-counter (OTC) drug application

Investigational New Drug Application

- The safety and efficacy of new drugs have to be demonstrated and confirmed before they can be introduced into clinical practice.

- In Europe the principle document guiding the clinical development plan is ICH-GCP guidelines which incorporates a series of requirements imposed by US- FDA.

- Innovators are required to complete preclinical trials and incorporate them in the IND application that is required to be approved before clinical trails can be initiated.

- In US the federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed. IND application is the means through which a sponsor technically obtains this exemption from the FDA.

- In India IND application must be submitted to DCGI where it will be reviewed further.

- The USFDA Investigational New Drug (IND) program is the means by which a pharmaceutical company obtains permission to send the drug to clinical investigators before a marketing application for the drug has been approved.

- The FDA reviews the IND application for safety to assure that research subjects will not be subjected to unreasonable risk.

- If the application is cleared, the candidate drug usually enters a Phase 1 clinical trial.

- An Investigational New Drug Application (IND) is a submission to the Food and Drug Administration requesting permission to initiate a clinical study of a new drug product.

TYPES OF IND

- 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.

- 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. it is also used for patients who do not meet the criteria of an existing study protocol.

- 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.

- Non-commercial(Research)IND allows the sponsor to use the drug in research or early clinical investigation to obtain advanced scientific knowledge of the drug. And there is no plan to market the drug.

- Commercial IND are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product. It permits the sponsor to collect data on clinical safety and effectiveness needed for application for marketing in the form of a NDA

Criteria for an Application

- An IND goes into clinical study if it supports:
  - New indication
  - Change in the approved ROA or dosage level
  - Change in the approved patient population (e.g. pediatric) or a population at greater or increased risk (elderly, HIV
  - positive, immunocompromised)
  - - combination with another drug and the combination is not approved

Information in IND application

- **Animal Pharmacology and ToxicologyStudies**
  - An assessment as to whether the product is reasonably safe for initial testing in humans
  - Any previous experience with the drug in humans

- **ManufacturingInformation**
  - composition, manufacturer, stability, and controls used for manufacturingthe drug

- **Clinical Protocols and InvestigatorInformation**
  - 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.

Resources for IND application

- **Pre IND consultation program**
  - Offered by CDER to foster early communication b/n sponsors and new drug review divisions in order to provide guidance on the data necessary to warrant IND submission.

- **Guidance documents for IND**
  - Documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content and evaluation/approval of applications and also to the design, production, manufacturing and testing of regulated products.

- **Guidance documents to help prepare IND include:**

I. Safety reporting requirements for INDs and BE/BA studies

II. Content and format of IND applications for phase 1 studies of drugs, including well characterised ,therapeutic, biotechnology derived products.

III. IND exemptions for studies of lawfully marketed drugs or biological products for treatment of cancer.

IV. Immunotoxicology evaluation of IND.

Laws,Regulations, policies, procedures

- The Federal Food, Drug, and Cosmetic Act, is the basic food and drug law of the U.S The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labelling and packaging is truthful, informative, and not deceptive.

Code Of Federal Regulations (CFR)

- The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR.

- The CFR is divided into 50 titles that represent broad areas subject to Federal regulations.

- The FDA's portion of the CFR interprets the The Federal Food, Drug, and Cosmetic Act and related statutes.

- Section 21 of the CFR contains most regulations pertaining to food and drugs.

The following regulations apply to IND application process.

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

- The regulations in 21 CFR 312 cover procedures and requirements for Investigational New Drug Application.

- These regulations define the roles and responsibilities of FDA reviewers, IND sponsors, and clinical investigators.

- FDA s primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects.

- For the purpose of regulatory supervision-CDER,CBER etc.

MANUAL OF POLICIES AND PROCEDURES(MAPPs)

CDER publishes a MAPP.

These are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities.

MAPPs of particular interest to IND sponsors include:

- 5240.4 submission of an IND application to the office of generic drugs(OGD). OGD policy and procedures regarding submissions on INDs for BE studies. These INDs are called Bio-INDs to distinguish them from clinical INDs submitted to CDER's new drug reviewing divisions
- 6030.2INDs: Review of informed consent documents.
- 6030.4 INDs: Screening INDs. This MAPP describes procedures for the review of multiple active moieties or formulations under single IND application called a screening IND.

