Unit I
New Drug Discovery and development

Stages of drug discovery, Drug development process, pre-clinical studies, non-clinical activities, clinical studies, Innovator and generics, Concept of generics, Generic drug product development.

STAGES OF DRUG DISCOVERY

INTRODUCTION

- Drug discovery is a process of identifying a compound therapeutically useful in treating and curing a disease.
- Typically a drug discovery effort addresses a biological target that has been shown to play a role in the development of the disease or starts from a molecule with interesting biological activities.
- It involves the identification of candidates, synthesis, characterization, screening, and assays for therapeutic efficacy.
- An expensive process due to the high costs of R&D and human clinical tests.
- The average total cost per drug development varies from US$ 897million to US$ 1.9 billion.
- The typical development time is 10-15 years.

STAGES OF DRUG DISCOVERY

1. Target Identification
2. Target Validation
3. Lead Identification
4. Lead Optimization
5. Pre-clinical Safety
6. Clinical Trails

1. TARGET IDENTIFICATION

- Target Identification is the first and key step in drug discovery channel.
- A drug target is the specific binding site for a drug in vivo through which it exerts action.

- Usually, drug target refers to a single biomolecule.

A specific drug target has following characteristics:

- The drug target can be a biomolecule i.e; protein
- The biomolecule have a special sites or locations.
- The biomolecule structure may change when it binds to drugs.
- With the change in the biomolecule structure various physiological response occurs.
- Physiological response play a major role in regulation of complex function of cells that exerts a therapeutic effects.
- Structure of biomolecule may change over the duration of the pathological condition.

2. TARGET VALIDATION

Target validation helps to new drug research and development and provide more views on pathogenesis of target-related disease.

The validation process includes:

- Discovery of the biomolecule of interest.
- Evaluation of its potential as a target.
- Designing a bioassay to measure its biological activity.
- Constructing a high-throughput screening method.
- Performing screening to find hits.
- Evaluation of hits.

3. LEAD IDENTIFICATION

Lead identification is one of the most important steps in drug development.

- The chemical structure of the lead compound is used as a starting point for chemical modifications in order to improve potency, selectivity, or pharmacokinetic parameters.
- Once a molecule is identified, the next step is to check its ADMET (Adsorption, Distribution, Metabolism, Excretion, and Toxicity) properties.
- If the molecule has no toxicity and no mutagenicity either, it has potential for use as a lead molecule.

4. LEAD OPTIMIZATION

- Molecules are chemically modified and subsequently characterized in order to obtain compounds with suitable properties to become a drug.
- Leads are characterized with respect to pharmacodynamic properties such as efficacy and potency in vitro and in vivo, physiochemical properties, pharmacokinetic properties, and

toxicological aspects.

- Once compounds with desirable in vitro profiles have been identified, these are characterized using in vivo model.

5. PRE-CLINICAL DEVELOPMENT

- In drug pre-clinical safety is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data collected.

- The main goals of pre-clinical studies (also named preclinical studies and nonclinical studies) are to determine a product's ultimate safety profile.
- Products may include new or iterated or like-kind medical devices, drugs, gene therapy solutions, etc.

6. CLINICAL DEVELOPMENT

- **Phase I Clinical Development (Human Pharmacology)**

  Phase I studies are used to evaluate pharmacokinetic parameters and tolerance, generally in healthy volunteers. These studies include initial single-dose studies, dose escalation and short-term repeated-dose studies.

- **Phase II Clinical Development (Therapeutic Exploratory)**

  Phase II clinical studies are small-scale trials to evaluate a drug's preliminary efficacy and side-effect profile in 100 to 250 patients. Additional safety and clinical pharmacology studies are also included in this category.

- **Phase III Clinical Development (Therapeutic Confirmatory)**

  Phase III studies are large-scale clinical trials for safety and efficacy in large patient populations.

Drug development process

Introduction

- Drug development is the process of bringing a new pharmaceutical drug to the market, once a lead compound has been identified through the process of drug discovery
- It includes preclincal studies on animals and micro organisms and filing the IND application to USFDA to initiate clinical trials.
- To market the drug one has to take regulatory approval with new drug application, this also comes under drug development process

Stages of drug development process:

1. **Filing of IND application**

- After successful preclinical studies, the researchers must file an IND application with the respective regulatory authority
- This application includes information on the preclinical studies, the chemistry of the molecule and pharmacodynamics and toxicological effects
- After the filing of application, the regulatory authority will review the application to assure the benefits fore seas the risk of human
- In addition to this, institutional review board(IRB) must also grant the permission to initiate the trials
- Informed consent process plays a vital role in clinical studies after through review both the regulatory authority and IRB grant the consent to initiate trials
- The sponsor must update the results consistently to the authority and IRB on the going studies

2. **clinical studies/development:**

- Clinical research via clinical trials is the next step in during development and it serves to the test the safety and efficacy of compounds in humans
- Clinical research is typically divided into 4 phases

a) Phase 0 clinical trials:

- Phase 0 trials are the first clinical trials done among people
- The aim to learn how a drug processed in the body and how it effects the body
- In these trials, very small dose of drug is given to about 10-15 people

b) Phase-1 clinical trials:

- During phase -1 studies, researchers test a new drug in a normal volunteers(healthy people)
- In most cases 20-80 healthy volunteers participate in phase-1
- However, if a new drug is intended for use in cancer patients researchers conduct phase-1 studies in patients with that type of cancer
- Phase -1 studies are closely monitored and gather information about how a drug interact with human body

- Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can tolerate and what it's acute side effects
- This is important to design of phase-2 studies
- Approximately 70% of drugs move to the next phase

c) phase-2 clinical trials:

- In phase-2 studies researchers administer the drug to a group of patients with the disease or condition for which the drug is being developed
- Typically involving a few hundred patients, these studies are not large enough to show whether the drug will be instead
- Phase-2 provide researchers with additional safety data
- Researchers use these data to refine research questions, research methods and design new phase -2 research protocols
- Approximately 35% of drugs move to the next phase

d) phase -3 clinical trials:

- Researchers design phase-3 studies to demonstrate whether or not a products offers a treatment benefit to a specific population
- These studies involves 300-3000 participants
- Phase-3 studies provide most of the safety data
- In previous studies, it is possible that less common side effects might have gone undetected, because these studies are larger and longer in duration, the results are more likely to show long term or rare side effects
- This enables them to generate the data on safety, efficacy and benefit risk ratio of drug
- Safety and effectiveness of the trials is determined on the basis of the study
- Approximately 25-30% of drugs move to next phase

3.Filing of new drug application and it's approval process:

- If the drug is found to be safe and effective, the sponsor shall file the NDA application to the respective regulatory authority
- The drug developer must include everything about a drug from preclinical data to phase -3 trail data in an NDA
- Developers must include reports on all studies, data and (2)
- Along with clinical results developers must include:
  - Proposed labelling
  - Safety updates
  - Drug abuse information

UNIT -1

- Patent information
- Any data from studies that have been conducted out side the us
- IRB compliance information
- Directions for

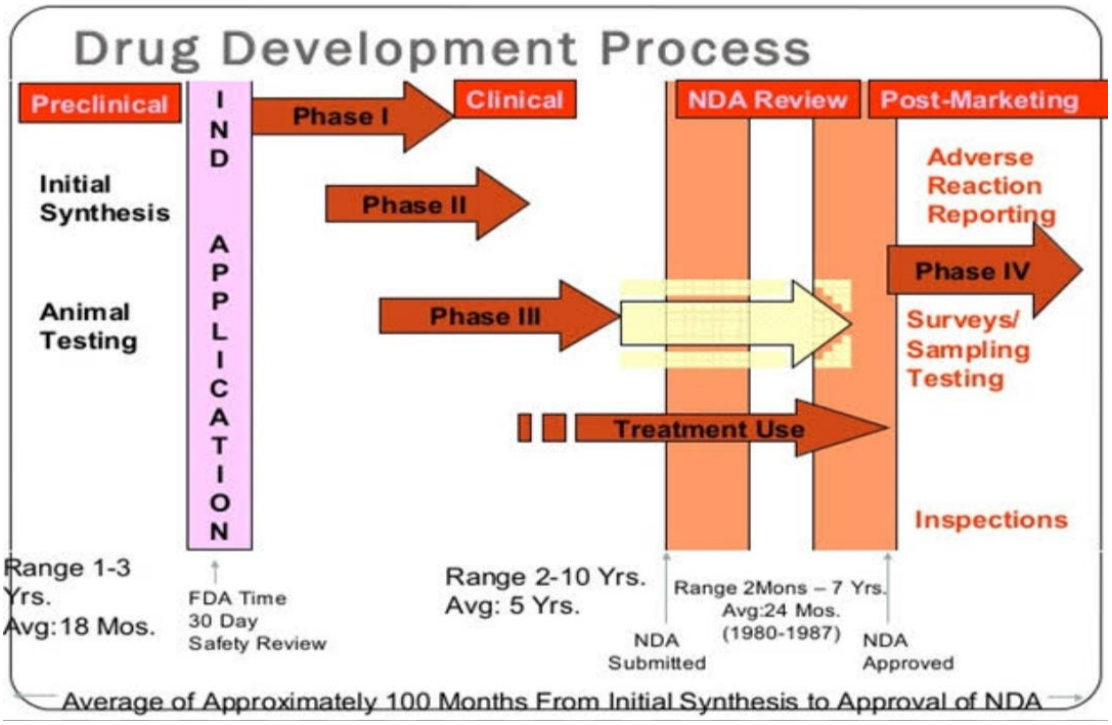
- The regulatory authority conducts the stringent review on NDA and may approve or reject the application or may ask the sponsor to provide additional information in regards to NDA
- After successful approval of new drug, the sponsor begin the manufacturing of new drug on large scale abiding the regulations of the regulatory authority
- The drug will be manufacturing on the basis of "Good manufacturing practices"

4.post marketing monitoring

- This phase of testing involves after the product commercialization
- The FDA requires drug companies to monitor the safety of its drug using the FDA adverse event reporting system (FAERS) database following drug approval and manufacturing
- As the large number of people use the drug, continuous monitoring is required
- The sponsor is obligated to provide annual reports as required by the authority
- These may include reporting and investigation of the incidence and severity of rare ADR, cost effectiveness analyses comparative trails and quality of life studies
- Manufacturers, health professionals and consumers report problems with approval

Overview of clinical trail phases:

Phases	Study participants	Length of the study	Purpose of the study
Phase-1	20-100	Several methods	Safety and dosage
Phase -2	100-500	Several months to two years	Efficacy and side effects
Phase-3	300-3000	1-4 years	Efficacy and monitor adverse events
Phase-4	Several thousands	Until the drug is in market	Safety and efficacy



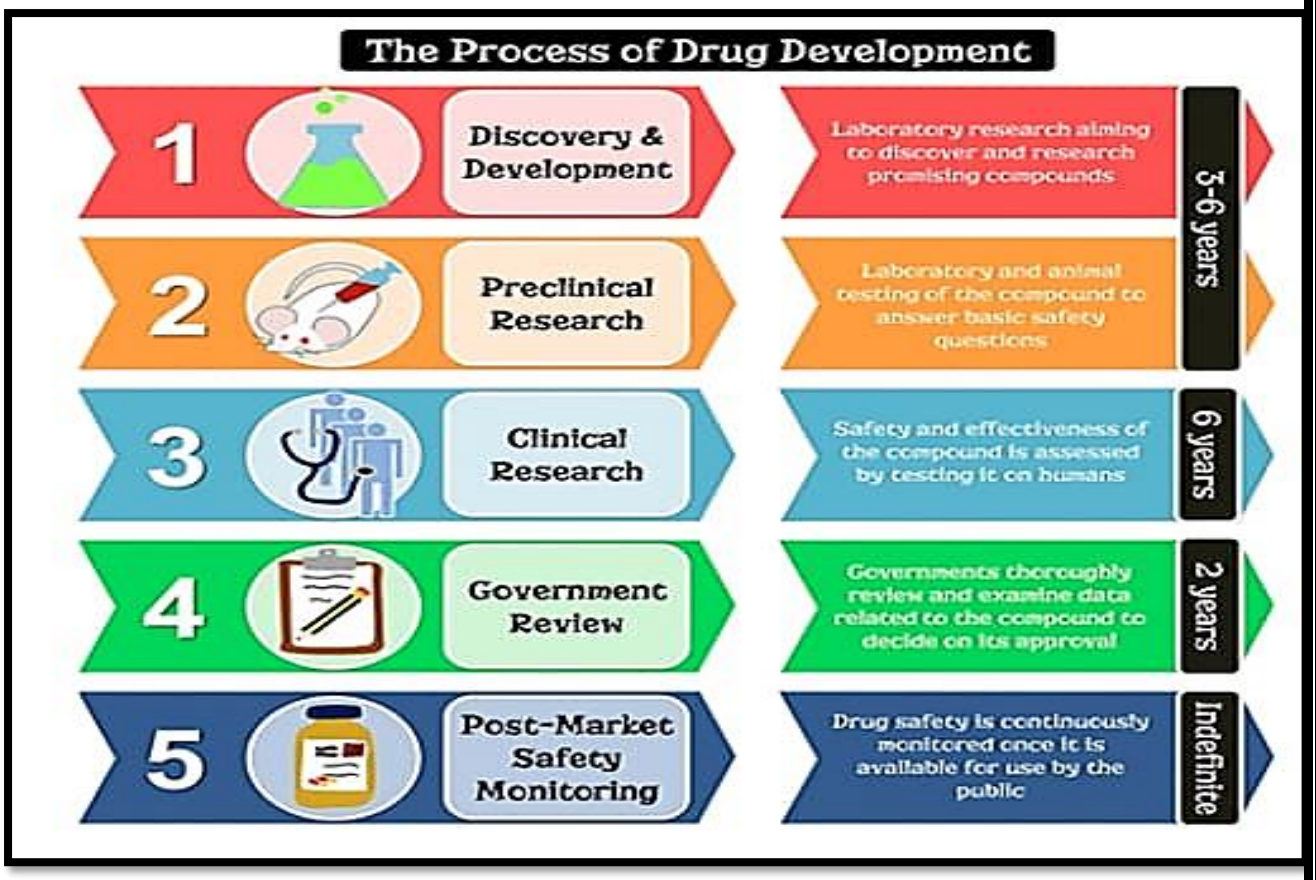
PRE – CLINICAL STUDIES

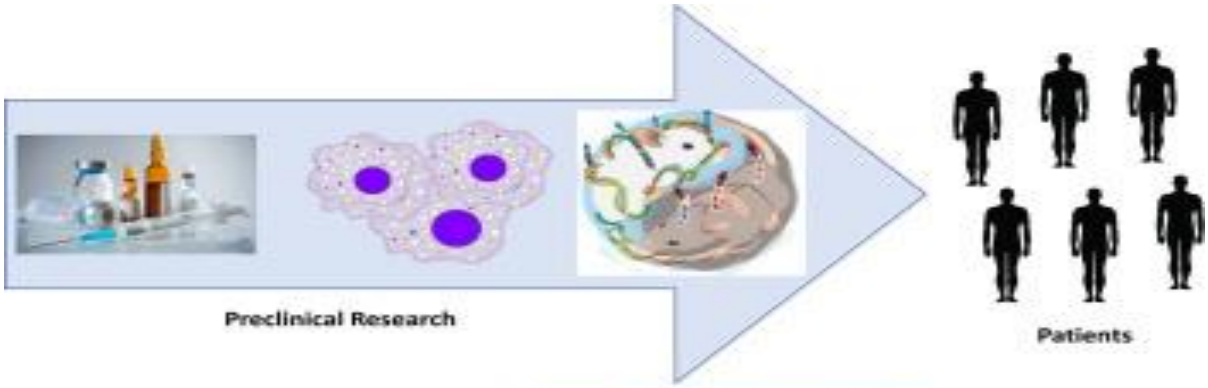
INTRODUCTION :

- Preclinical trials or non clinical trials - are laboratory test of a new drug substance or medical devices, usually done on animal subjects, to see whether the treatment really works and if it is safe to test on humans.
- The main goals of pre-clinical studies are to determine a product's ultimate safety profile.
- Products may include new medical devices, drugs, gene therapy solutions, etc.
- After identifying a compound, it is tested animals to expose the whole pharmacological profile.
- Experiments are generally performed on rodent like mouse, rat, guinea pig, hamster, rabbit.
- After successful result, experiments are performed on larger animals like cat, dog, monkey.
- As the evaluation progresses unfavorable compounds get rejected at each step.
- So, that only few out of thousands reach the stage when administration to man is considered.

DRUG DEVELOPMENT PROCESS :

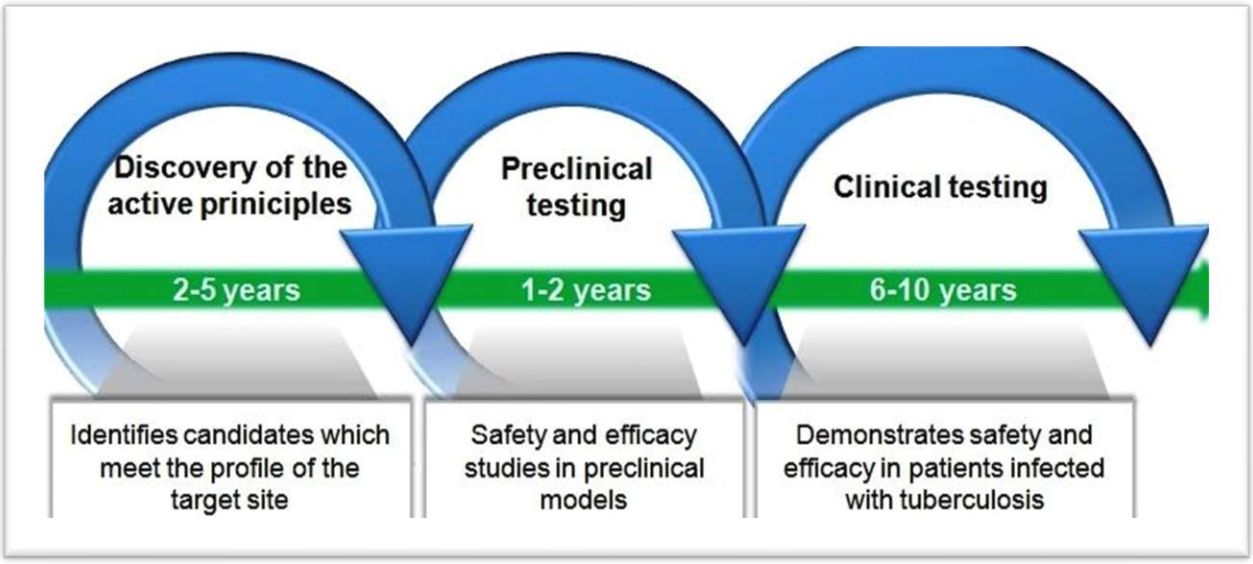
UNIT -1





Animal Models are essential for translation of novel drugs from bench to bedside. Careful model selection helps to overcome logistical hurdles and generate clinically relevant data

UNIT -1



STEPS INVOLVED WITH DOING A PRE – CLINICAL STUDIES :

Identify a drug target

↓

Develop a bioassay

↓

Screen the drug in the assay

↓

Establish effective and toxic doses

↓

File for approval as an investigational new drug (IND)

OBJECTIVES OF PRE – CLINICAL STUDIES :

- The purpose of pre-clinical study is to develop adequate data to decide that it is reasonably safe to proceed with human trials of the drug.
- Means, a laboratory test of a new drug or a new medical device, usually done on animal subjects, to see if the treatment really works and if it is safe to test on humans

- However the main objective is to collect the data to submit to the FDA for IND filing.

TYPES OF PRE – CLINICAL STUDIES :

1.Screening Test

2. Tests on isolated organs, bacterial cultures

3. Tests on animal models of human disease

4. General observational test

5. Confirmatory tests and analogous activities

6. Mechanism of action

7. Systemic pharmacology

8. Quantitative test

9. Pharmacokinetics

10.Toxicity test

1. Screening test:

- ✓ These are simple and rapidly performed tests to indicate presence OR absence of a particular pharmacodynamic activity.

For example, analgesic OR hypoglycemic activity.

2. Tests on isolated organs, bacterial cultures:

- ✓ These also are preliminary tests to detect specific activity, such as anti-histaminic, anti-secretory, vasodilator, antibacterial, etc

3. Tests on animal models of human disease:

- ✓ Animal models used such as kindled seizures in rats, genetically hypersensitive rats, experimental tuberculosis in mouse, etc.

4. General observational test:

- ✓ Drug is injected in tripling doses to small groups of mice which are observed for overt (hidden) effects.
- ✓ Preliminary clues are drawn from the profile of effect observed.

5.Confirmatory tests and analogous activities:

- ✓ Compounds found active are taken up for detail study by more elaborate (Complex) tests which confirm and characterize the activity.
- ✓ Other related activities also measured, like antipyretic and anti-inflammatory activity in an analgesic.

6. Mechanism of action:

- ✓ Attempts are made to find out the mechanism of action.

E.g. whether an anti-hypertensive is an a blocker/B blocker/ ACE inhibitor/ calcium

channel blocker, etc.

7. Systemic pharmacology:

- ✓ Irrespective of the primary action of the drug, its effect on major organ systems such as nervous, cardio-vascular, respiratory, renal are worked out.

8. Quantitative test:

- ✓ The dose-response relationship, maximal effects and comparative efficacy with existing drug is carried out.

9. Pharmacokinetics:

- ✓ The dose-response relationship, maximal effects and comparative efficacy with existing drug is carried out.

10. Toxicity test:

Acute toxicity:

- ✓ Single high doses are given to small groups of animals that are observed for overt (hidden) effects and mortality for 1-3 days.
- ✓ The dose which kills 50% animals is called as LD50.
- ✓ Organ toxicity is examined by histopathology on all animals.
- ✓ These whole tests are carried out under standardize procedure under "Good Laboratory Practice" (GLP).
- ✓ The original GLP regulatory mandate was promulgated in 1978 by US-FDA and published in the Federal Register 43 FR 59985-60020.

1. FR 312.38:

- ✓ Before the human studies can begin, an IND mus submitted to the Agency containing, among other things, information on any risks anticipated based on the results of

pharmacologic and toxicological data collected during studies of the drug in animals (21 CFR 312.23(a)(8)).

- ✓ These basic safety tests are most often performed in rats and dogs.
- ✓ Pharmacology and toxicology information: Adequate information about the 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.

pre clinical testing :

1. General principles
2. Biological activity
3. Animal species selection
4. Number / gender of animal
5. Dose selection and administration
6. Immunogenecity[1]

Specific considerations in pre clinical testing:

1. Safety pharmacology
2. Toxicology and pharmacokinetics
3. Immunotoxicity
4. Reproductive performance and developmental toxicity

Following properties was determined by the researchers:

1) Absorption, distribution, metabolisation, and excretion information

2) Potential benefits and mechanisms of action

3) Best dosage, and administration route

4) Side effects/adverse events

5) Effects on gender, race, or ethnicity groups

6) Interaction with other treatments

7) Effectiveness compared to similar drugs

Types of Preclinical Testing:

1. Short Term Animal Studies (Acute):
   - ✓ Determine pharmacological action and toxicity

Long Term Animal Studies (Chronic):

- ✓ Look for potential side effects that may result from long term use such as carcinogenicity
- ✓ Look for reproductive effects.[3]

IMPORTANCE OF PRE – CLINICAL STUDIES :

- To determine the dose, toxic dose, pharmacological action, etc.
- It is the requirement of regulatory body for performing clinical trials.
- As ethical view point, it is necessary to check safety of drug on animals before starting.
- To check the kinetic profile of drug & based on it, select the route of administration in human for clinical trials.

Non clinical activities in new drug discovery and development

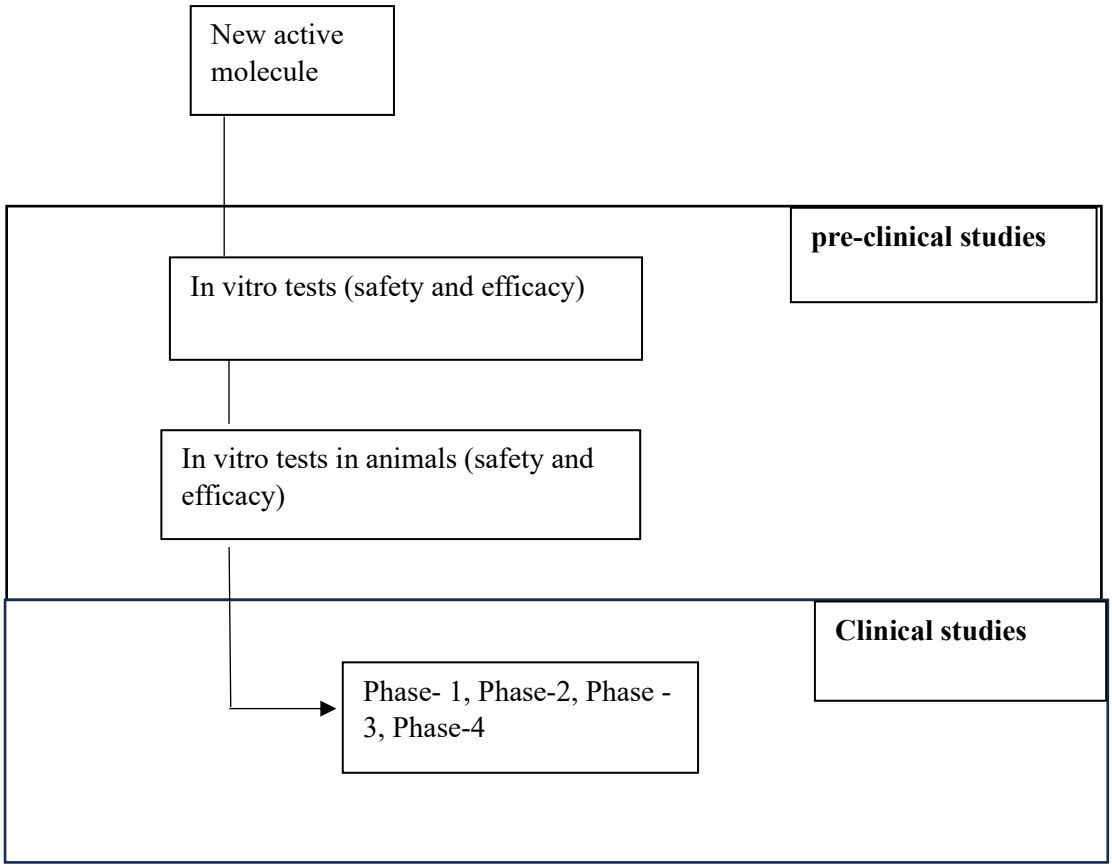
Introduction:

Non-clinical drug development (or pre-clinical drug development) is a risk-based process involving evaluation of safety and efficiency of drugs in animal. The pre-clinical pharmacological and toxicological drug responses in comparison to dose schedule and route of administration allows initiating and continuing research in humans. Generally, preclinical studies are conducted to forecast the safety and efficiency data from animal models that assist in conducting research in humans. Before using a new active substance as a medicinal product, its safety and efficiency is tested in animals before using it in humans is known as a pre-clinical study. The pre-clinical study also require approval from the regulatory authorities that should assure that the clinical trials are being performed ethically and safely and should give approval only for safe and effective drugs.

The non-clinical (or pre-clinical) development primarily aims to identify potential drugs for the greatest possibility of success, assess its safety, and build a solid scientific base before shift it into the clinical development phase. At this stage, the candidate drug is supposed to meet non-medical objectives, including defining the intellectual property right (IPR) and making enough medicinal products available for clinical trials. The non-clinical phase is complex and regulatory-driven. In this phase pharmacodynamics, pharmacokinetics, and toxicology data of the candidate drug are identified before its use in humans. Also, the data from non-clinical studies are used to refine, consolidate, and add information to update the safety profile of the candidate drug at the time of registration, and during the life-cycle of the approved medicinal product.