IND FORMS AND INSTRUCTIONS

- The imp. Forms for use in submitting INDs include
  - FDA 1571investigational new drug application
  - FDA 1572 statement of investigator

- These forms comes with instructions for completing the forms

- The instruction for filling the FDA 1571 is both exhaustive and self explanatory, it helps sponsors file the relevant data for consideration by the CDER for permission to conduct human studies.

- FDA 1572 helps the regulators to assess the investigators ,their facilities and the IRB ,with a view to ascertain the safety of the trial subjects.

IND Content requirements 21CFR312.23

A. Cover Sheet (Form FDA 1571)
B. Table of Contents
C. Introductory Statement & General investigational plan
D. Investigator's Brochure
E. Study Protocols
F. Investigator facilities and IRB data
G. Chemistry, Manufacturing & Control data
H. Pharmacology and toxicology data
I. Previous Human Experience with the Investigational Drug
J. Additional Information

A.COVER SHEET (FORM FDA 1571)

1. Name, address, telephone no. of sponsor, date of application and name of new drug
2. Identification of phases
3. Commitment not to begin clinical investigations until IND approval
4. Commitment by IRB- Form 56
5. Commitment for conducting CT- accordance with regulations
6. Name, title of person Monitoring the conduct
7. Name, title – person(s) for reviewing the conduct
8. Name, Address of CRO, if any
9. Signature of sponsor

Introductory statement and general investigational plan

- A brief intro on active ingredient, pharmacological class, structural formulae
- ,formulation to be used ,route of administration and planned duration of the investigations.
- Summary of previous human experience with the drug ,investigational or marketing experience in other countries
- Identification of countries where the drug was withdrawn (if any) and the reasons for the same
- A brief description of overall plan :
- - rationale for the drug or research studythe phase and type of study to be conducted with details about the comparator drugs
  - brief method of eliminating bias and randomization of patients
  - no. of centres and expected no. of patients to be enrolled at each centre.

Investigator's brochure

- INDs are new and information on them is not in the public domain. Investigators are likely to have no detailed information about them. In order to ensure the safety of their patients maximum information must be provided.

- **STUDY PROTOCOL**
- Document that details each aspects of clinical trail.

- **INVESTIGATOR ,FACILITIES AND IRB DATA**
- The FDA requires details on investigator ,the facilities and IRB. This data is filled in FDA 1572.

Chemistry, Manufacturing And Control Data

- Detailed info on the drug chemistry, the specifications and method of analysis. The method of preparation and testing is also required. The FDA also requires a statement on possible impact of the manufacturing process on the environment.

PHARMACOLOGY AND TOXICOLOGY DATA

- Before the human studies can begin an IND must be submitted to the agency ,containing information on any risks anticipated, based on the results of pharmacologic and toxicological data collected during studies of the drugs in animals.
- The studies are designed to permit :
  - The selection of a safe starting dose for humans
  - To gain an understanding of target organs of toxicity
  - To estimate the margin of safety
  - To predict pharmacokinetic and pharmacodynamic parameters

- Many resources are invested in, and thus wasted on candidate products that subsequently found to have unacceptable profiles when evaluated in humans. Less than 10% of INDs for new molecular entities(NME) progress beyond the investigational stage to submission of a marketing application (NDA)

- **Previous human experience**
- In large number of INDs the drug has been exposed to humans, either in another country or for another indication. Very often this data is of extreme importance of seeing an IND through. However in large number of cases where the application is for a phase1 study no such data would be available.