Each new drug molecule should cross the hurdle of pre-clinical phase to enter clinical trial phases. A drug which successfully finishes this phase has only 24 probability to reach the market. Pre-clinical studies restrict the risks to patient minimum. It is essential to harmonise all the drug characteristics as per the ethical principles of medicine and animal protection.

UNIT -1



Objectives:

a) The objective of non-clinical development is to fulfil all the necessities that require to be filled before a new compound is considered ready to be tested for the first time in human.
b) Selecting drug molecules in late discovery for transferring the drug candidate to initial development.
c) Evaluating the safety and bioavailability of drug candidates for long-term treatment, involving women of child bearing age and children in trials, combining with other drugs, introducing new formulations and administration routes.
d) Evaluating the carcinogenicity potential of drugs under development.
e) Elucidating the mechanisms of toxic action and estimating their significance in man.
f) Studying the toxicology and Geno toxicology conditions of drug impurities.
g) Evaluating the safety of intermediates in drug manufacturing occupational health and safety.
h) Evaluating the safety of excipients used in formulations.
i) Elucidating the mechanisms of toxic action in translational drug research.

FDA /Development [Non-clinical activities]:

The non- clinical activities in drug development process are FDA review and post-marketing monitoring of the drug.

FDA Review:

After the testing efficacy and safety of the new drug and the results are available from clinical trials, then it is forwarded for wholistic FDA review. At this time, the drug application submitted by the drug development company is reviewed, may be approved or not approved by the FDA.

Regulatory Approval Timeline

Depending on its application and necessity for patients the new drug regulatory approval timeline may be standard, fast track, breakthrough, accelerated approval, or priority review. The approval timeline may be up to a year if standard or priority review is required. Fast track, breakthrough, or accelerated agreements may occur sooner.

IND Application:

Before starting clinical trials, IND applications are submitted to the FDA. Developers may start the trials if clinical trials are ready to be conducted, and the FDA has not responded negatively about the drug.

NDA/ANDA/BLA Applications:

After clinical trials demonstrate drug safety and efficacy, NDA abbreviated new drug application (ANDA), or BLA is submitted to the FDA. Before making final decision the FDA reviews study data to decide whether to grant approval or not. Additional research or an expert advisory panel may be required before a final decision is made.

Orphan Drug

An orphan drug is intended to treat disease so rare that financial sponsors are unwilling to develop it under standard marketing conditions. These drugs may not be approved quickly or at all.

Accelerated Approval:

If there is strong indication of positive impact on a surrogate endpoint instead of evidence of impact on actual clinical benefits the drug provides, then the new drugs may be granted accelerated approval. The medication can help treat a severe or life-threatening condition which is called Expedition of approval.

These Non clinical activities include:

Target Identification and Validation: Identifying potential drug targets (e.g., proteins, genes) implicated in a disease and validating their relevance.

Lead Discovery and Optimization: Finding molecules (leads) that interact with the target and optimizing their properties for efficacy, safety, and pharmacokinetics.

In vitro Studies: Conducting experiments in controlled laboratory settings using cell cultures or biochemical assays to assess the activity and selectivity of potential drug candidates.

In vivo Studies: Testing drug candidates in animal models to evaluate their efficacy, pharmacokinetics, and toxicity profiles before advancing to human trials.

Formulation Development: Developing the appropriate formulation (e.g., tablets, injections, patches) to deliver the drug effectively and safely.

Safety Pharmacology: Assessing the potential adverse effects of drug candidates on vital physiological functions in animal models.

Toxicology Studies: Investigating the safety profile of drug candidates by assessing their potential toxicity in animals, including acute, sub chronic, and chronic toxicity evaluations.

Pharmacokinetics and Pharmacodynamics (PK/PD): Studying how drugs are absorbed, distributed, metabolized, and excreted in the body, as well as their pharmacological effects.

Bioanalytical Method Development: Developing analytical methods to measure drug concentrations in biological samples accurately.

Regulatory Compliance: Ensuring that non-clinical studies adhere to regulatory guidelines and requirements set by regulatory agencies such as the FDA or EMA.

Overview of non-clinical activities:

The evaluation of non-clinical activity (efficacy) of a new drug candidate includes in vitro, ex vivo and in vivo assays that can be carried out throughout all stages of drug development. These tests are essential to provide the basic knowledge about the drug pharmacodynamics and are required for later entering into clinical studies.

Due to improvements in the basic sciences of the biomedical field, it is natural that the methods for analysing the non-clinical efficacy of a drug candidate are thus constantly advancing. Although it is currently essential to use experimental animals, efforts have been made to reduce the use of in vivo techniques to a minimum.

Advantages of non-clinical activities:

Non-clinical activities in drug discovery offer several advantages:

Early-stage Assessment: They allow researchers to evaluate the safety and efficacy of potential drug candidates in laboratory settings before advancing to clinical trials, saving time and resources.

Risk Reduction: Non-clinical studies help identify potential safety concerns and toxicities early in the drug development process, reducing the risk of adverse effects in human trials.

Mechanism of Action Understanding: They provide insights into the mechanism of action of potential drugs, aiding in the optimization of lead compounds and development of more effective therapeutics.

Dose Selection: Non-clinical studies help determine appropriate dosages for clinical trials, ensuring that patients receive safe and effective treatment.

Regulatory Compliance: Data from non-clinical studies are crucial for regulatory submissions and approval processes, demonstrating the safety and efficacy of new drugs to regulatory agencies.

Cost-effectiveness: By addressing potential issues early in the drug development process, non-clinical activities can help avoid costly failures during later stages of clinical development.

UNIT -1

CLINICAL STUDIES/TRAILS

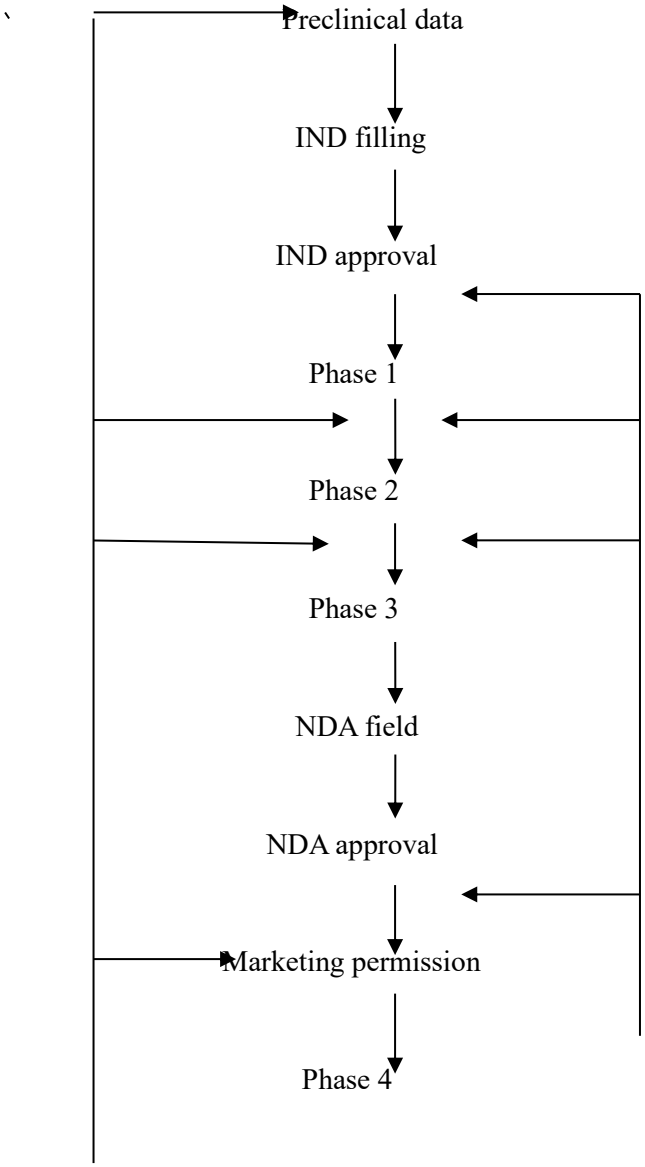
INTRODUCTION:

- Clinical trails are experiments or observations done in clinical research .
- Such prospective bio medical or behavioral research studies on human participants.
- The phases of clinical research of the steps in which scientists do experiments with a health intervention in a process which would be useful as a medical treatment.
- Clinical trials is mainstay of bringing out new drugs to the market.

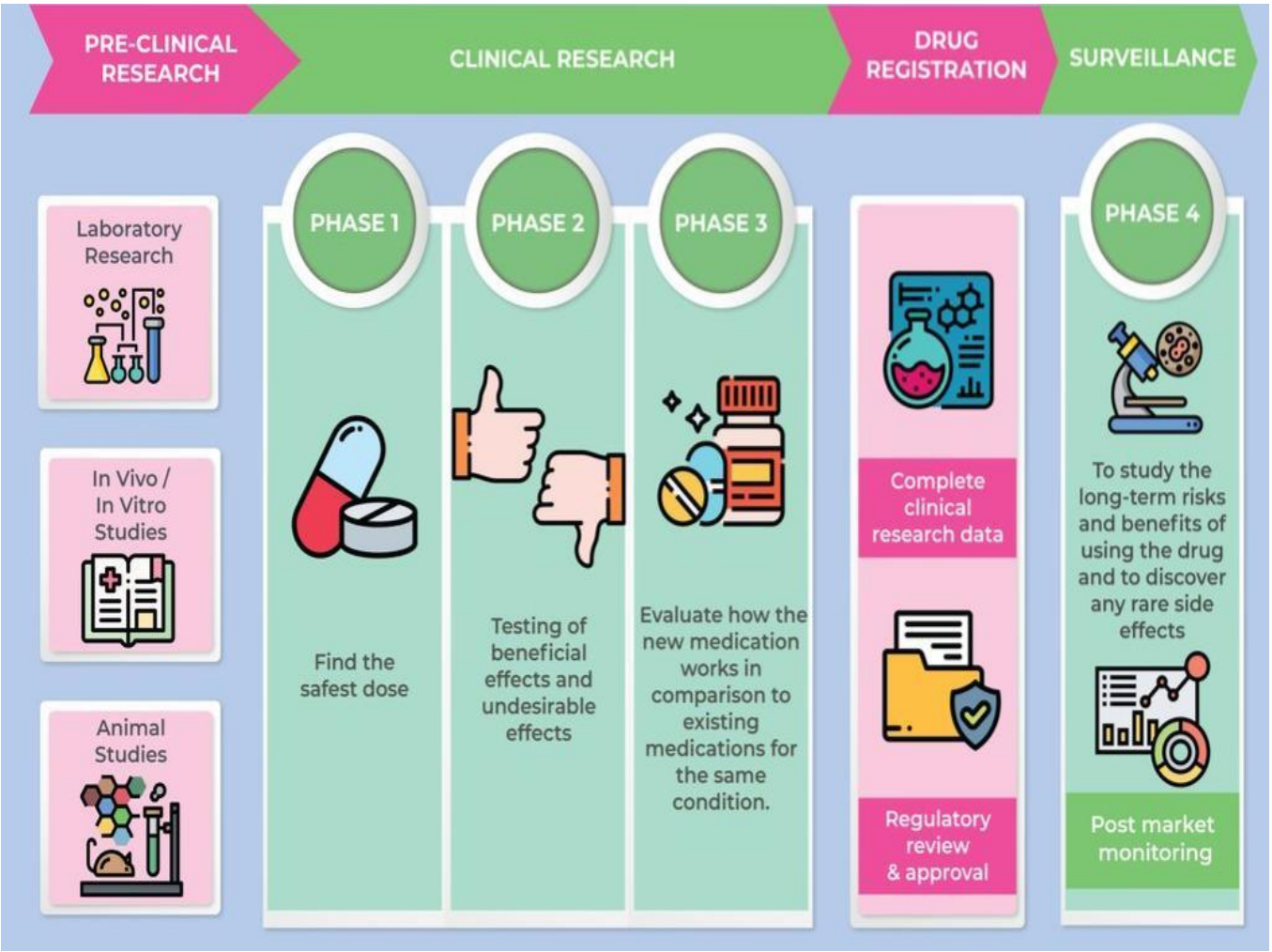
DRUG REVIEW STEPS:

1. Preclinical (animal) testing
2. An investigational new drug application (IND)
3. Phase 1 studies
4. Phase 2 studies
5. Phase 3 studies
6. Submission of new drug application (NDA)
7. FDA reviewers will approved the application
8. Phase 4 studies

Clinical drug development phase



Drug Development process of clinical studies:



preclinical evaluation phase (animal studies):

Major areas are:

- Pharmacodynamics studies in vivo in animals, In vitro preparation
- Absorption, distribution, elimination studies (pharmacokinetics)
- Acute, sub acute, chronic toxicity studies (toxicity profile)
- Therapeutic index (safety & efficacy evaluation)

IND Application Filing:

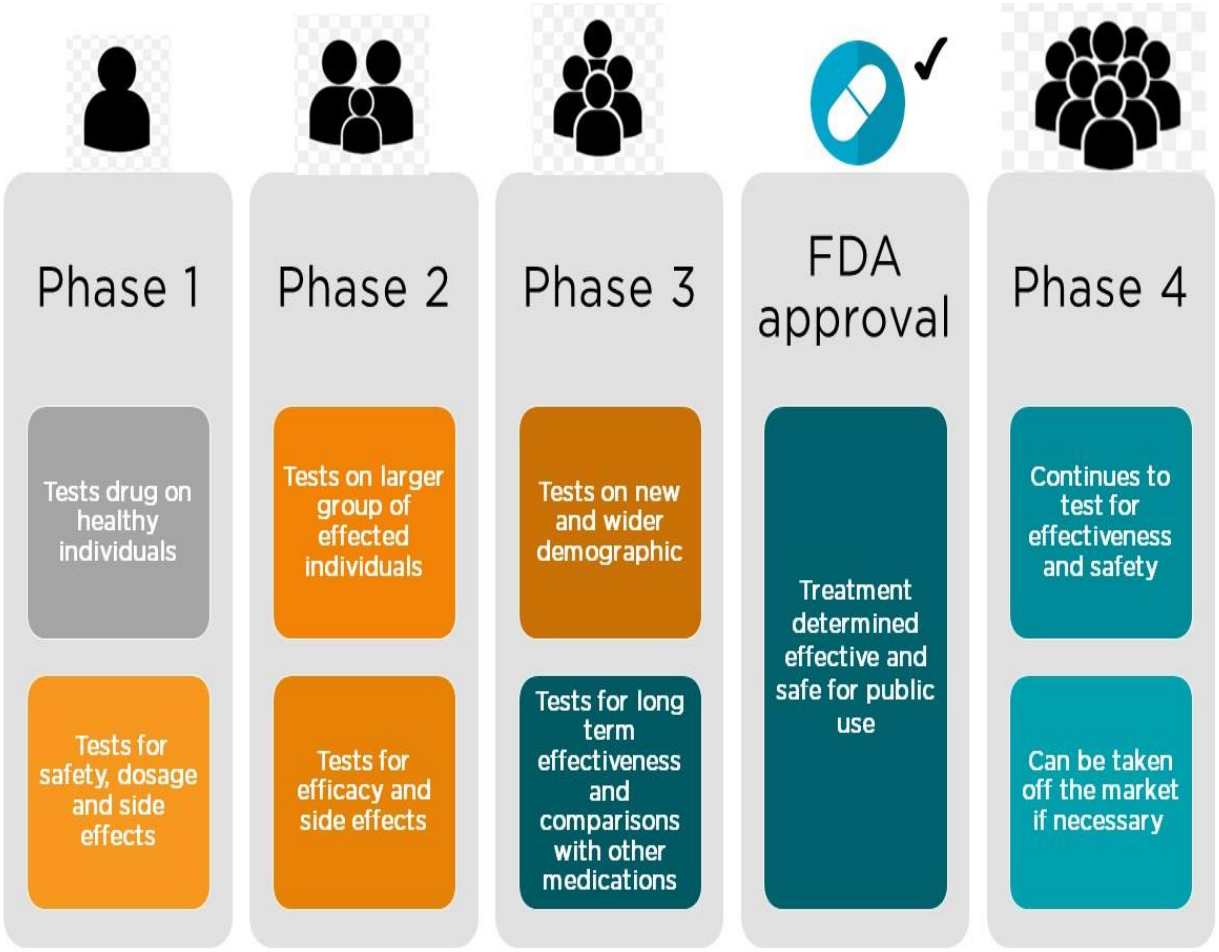
- Once preclinical studies have indicated the safety and efficacy of a drug an IND application has to be filed with the regulatory authorities
- for obtaining regulatory Approval for Phase I, phase II and Phase III clinical evaluation.
- Contents of IND application

- Preclinical Data (All data from animal studies)
- Information on composition and source of drug
- Chemical and manufacturing information
- Proposed clinical plans and protocol
- Ethical Committee Clearance

IND Application

- Clinical Evaluation needs Prior Regulatory and IRB Clearance.
- Phase-wise clearances have to be obtained.
- The End Result of Phase I-III studies is the filing of NDA (New Drug Application) for obtaining Marketing Permission from DCGI.

Phases of clinical trials:



Phase 0:

- Phase 0 is a recent designation for optional exploratory trails conducted in accordance with the united states food and drug administrations (FDA) 2006 guidance on exploratory investigational new drug (IND) studies.
- Phase 0 trails are also known as " human micro dosing studies " and are designed to speed up the development of promising drugs are imaging agents by establishing very early on whether the drug.
- Phase 0 study gives no data on safety or efficacy, being by definition a dose to low to cause in the therapeutic effect.
- The administration of single sub therapeutic dosage of the study drug to a small number of subjects (10 to 15).

Phase 1

- Phase 1 trails were formerly referred to as "first-in-man studies" but the field generally moved to the gender-neutral language phrase "first-in-humans" in the 1990.
- They are designed to test the safety, side effects, best dose, and formulation method for the drug.
- A small group of 2-100 healthy volunteers will be recruited.
- Patients: Anticancer drugs, AIDS therapy.
- Duration – 6-12 months.
- No blinding/open labeled.

Kinds of phase 1

1) SAD: single ascending dose studies
2) MAD: multiple ascending dose studies

Single ascending dose studies:

- Small groups (3) of subjects are given a single dose of the drug while they are observed and tested for a period of time
- If no adverse effects- dose is escalated with 3 news healthy subjects
- If toxicity is observed then- 3 more subjects are given the same dose
- If found toxic- the dose is considered as max. tolerated dose (MTD).

Multiple ascending dose studies:

- Conducted to understand the pharmacokinetics and pharmacodynamics of multiple dose of drug.
- A group of patients receives multiple low doses of the drug.
- Samples (of blood, and other fluids) are collected at various time points.
- Analyzed: flow the drug is processed within the body

Phase 2

- Once a dose or range of doses is determined, the next goals is to evaluate whether the drug has any biological activity or effect.
- Phase 2 trails are performed on larger groups (100-300).
- To confirm effectiveness, monitor side effects, & further evaluate safety.
- First in patients (who have the disease that the drug in expected to treat)
- Duration: 6 months to several years.
- Phase 2 studies pre- requisites- review of phase 1 data, innovator/experts, IRB and DCGI is mandatory .

- Phase 2 studies are sometimes divided in to phase IIA and phase IIB
  - **Phase IIA studies** are usually pilot studies designed to demonstrate clinical efficacy or biological activity.
  - **Phase IIB studies** look to find the optimum dose at which the drug shows biological activity with minimal side effects.

    Some trails combine phase 1 and phase 2, and test both efficacy and toxicity.

Phase 3

- This phase is designed to assess the effectiveness of the new intervention and, thereby, it's value in clinical practice
- Large scale, multicentre, randomized, controlled trails.
- Target population: several 100 to 300 patients.
- Takes a long time: up to 5 years.
- To establish efficacy of the drug against existing therapy in larger number of patients, method of usage, & to collect safety data etc.

Kinds of phase 3

Phase IIIA:

- Prior to NDA
- Generates data on safety and efficacy.

Phase IIIB:

- After the NDA but Prior to the approval and launch.
- These may supplement or complete the earlier trails or may be directed to phase 4 trails.

Phase 4

- A phase 4 trails is also known as post marketing surveillance trails, or informally as a confirmatory trail.
- Phase 4 trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold (e.g after approval under the FDA accelerated approval program).
- The safety surveillance is designed to defect any rare or long term adverse effects
- Harmful effects discovered by phase 4 trails may result in a drug being no longer sold, or restricted to certain uses, recent example involve cerivastatin, troglitazone, refecoxib.
- The minimum time period mandatory for phase 4 clinical trails is 2 years.

UNIT -1

UNIT -1

INNOVATOR AND GENERIC DRUGS

INNOVATOR

The first drug created containing its specific active ingredient to receive approval for use is called an innovator drug. Safety, efficiency and quality for the product have been fully established for this drug.

When a new drug is made by a company then it is firstly made patent for up to 20 years. Other companies cannot make or sell the same drug until the patent expires.

Examples of Innovator

Active ingredients	Innovator
1.Ranitidine Hcl	Zantac
2.Mefenamic acid	Ponstan
3.Piroxicam	Feldene

Advantages

1.Improved productivity

2.Reduced costs

3.Increased competitiveness

4.Improved brand recognition and value

5.New partnerships and relationships

Disadvantages

1.Social distress

2.Safety concerns

3.Economis disparities

4.Educational disparities

GENERICS

A generic drug is a medication made that is same as an already marketed brand-name drug in terms of dosage form. safety, strength, route of administration, quality, and performance characteristics.

Generic drug cases same effect as an innovator drug because they have the same active ingredient and also have similar risks and benefit.

Because of certain inactive ingredients like color and flavoring agent, generic drugs may look different. The performance, safety and effectiveness are not affected by these ingredients.

Examples of Generics

Active ingredients	Generics
1.Ranitidine Hcl	X'tac
2.Mefenamic acid	Mefetab
3.Piroxicam	Apo-piroxicam

Myths and Facts of Generic Drugs

1) Myth: Duplicate drugs

Fact: Some people may think that the drugs are duplicated as they have different brands name or shape of the dosage packing.

2) Myth: Fake and Rejected drugs.

Fact: It is usually thought that generic drugs are rejected form the company as they are available at cheap price.

3) Myth: Ineffective drugs

Fact: People think that there is something wrong with drugs sold at cheap price and that costlier drugs are effective.

4) Myth: Generic is often made in sub-standard facilities and brand-name drugs are made a sub-standard facilities.

Fact: FDA doesn't permits sub-standard facilities.

Advantages of Generic Drugs

1) These drugs are somewhat cheaper.

2) On the part of the patient they save out over spending of money.

3) A generic drug ends the link between the pharmaceutical companies and the doctors. The doctors receive incentives, gifts, etc. to promote a specific brand of medicine which results in the prescription

of expensive medicine increasing the burden on the patient. 4) An attractive market overseas has been found by the generic medicines. These drugs are being exported to both developing and developed nations by a number of pharmaceutical companies. A considerable volume of foreign exchange is earned by the pharmaceutical companies through this trade. I helps the Indian pharmaceutical sector and is also helpful in making the Indian pharmaceutical industry recognised on a global level. 5) The pharmaceutical companies invest in research and development by using these profits.

Disadvantages of Generic Drugs

1) During reformulations of generic drugs there may be some variation.

2) Certain patients might be allergic to new color, flavor, etc used in the formulation.

3) It takes long time for any patent to get expired so generic drugs are not possible to be manufactured in all cases.

4) Bioequivalence studies are less accurate than bioavailability studies i.e.. during bioequivalence studies some errors may arise which may lead to some complication.

Comparison of innovator and generic drugs

S. No.	Parameters	Innovator drug	Generic drug
1.	Active ingredients	Same	Same
2.	Safety and efficacy	Same	Same
3.	Quality and strength	Same	Same
4.	FDA inspection of manufacturing facilities	Yes	Yes
5.	Performance and standards	Same	Same

Are innovator drugs and generic drugs similar?

There are similarities between generic and innovator drug, such as:

- Active ingredient
- Strength (dose)
- Therapeutic effect

- Side effects
- How to take

Differences between innovator and generics

S.No	Innovator	Generics
1.	Protected by patent	Low cost version of brand
2.	Supplied by single company	Produced by generic companies
3.	Initially marketed as new chemical entities	Copies of innovator
4.	First version sold by the innovator	Produced after original patent expires
5.	Marketed under a brand name	As safe and effective as brand
6.	Drug prices are decided by the pharmaceutical companies	Drug price are decided by generic companies[5]

CONCEPT OF GENERICS

INTRODUCTION

Definition:

A generic drug is defined as "**A drug product that is comparable to brand/innovator drug in dosage from, strength, route of administration, quality and performance characteristics and intended use".** It should contain the same active ingredients as the original formulation.

According to the FDA, generic drugs are identical or within an acceptable bioequivalent range to the brand-name counterpart with respect pharmacokinetics and pharmacodynamic properties.

The first drug created containing its specific active ingredient to receive approval for use is called an innovator drug. Safety, efficiency and quality for the product drug have been fully established for tis drug. When a new drug is made by a company hrough, then it is firstly made patent for up to 20 years.

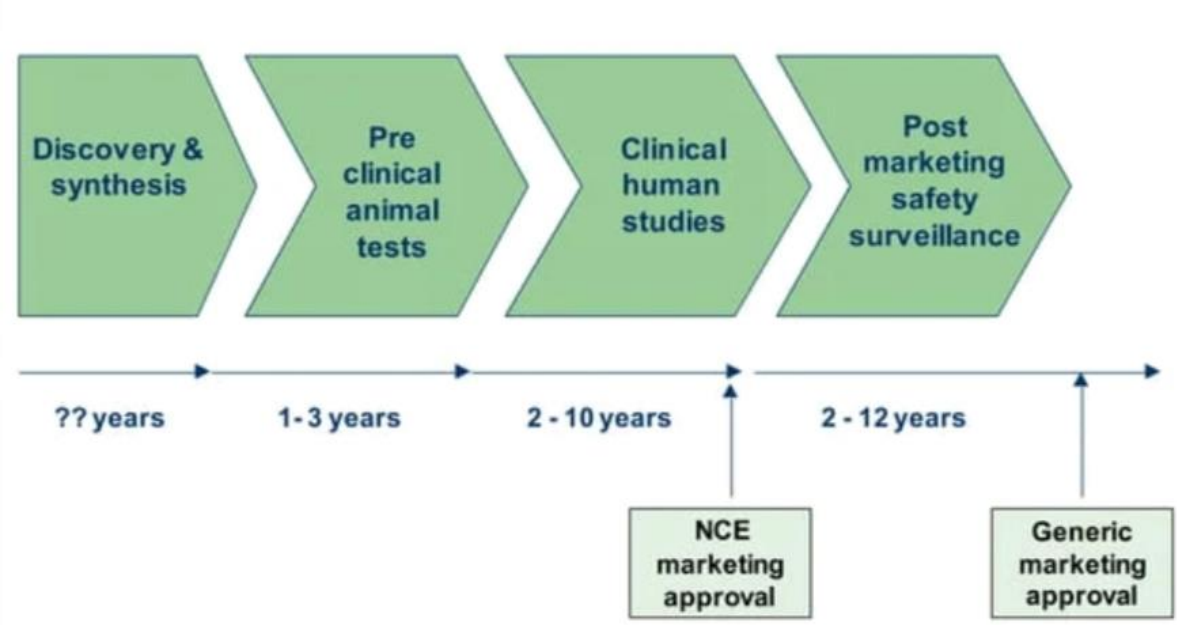
Other companies cannot make or sell the same drug until the patent expires. A generic drug is a medication made that is same as an already marketed brand-name drug in terms of dosage form, safety, strength, route of administration, quality, and performance characteristics.

Generic drug cases same effect as an innovator drug because they have the same active ingredient and also have similar risks and benefit. Because of certain inactive ingredients like color and flavoring agent, generic drugs may look different. The performance, safety and effectiveness are not affected by these ingredients.