REVIEW OF IND

The review of IND is a multidisciplinary one and involves a no.of experts. At the CDER the medical, chemical, pharmacological/toxicological and statistical data are reviewed prior to a safety review. It is only after this a clinical hold decision may be taken. In such cases the sponsor is asked to provide additional data for review. Only after satisfaction of the concerned experts permission for phase 1 trial is granted

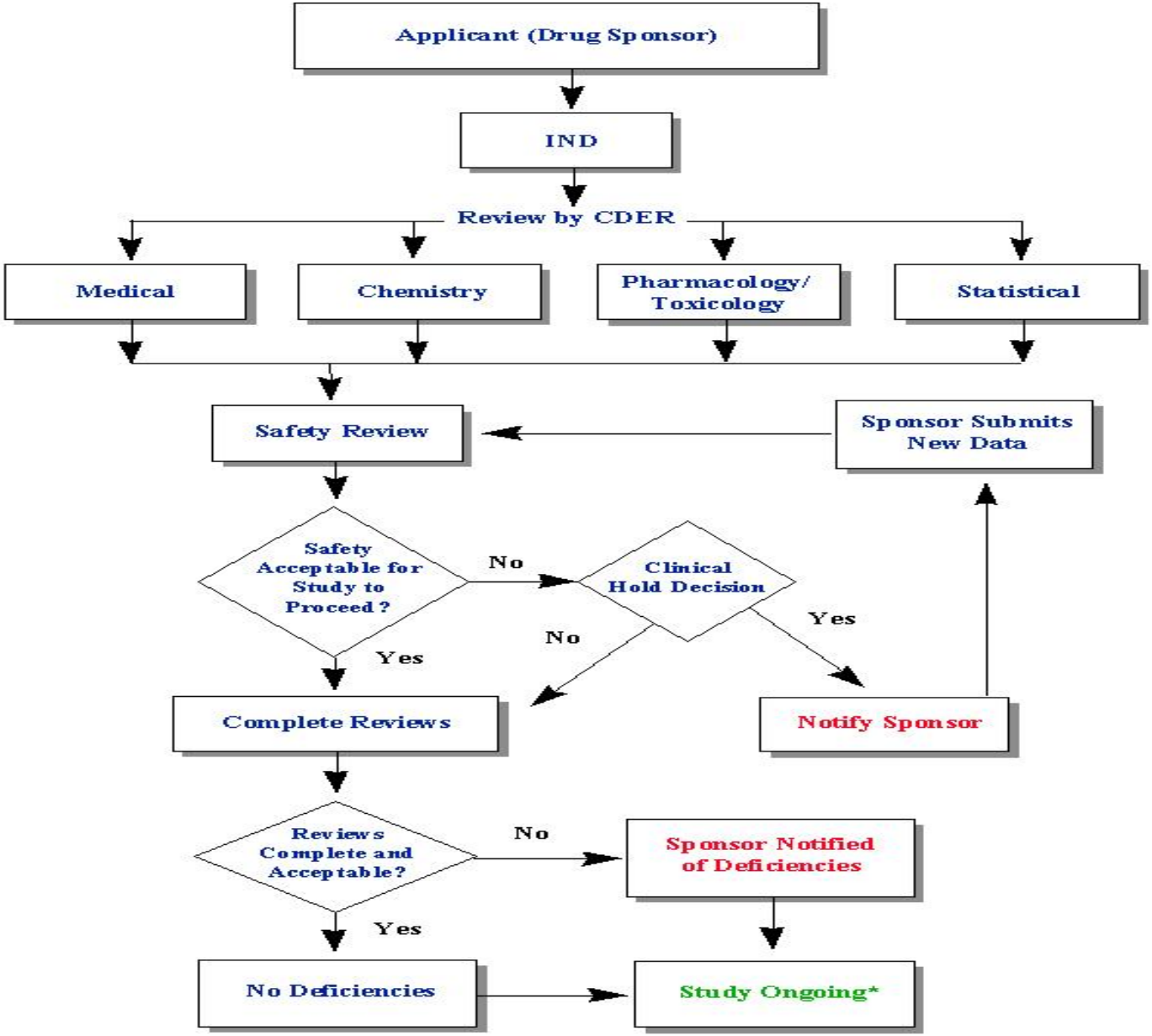
CONCLUSION

The process of filing an IND is a complicated process and the data required differs for different drugs. The FDA has a large no. of guidelines that have been issued for the use of the sponsors.

As stated earlier, in the light of economy and saving time ,it may be useful to go for a pre IND consultation, to understand exactly what the agency expects from the sponsor.

The general guidance of the agency on the IND process is an important document that can guide the preparation of the IND.

IND Review Process



*While sponsor answers any deficiencies