Similarities between Generic and Innovator Drugs

- ✓ Active ingredient
- ✓ Dose of Administration
- ✓ Therapeutic Effect
- ✓ Side effects
- ✓ Route of Administration .

- ✓ A generic drug (or simply generic) is a pharmaceutical drug that contains the same chemical substance as a drug that was originally protected by chemical patents. Generic drugs are allowed for sale after the patents on the original drugs expire.
- ✓ Generic Drugs are usually subject to government regulation in the countries in which they are dispensed not to a company manufacturing it. They are labelled with the name of the manufacturer and a generic non-proprietary name such as the United States Adopted Name (USAN) or International Non-proprietary Name (INN).
- ✓ The active ingredient of the generic drug must be same as that of the original brand-name formulation. Generic drug is required to be identical or within an acceptable bioequivalent range of their brand-named counterparts, with respect to pharmacokinetic and pharmacodynamics properties according to U.S. Food and Drug Administration (FDA).
- ✓ Biopharmaceuticals, differ biologically from small molecule drugs such as monoclonal antibodies. Bio similar is not the same as generic drugs as the active ingredient is not the same as those of their reference products but bio similar has active pharmaceutical ingredient that are almost identical to the original product.



When the patent protection afforded to a drug's original developer expires, the generic product becomes accessible as per most of the cases. Competition often leads to substantially lower price for both the original brand-name product and generic equivalent when generic drug arrive the market.

Nomenclature of Innovator and Generic Drugs

BRAND NAME	GENERIC NAME
Amaryl	Glimepiride
Ambien	Zolpidem
Ativan	Lorazepam
Calan SR	Verapamil
Cardizem	Diltiazem ER
Celexa	Citalopram
Diabeta	Glyburude

In maximum countries, 20 years of protection is provided by the patent. Though in several countries and regions like European Union and the United States, if manufacturers meet specific goals like conducting clinical trials for paediatric patients then they may get grant up to five years of additional protection (patent term restoration).

"Branded generics" on the other hand are defined by the FDA and NHS as products if they are:

1) Either novel dosage forms of off-patent products produced by a manufacturer that is not the originator of the molecule, or
2) A molecule copy of an off-patent product with a trade name. Since the company making branded generics can spend little on research and development, it is able to spend on marketing alone, thus earning higher profits and driving costs down.

GENERIC DRUG PRODUCT DEVELOPMENT

Product Specific Guidance's for Generic Drug Development

Generic Drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval, FDA.

I. Generic Drug Approvals

FDA regularly updates a listing of first generic drug approvals.

II. PRE-ANDA Program

The Pre-ANDA Program is a valuable information resource for generic drug applicants.

III. List of OFF-Patent, Off-Exclusivity Drugs Without An Approved Generic.

The FDA maintains this list to improve transparency and encourage the development and submission of ANDAs in markets with little competition.

IV. Authorized Generic Drugs

The FDA List of Authorized Generic Drugs, updated quarterly, includes the drug trade name, the brand company manufacturer.

V. Quality by Design (QBD)

QBD is a scientific, risk-based, proactive approach to pharmaceutical development.

VI. Inactive Ingredient Database

Database provides information on inactive ingredients present in FDA-approved drug product.

VII. Hatch-Waxman Letters

FDA's decisions on 180-day exclusivity and other matters related to generic drug approvals.

VIII. FDA Letters to Industry.

This series of letters informs generic drug product manufacturers of policy and procedure developments with respect to the Drug Price Competition and Patent Term Restoration Act of1984.

Unit II

Regulatory Approval Process

Approval processes and timelines involved in Investigational New Drug (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA). Changes to an approved NDA / ANDA.

Regulatory authorities and agencies

Overview of regulatory authorities of India, United States, European Union, Australia, Japan, Canada (Organization structure and types of applications)

UNIT - 2

APPROVAL PROCESS &TIMELINE INVOLVED IN IND

Investigational new drug (IND)

It's an application filed to the FDA in order to start clinical trials in humans if the drug was found to be safe from the reports of Preclinical trials.

The Federal Food, Drug and Cosmetics act regulated through Title 21 of U.S. Code of federal Regulations, requires a new drug to be approved by FDA before legally getting introduced into the market. Investigational New Drug is defined under 21 CFR 312.3(b) as, "A new drug or biological drug that is used in clinical investigation".

An Investigational New Drug (IND) is an experimental drug that has not yet been approved for marketing by a regulatory agency, such as the FDA. But it is being tested in clinical trials to determine its safety and efficacy.

An IND is considered "investigational" because it is still in the process of being investigated, and its safety and effectiveness have not yet been fully established. The drug's sponsor must submit an Investigational New Drug application to the FDA to conduct clinical trials on the new drug.

The application must contain data from preclinical studies (pharmacokinetics, dose-response, formulation, toxicology studies), manufacturing information (labelling, production methods, batch records), information regarding the study site (facilities, equipment), and the proposed clinical trial protocol (study design, endpoints, informed consent, adverse event reporting). The FDA reviews the application to ensure that the proposed trials are scientifically sound and ethically conducted and that the drug is safe for use.

If the IND is approved, the sponsor will conduct clinical trials on patients to determine if the drug is effective and safe for use. If the clinical trials are successful, the sponsor may then submit a New Drug Application (NDA), also known as a marketing application, to the FDA for approval to market the drug to the public. NDAs are generally the final step in the drug development process.

After pre-clinical investigations when the new molecule has been screened for pharmacological activity and acute toxicity potential in animals the sponsor requires permission from FDA for its clinical trials in humans.

The sponsor submits the application for conduct of human clinical trials called Investigational New Drug (IND) application to FDA.

Once IND application is submitted, the sponsor must wait for 30 days before initiating any clinical trial.

Clinical trials in humans can begin only after IND is reviewed by the FDA and a local institutional review board (IRB).

IRBs approve clinical trial protocol, informed consent of all participants and appropriate steps to prevent subjects from harm.

If the FDA accepts the IND request within 30 days of submission, clinical testing of the new molecule on human may begin by the investigator.

At this point, the molecule under the legal status of FDA becomes a new drug subject to specific requirements of drug regulatory system.

If at any time during clinical testing, the data furnished to FDA indicate the Investigational Product (IP) to be toxic under the criterion of FDA's Benefit/Risk ratio, FDA can terminate clinical trial and its actions are not subject to any judicial review.

Types of INDs

There are two types of INDs:

- **Commercial**: A commercial IND is submitted by a sponsor, such as a drug manufacturer, that intends to market the investigational drug for commercial use once the regulatory agency has approved it.
- **Research:** A research IND is submitted by a single investigator or a group of investigators who want to study an investigational drug in a clinical trial. Research INDs are often used for early-phase clinical trials, such as phase 1 trials, when the primary goal is to determine the safety and pharmacokinetics of the drug.

TYPES OF IND APPLICATIONS:

- **Research IND or Investigator IND:** An application submitted by a physician who starts and carries out the study. The physician is responsible for administering or dispensing the investigational drug under their direct supervision. The IND may be submitted for approval to study a new, unapproved drug or for studying an approved drug's use in a new indication or patient population.
- **Emergency Investigational New Drug (EIND):** An application that, when approved, allows the use of an experimental drug in an emergency situation where there isn't enough time for a complete IND application submission. It is also utilized for patients who do not fit the criteria of an existing study plan or if there is no approved study plan available.
- **Treatment IND:** An application submitted for experimental drugs that demonstrate promise in clinical trials for severe or life-threatening conditions during the ongoing clinical studies and FDA review process.

IND Application Process Work:

The IND application process is a critical step in the drug development journey, as it allows drug manufacturers to request permission to conduct clinical trials in humans with an IND. Sponsors can take the following steps to apply for an IND in the US:

1. **Conduct preclinical testing:** Run laboratory and animal studies to determine the safety and efficacy of the drug.
2. **Prepare for the IND application:** Assemble all relevant information, including preclinical data, manufacturing information, proposed clinical trial protocols, and other required information.
3. **Submit the IND application:** Apply to the FDA electronically through the agency's Electronic Submissions Gateway (ESG) or by mail.
4. **Go through FDA review:** The FDA will review the IND application to determine if the proposed clinical trials are scientifically sound and ethically conducted and if the drug is safe for human subjects.

5. **Conduct clinical trials:** If the IND is approved, the sponsor, whether it's a drug manufacturer or clinical investigator, can then conduct clinical trials in humans to evaluate the safety and efficacy of the drug.
6. **Provide annual reporting:** Once clinical trials begin, an IND safety report must be sent to update the FDA on the study's progress. The annual report must be submitted by the sponsor of the IND within 60 days of the anniversary date of the IND submission and include updates on the safety of the IND, changes to the clinical protocols, and more.

Information and reporting requirements for IND applications may vary, making it important to consult with regulatory agencies like the FDA to understand the criteria for IND submissions. A clinical hold may be put in place after an application has been approved, stopping the trial's initiation or continuation.

IND Submission Process:

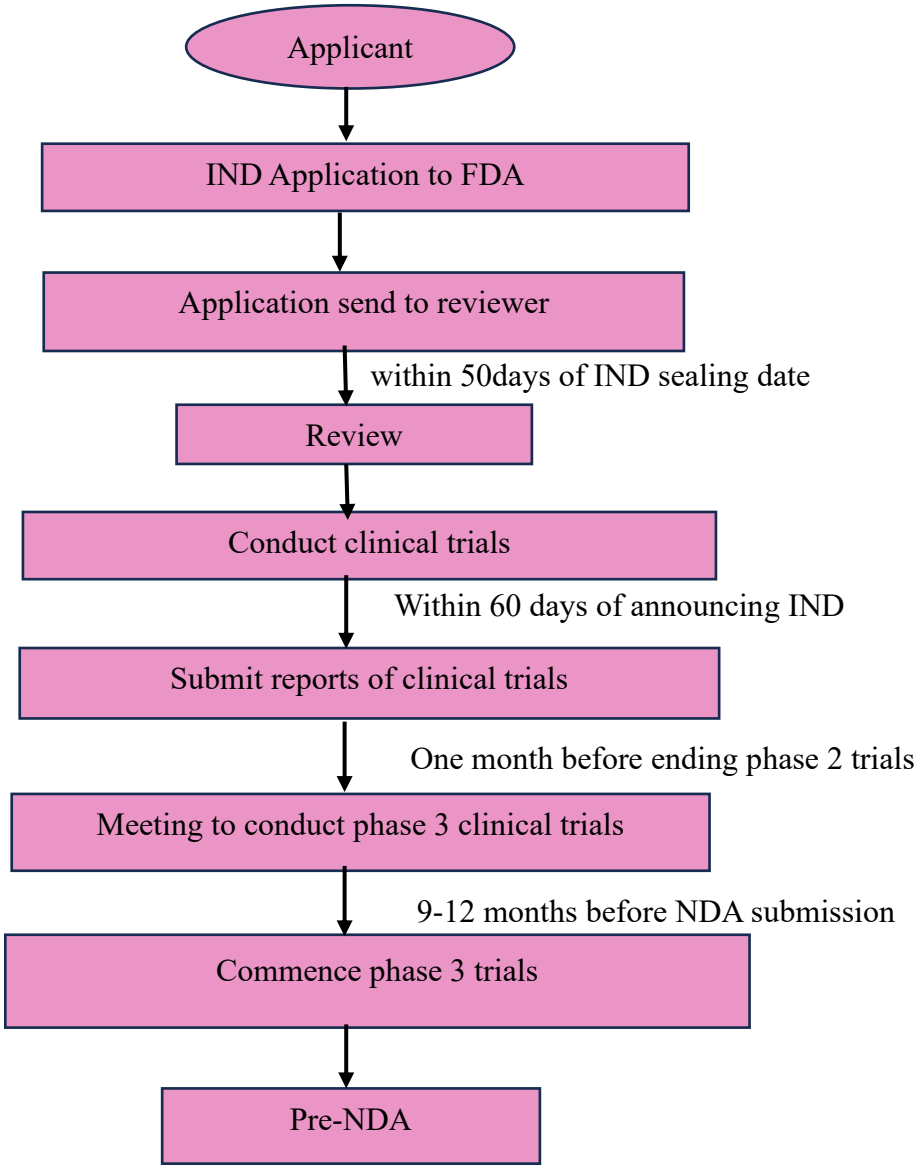
To successfully submit an IND application, you must collect and prepare the following information and materials:

1. **Preclinical data:** Laboratory and animal studies demonstrating the drug's safety and efficacy. The preclinical data must be detailed and provide a basis for the proposed clinical trials.
2. **Manufacturing information:** The drug's formulation, manufacturing processes, and quality control measures. This information must demonstrate that the drug can be manufactured consistently and reproducibly and meets appropriate quality standards.
3. **Clinical trial protocols:** Detailed information about the proposed clinical trials, including the trial design, inclusion/exclusion criteria, endpoints, and sample size.
4. **Investigational Brochure:** A document that provides an overview of the preclinical and clinical information available on the drug.
5. **Other relevant information:** The drug's pharmacology and toxicology data, as well as any additional information required by the FDA.

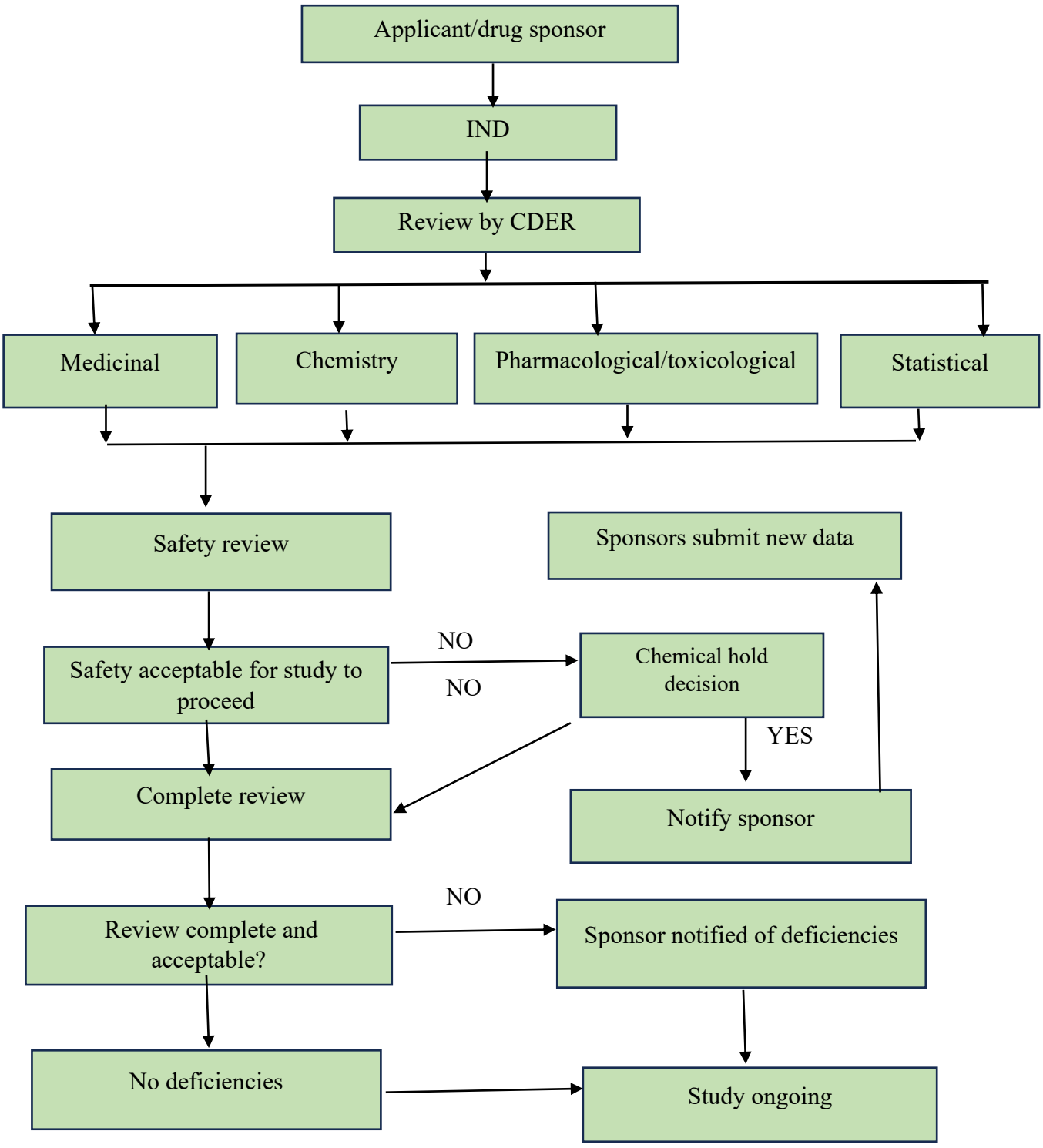
The IND application must be in the format specified by the FDA and include all required information and documentation. The FDA may request additional information or clarification during the review process.

Approval Process

a) An applicant should apply to the FDA with all the required information.
b) FDA forwards the application to the review team on receiving it.
c) The review team delivers its positive or no response that whether the sponsor can start clinical trials within 30 days after the IND sealing date.
d) The sponsor shall submit the reports of clinical trials. A meeting shall be conducted before one month of ending phase II trials within 60 days from announcing the IND.
e) Once the sponsor has completed phase III trials successfully the sponsor shall initiate pre-NDA from 9-12 months before NDA submission.



IND application chart:



Timelines involved in IND: Timeline of regulatory review process. After FDA IND submission, the FDA has 30 days to review the application and provide any concerns that must be addressed. The IRB submission process is similar, but typically has a longer timeline.

NEW DRUG APPLICATION

INTRODUCTION:

- If clinical studies confirm that a new drug is relatively safe and effective and will not pose unreasonable risks to patient. The manufacture files a new drug application the actual requestto manufacture and sell the drug in the united state.
- The new drug application is the vehicle through which the drug sponsors finally propose FDA to approve a new investigational drug for sale and marketing after phase-3 a pivot trials.
- The official definition of new drug is in selection 201(p) of federal drug, food and cosmetics act.
- Any drug the composition of which is such that is as a result of investigations to determine safety and efficacy for use has become recognized, but which has not, other wise in such investigations used to a material extent.

The following letter code describe the review priority of the drug:

These are two types:

1. S-STANDARD REVIEW.
2. P-PRIORITY REVIEW.

1. **S-STANDARD REVIEW :** For drugs similar to currently available drugs .
2. **P-PRIORITY REVIEW:** For drugs that represent significant advances over existing treatments.

NDA require the following documents to provide the information about the drugs:

A. Procedure of clinical test.

B. Ingridents of the drugs

C. Result of the animal studies .

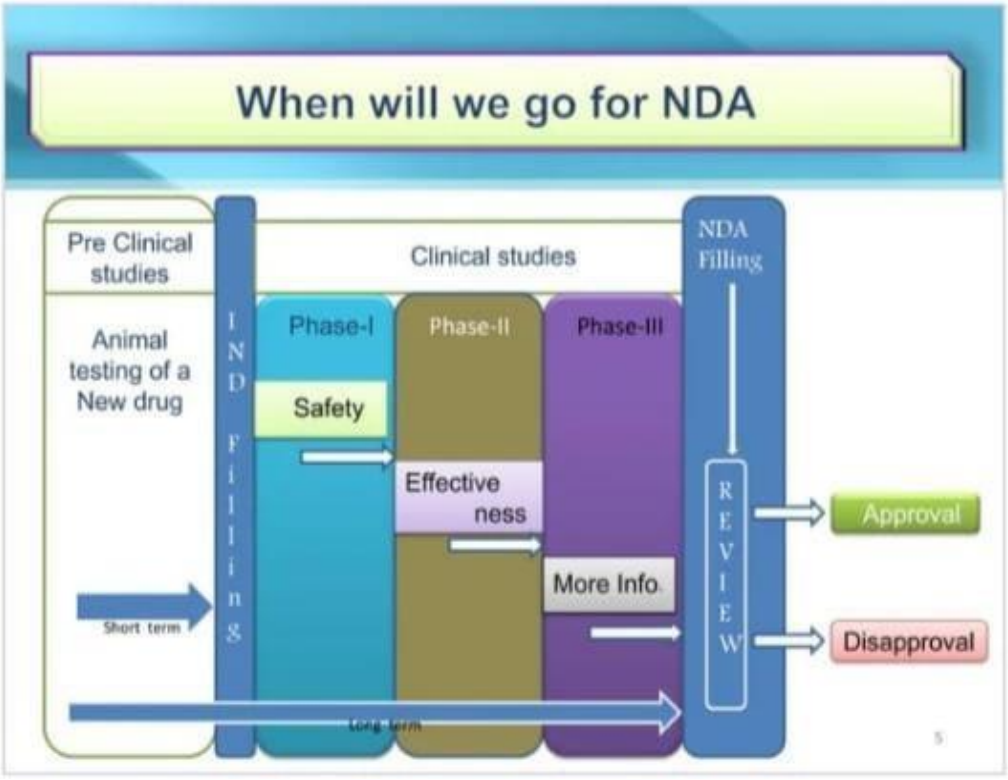
D. Pharmacokinetics.

E. Manufacturing, processing and packaging of drugs.

GOALS OF NDA:

- Safety and effectiveness of a new drug in its proposed use .

- Whether the drugs proposed labelling appropriate.
- Methods used in manufacturing the drugs and the controlled used to maintain the drugsquality are adequate to preserve the drugs identity.
- The benefits of the drug out weight the risk.



CLASSIFICATION OF NDA :-

Center of the drug evaluation and research (CDER) classifies new drug. Applications according to the type of drug being submitted and its intended use:

i. New molecular entity.

ii. New salt of previously approved drug.

iii. New formulation of previously approved drug.

iv. New combination of two or more drugs.

In following four types of application are submitted for approval of drug formarketing depending upon the type and nature of the drug .

1. New drug application.
2. Biological licence application.
3. Application U/S 505.
4. Supplimental new drug application (SNDA)

REQUIREMENTS FOR FILLING NDA:

The new NDA regulations require the application to be submitted in two copies that are:

a) **ARCHIVAL COPY**: It is a complete copy of application submission that serves as itspermanent record.

b) **REVIEW COPY**: It is divided into 6 technical section

a) Chemistry,Manufacturing & controls

b) Non-clinical pharmacology & toxicology

c) Human pharmacokinetics & bio availability

d) Microbiology

e) Clinical data

f) Statistical

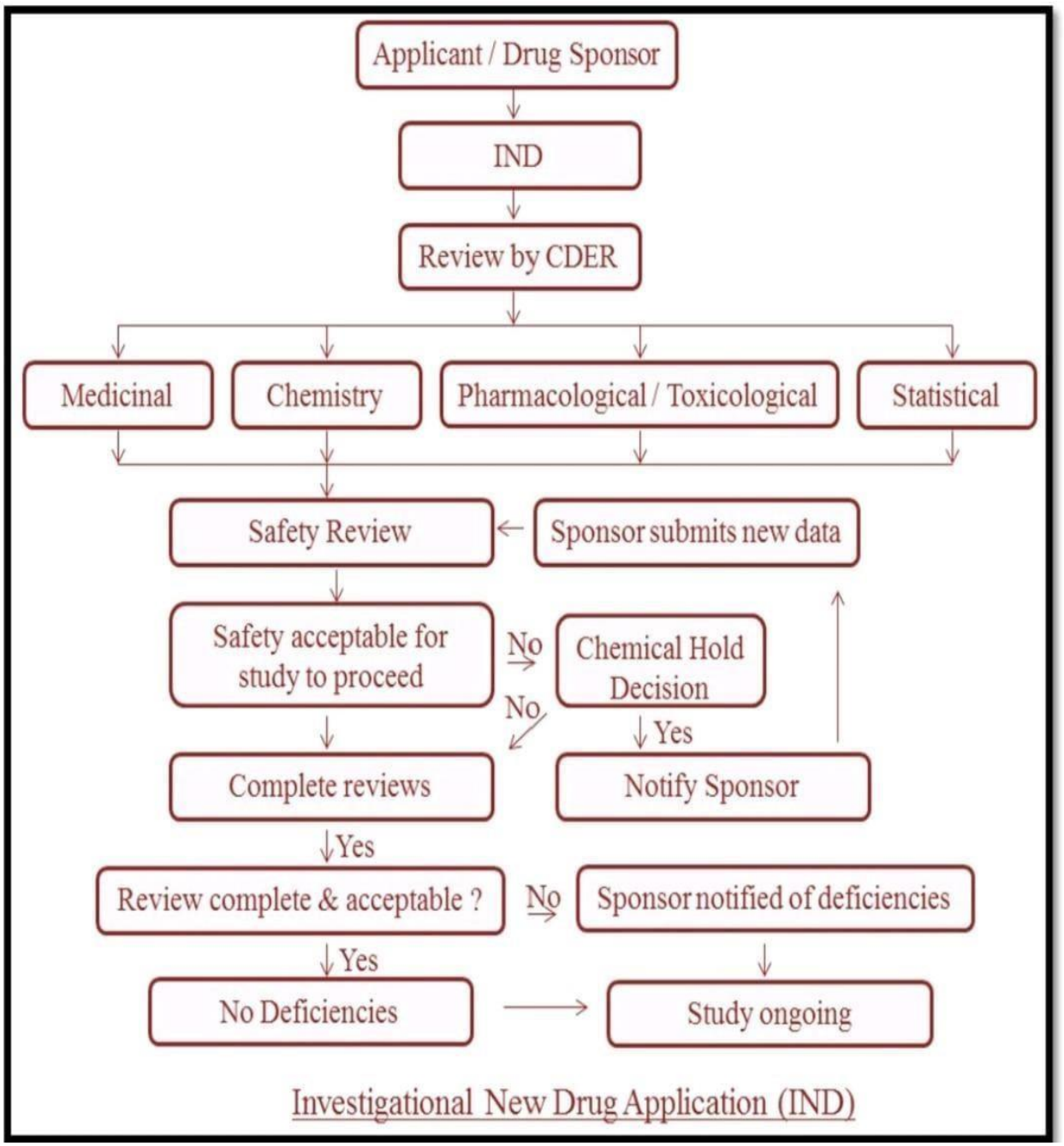
- FDA review the sample of clinical trails location to verify the accuracy of data submitted &inspects the manufacturing services for the drugs.
- The divisional director evaluates the reviews & makes FDA's decision.The FDA may
- Approve the drug for marketing.
- Approve the drug with condition when problem exist with the application that needs to beaddressed before approval.
- When the drug require additional research (or) reformation of the drug product,then mayrefuse to approve the drug.

FUNDAMENTALS OF NDA SUBMISSION:

- As outlined in form FDA-356th application to marked a new drug for human use (or) As onantibiotic drug for human use

- 15 different sections.They are

1) Index
2) Labeling
3) Application summary
4) Chemistry,Manufacturing & control
5) Non-clinical pharmacology & toxicology
6) Human pharacokinetics & bioavailability
7) Microbiology
8) Clinical data
9) Saftey data
10) Statistical
11) Case report tabulation
12) Case report forms
13) Patent information
14) Patent certification
15) Other information


Applicant / Drug Sponsor
IND
Review by CDER
Medicinal
Chemistry
Pharmacological / Toxicological
Statistical
Safety Review
Sponsor submits new data
Safety acceptable for study to proceed
No
Chemical Hold Decision
No
Yes
Complete reviews
Notify Sponsor
Yes
Review complete & acceptable ?
No
Sponsor notified of deficiencies
Yes
No Deficiencies
Study ongoing
Investigational New Drug Application (IND)

ABBREVIATED NEW DRUG APPLICATION

An **Abbreviated new drug application (ANDA)** is specifically designed for an approval of generic drug product".

Application for products similar to "already approved drugs" in terms of same dosage form, same route of administration, active ingredients and other conditions.

Such applications were required to show bioequivalence If FDA thought the products have potential bioavailability problem.

GENERIC DRUG

To nominate a generic drug, it must be a drug product that is comparable to an innovator drug product in :-

- Dosage form.
- Strength.
- Route of administration.
- Quality.
- Performance characteristics
- Intended use.

GOAL OF ANDA

- To Reduce the Price of drug
- To Reduce the Time Development
- Increase the Bioavailability of the drug in comparison to reference list of drug.

OBJECTIVES OF ANDA

- ✓ To reduce the price of the drug.
- ✓ To reduce the time development.
- ✓ To increase the bioavailability of the drug in comparison to references list drug.
- ✓ To check weather the control used to preserve the drugs quality and the methods used in developing the drugs are adequate to preserve the drugs identity , strength , quality , and purity.

INFORMATION REQUIRED FOR FILLING ANDA

- ➢ An Index
- ➢ Signed FDA form 356h
- ➢ Product's formulation
- ➢ Manufacturer's procedure Control procedure
- ➢ Testing
- ➢ Facilities
- ➢ Dissolution profile
- ➢ Labeling
- ➢ Human pharmacokinetics and bioavailability.
- ➢ Samples
- ➢ Analytical method for drug substance and drug product.

FORMAT OF ANDA

- **An archival Copy**
- **A review Copy**
- **A field Copy**

ARCHIVAL COPY

- ❖ It must contain four copies of the Labeling section.
- ❖ It must contain three additional copies of the CMC and Methods Validation Package in a separate binder.

- ❖ The archival copy is the only copy that contains the Case Report Tabulation and Case Report Forms.

REVIEW COPY

- ❖ The Review Copy Intended for corresponding technical disciplines.
- ✓ Addition to the appropriate technical section, each review copy also includes The cover letter, Form FDA- 356h, The administrative sections, Comprehensive NDA index Individual table of contents, The Labeling section, and The Application Summary.

FIELD COPY

- ❖ The Field Copy required since 1993 for use by FDA inspectors during pre approval facilities inspections
- ✓ It includes the Cover letter and Form FDA-356h, the administrative sections, the comprehensive NDA index Individual table of contents, The Labeling section, The Application Summary, and CMC and Methods Validation Package.

ANDA CONTENTS

- ➢ Section 1: Overall ANDA index
- ➢ Section 2: Labeling
- ➢ Section 3: Application summary
- ➢ Section 4: Chemistry, manufacturing and con*
- ➢ Section 5: Nonclinical pharmacology and toxicology*
- ➢ Section 6: Human Pharmacokinetics and bioavailability
- ➢ Section 7: Microbiology
- ➢ Section 8: Safety data
- ➢ Section 9: Statistical data
- ➢ Section 10: Case report tabulation

APPROVAL OF ANDA

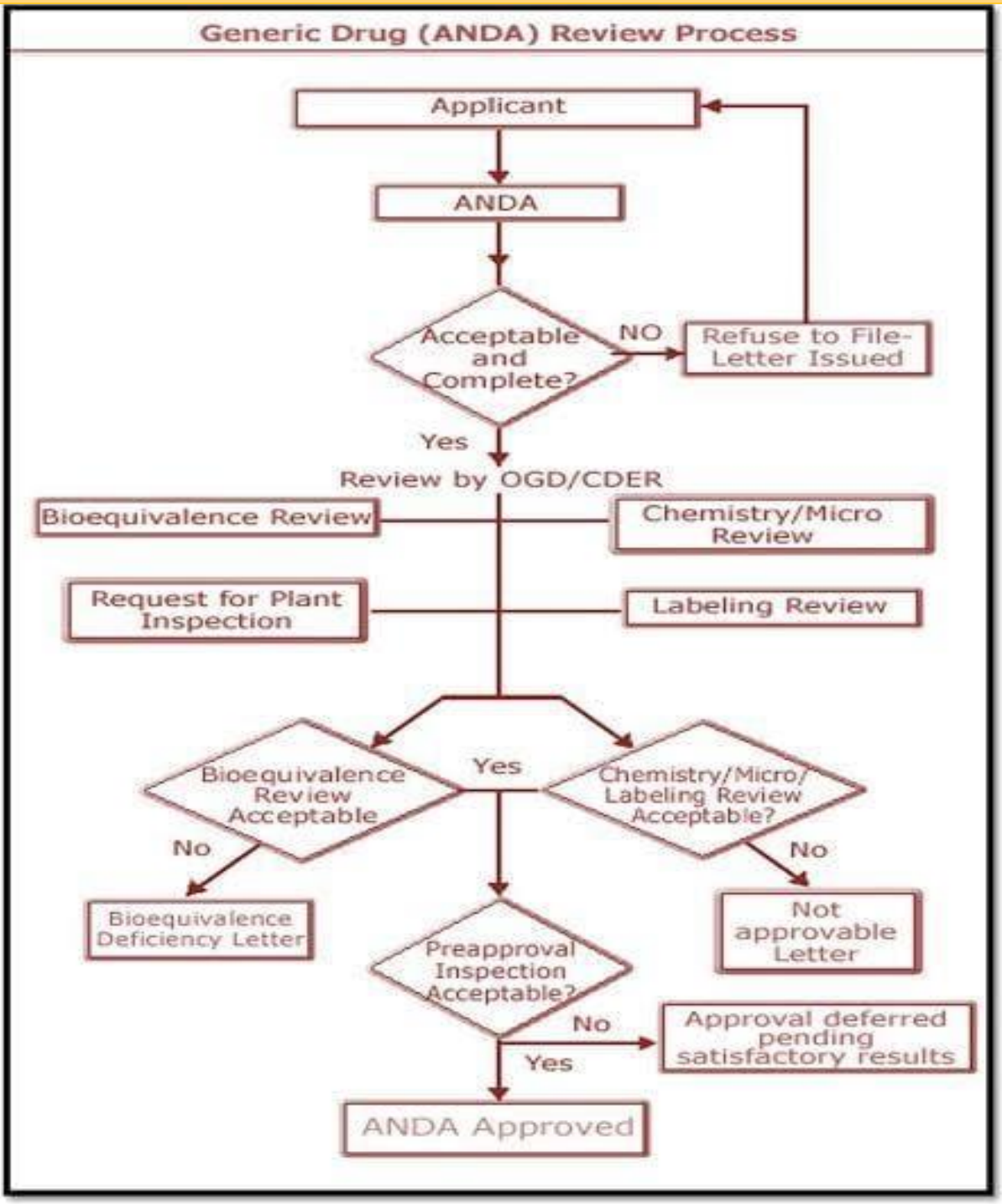
Under section 505(j) Application for ANDA is made to FDA.

2) To determine whether the application is sufficiently complete to permit substantive review a filing review is conducted.

3) Based on the completeness of the Abbreviated New Drug Applicat Acceptance/Refuse to Receive Letter is issued.

4) The OGD of CDER issue market is approved if all the information submitto by the applicant is accepted.

ANDA REVIEW PROCESS



CHANGES TO AN APPROVED NDA / ANDA

This guidance provides recommendations to holders of new drug applications (NDA) and abbreviated new drug application (ANDA) who intend to make post approval change in accordance with section -506A of federal food, drug and cosmetic act.

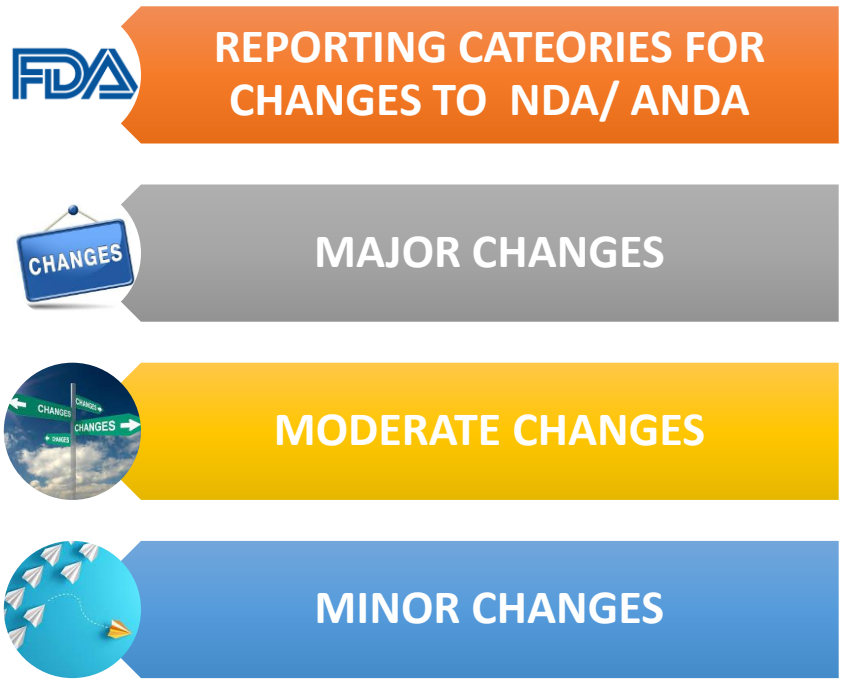
In **November 1999**, FDA issued a guidance document entitled " Changes to an Approved NDA/ ANDA".

In **April 2004**, the agency issues its first revision of the document, which takes the place of the original document (Nov.1999).

These recommendations include post approval changes in:

1. COMPONENTS AND COMPOSITION
2. MANUFACTURING SITES
3. MANUFACTURING PROCESS
4. SPECIFICATIONS
5. CONTAINER CLOSURE SYSTEM
6. LABELLING
7. MISCELLANEOUS CHANGES
8. MULTIPLE RELATED CHANGES

https://www.fda.gov/cder/guidence/index.htm



MAJOR CHANGES

A major change is a change that have an adverse effect on the effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

- ✓ This type of supplement is called **Prior approval supplements**.

MODERATE CHANGES

A move to a different manufacturing site for the manufacture or processing of any drug product, in process material (or) drug substance.

- ✓ 2 types of moderate changes;
- ✓ Moderate Change/supplement changes - Being Effected in 30 days
- ✓ Moderate change / supplement -changes Being Effected.

MINOR CHANGES

- ✓ A move to different manufacturing sites for secondary packaging.
- ✓ A move to different manufacturing site foe labelling.
- ✓ No need to taking approval from FDA.
- ✓ Must be described in the next **Annual Report.**

COMPONENTS AND COMPOSITION

- ✓ Changes in components and composition that may be require a changes being effected supplements (or) an annual report are not addressed in this guidance document
- ✓ Any changes in the quantitative or qualitative formulation including; inactive ingredients, are considered as major changes.
- ✓ Requires submission of PAS.

MANUFACTURING SITES

- ✓ Manufacturing changes to manufacturing site that is different from those specified in the approved applications.
- ✓ Sites can include those used by an applicant to
- ✓ Manufacture (or) process drug products.
- ✓ Packaging drug products.
- ✓ Label drug products.
- ✓ Drug product containers.

✓ Sites include those owned by the applicant (or) contract sites used by an applicant.

MANUFACTURING PROCESS

According to the guidance document, ''The potential for adverse effects on the identity, strength, quality, purity of a drug product as these factors may relate to the safety of the drug product depends on the type of manufacturing process and the changes being instituted for the drug substance''.

In these situations, a change must be submitted to the FDA in a prior approval submission.

SPECIFICATIONS

In the guidance FDA defines specifications as "The quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, In-process materials, container closure systems, and other materials used in production of a drug product''

CONTAINER CLOSURE SYSTEM

The potential that a change in a product's container closure system will have an adverse effect on the identity, strength, quality, purity, potency of a drug's safety.

- ✓ Drug's route of administration, performance of the container closure system and interaction between the packaging component and the dosage form.(2)

LABELLING

A change in a drug's labeling includes changes in one of the following ;

- ✓ Package inserts
- ✓ Package labelling
- ✓ Container label

All promotional labeling and advertising must be promptly revised to be consistent with any labelling changes implemented.

MISCELLENEOUS CHANGES

UNDER MAJOR CHANGES

Addition of a stability protocol or comparability protocol.

UNDER MODERATE CHANGES

Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, of the drug product. Extention of expiry period should be submitted in a changes-being-effected-in-30-days.

UNDER MINOR CHANGES

An extention of expiration date period based on full shelf-life data on production batches obtained under a protocol approved in the application.

MULTIPLE RELATED CHANGES

For multiple related changes involve various combination individual changes. If an applicant has multiple related changes that fall into different recommended reporting categories ‘CDER recommends that the submission be in accordance with the reporting category for the individual changes’.

REGULATORY AUTHORITIES AND AGENCIES

OVER VIEW OF REGULATORY AUTHORITIES OF INDIA

INTRODUCTION

Most of the legislation and regulations on pharmaceuticals are developed and implemented by **the Drug Regulatory Authority(DRA).**

The main task of this agency is to assure the **quality, safety, efficacy** of drugs and the accuracy of product information.

The rules and regulations as well as the guidelines issued for drug development:

- Licensing
- Registration
- Manufacturing
- Marketing
- Labelling

Of pharmaceutical product enforced by the particular regulatory authority of each country. It also ensures the regulation of

- Production
- Import
- Storage and distribution
- Sales and supply of drug.

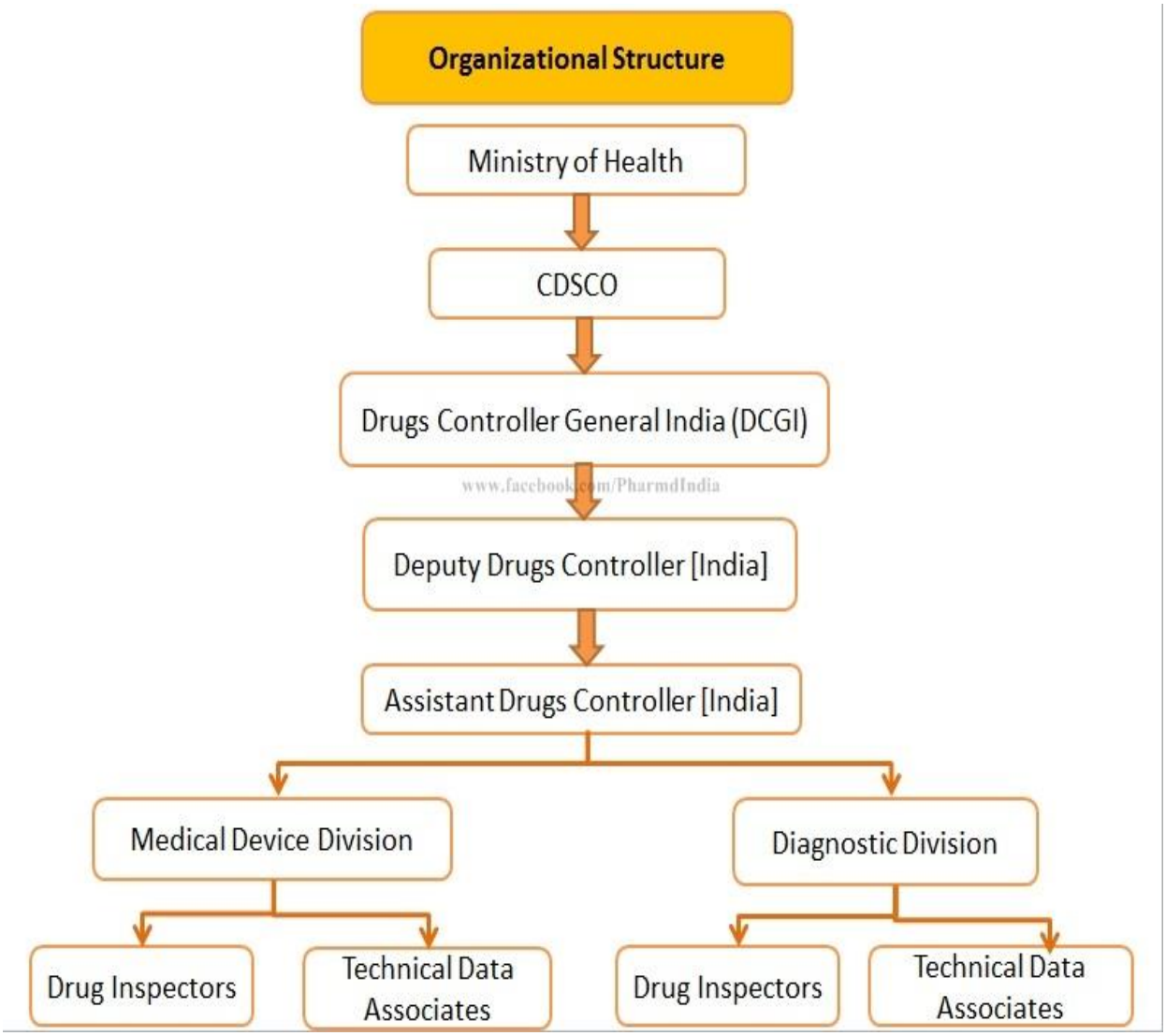
DRUG REGULATORY AGENCIES IN INDIA

INTRODUCTION

INDIA is now amongst the leading market for pharmaceutical products.

The **Drugs and cosmetic Act,1940** was introduced in India for the regulating the import, manufacturing, distribution, and sales of drugs and cosmetics.

Till date in India, a separate regulation for regulating the import, manufacture, distribution, sales of medical devices is not introduced by the government of India.



MAIN BODIES:

1.CENTRAL DRUG STANDARD CONTROL ORGANIZATION [CDSCO]

2.NATIONAL INSTITUTE OF HEALTH AND FAMILY WELFARE [NIHFW]

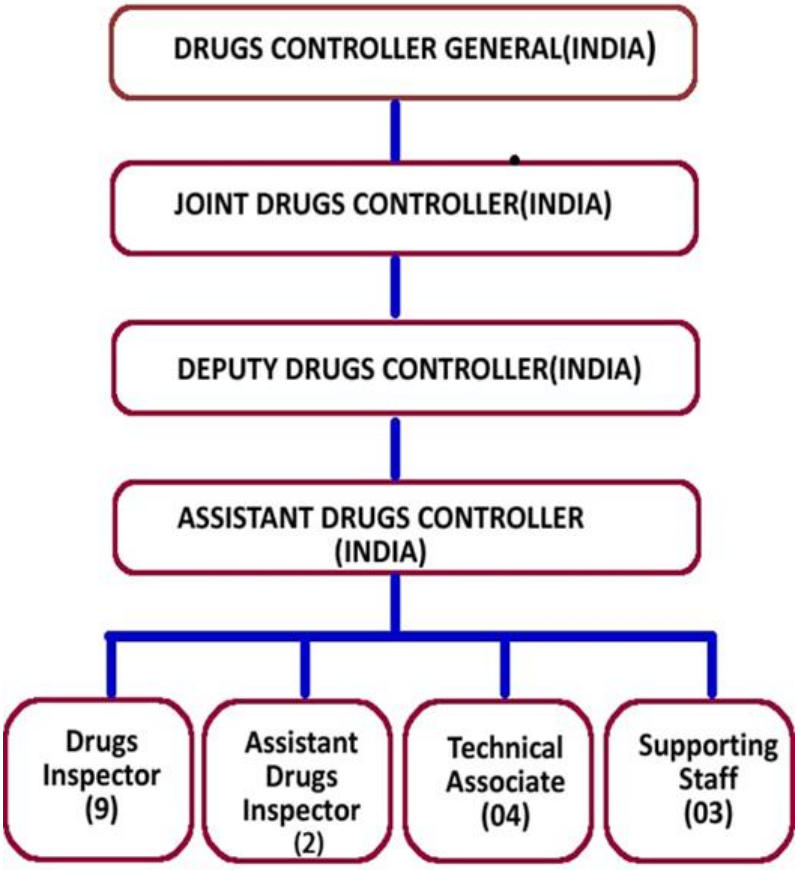
3.DRUG TECHNICAL ADVISORY BOARD {DTAB}

4.CENTRAL DRUG TESTING LABORATORY [CDTL}

CENTRAL DRUG STANDARD CONTROL ORGANIZATION [CDSCO]

- The main regulatory body of India for regulating pharmaceutical, medical devices and clinical trails is the CDSCO.
- Head office of CDSCO is located in new Delhi.

ORGANISATIONAL STRUCTURE:



TYPES OF APPLICATION:

UNDERTAKEN BY THE CENTRAL AUTHORITY:

- ✓ To regulate market authorization of new drugs.
- ✓ To publish Indian pharmacopoeia.

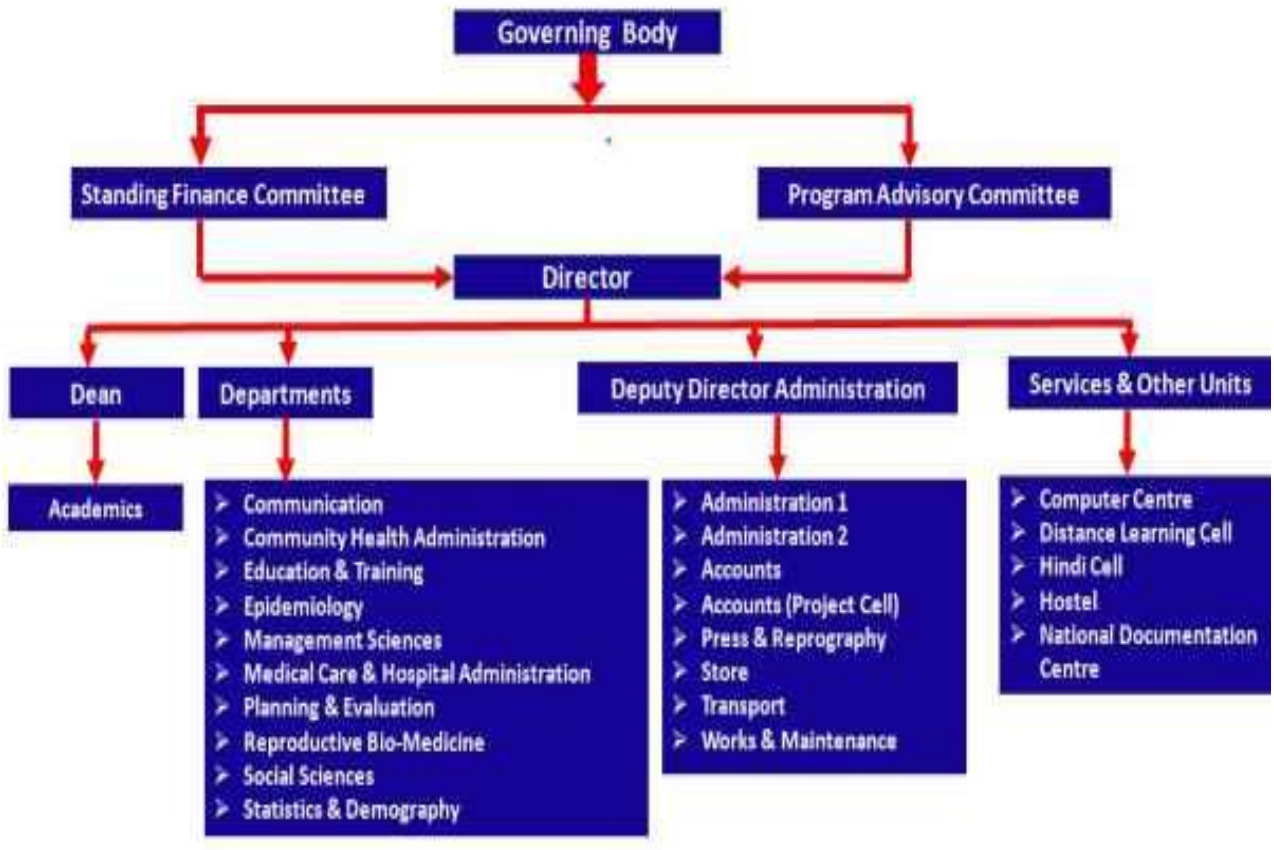
UNDERTAKEN BY THE STATE AUTHORITY:

- ✓ To issue license to drug testing laboratories.
- ✓ For administrative actions.

NATIONAL INSTITUTE OF HEALTH AND FAMILY WELFARE[NIHFW]

On **9 th march,1977,** the national institute of health administration and education [NIHAE] and the national institute of family planning[NIFP] merged together to form **the national institute of health and family welfare [NIHFW].**

❖ ORGANISATIONAL STRUCTURE:



TYPES OF APPLICATIONS:

- ✓ To assess the disease.
- ✓ To test the food material.
- ✓ To release fund on the advice of the ministry.

DRUG TECHNICAL ADVISORY BOARD[DTAB]

DTAB is introduced by the central government for advising the central and state government regarding arise of technical matters from the administration of D&C act,1940.

- **ORGANISATIONAL STRUCTURE:**

➢ **EX-OFFICIO:**

✓ Director general of health services.

✓ Drugs controller, India.

✓ Director of the central drugs laboratory.

✓ Director of the central research institute, kasauli.

➢ **NOMINATED**

✓ 2 persons among persons who are in charge of drugs control in the states.

✓ 1 person from pharmaceutical industry.

✓ 1 persons holding the appointment of government analyst.

➢ **ELECTED**

✓ one person, to he elected by the Executive Committee of the Pharmacy Council of India.

✓ one person, to he elected by the Executive Committee of the Medical Council of India.

✓ one pharmacologist to be elected by the Governing Body of the Indian Council of Medical Research;

✓ one person to to be elected by the Central Council of the Indian Medical Association;

✓ one person to be elected by the Council of the Indian Pharmaceutical Association

➢ **TYPES OF APPLICATION:**

✓ To advise the Central Government, the State Governments and the Drugs Technical Advisory Board regarding any other matter tending to secure uniformity throughout India in the administration of this Act.

✓ To organise meeting of Drugs Consultative Committee whenever required.

✓ To regulate its own procedure.

CENTRAL DRUG TESTING LABARATORY[CDTL]

It is established under the D&C act, 1940. is ensured by the Central Drug Testing Laboratory, Kolkata that is National statutory laboratory of the government of India. It is the oldest quality control laboratory of the drug control authorities in India.

ORGANISATIONAL STRUCTURE:

- ✓ Pharmacopoeia Commission (IPC).
- ✓ General Body 19 Members.
- ✓ Governing Body 10 Members.
- ✓ Scientific Body 23 Experts.
- ✓ CIPL Lab IPC Secretariat Indian Pharmacopoeia was prepared by Indian Pharmacopoeia Commission (IPC).

TYPES OF APPLICATIONS:

- ✓ To perform analytical Q.C of the imported samples.
- ✓ To maintain the microbial cultures.
- ✓ To collect, store and distribute the internal standards.

OVER VIEW OF REGULATORY AUTHORITIES OF UNITED STATES: (FDA)

NATIONAL AUTHORITY:

- The Food and Drug Administration (FDA) a federal agency of the United States Department of Health and Human Services, one of the United States federal executive departments
- The FDA is responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and over the counter pharmaceutical drugs, vaccines, biopharmaceutical, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED) cosmetics, animal food and feed and veterinary products
- The FDA is led by the Commissioner of Food and Drugs, appointed by the President with the advice and consent of the Senate. The FDA has its headquarters in unincorporated Wh Oak, Maryland. The agency also has 223 field offices and 13 laboratories located throughout the 50 states, the United Stat Virgin Islands and Puerto Rico.
- The Food and Drug Administration (FDA) was established in 1906 U.S. Department of Health and Human Services in the regard with the F Food and Drugs Act. The Center for Drug Evaluation and Research (CDE part of the U.S. Food and Drug Administration (FDA) that observes most drugs that comes under Food, Drug, and Cosmetic Act. FDA approval begins once the Investigational New Drug (IND) application has been submitted
- The agency is divided into different parts to administer the obligations of m the organisations regarding food, drugs, cosmetics, animal food, supplements, medical devices, biological goods, and blood products.
- It composed of six product centres, one research centre, and two offices. The Commision of Food and Drugs, who is appointed by the President and confirmed Senate is responsible for its regulation
- The FDA is Department of Agency Dwithin the Us. Afealth and Human Services. centre One2 g+ Consista product Centred, and fro offices. Mesearch Centre, andFDA is Responsible four Exfell to 50 United States
- The USFINA has its Headquapar at white Oak, Maryland. The USFDA was State congres to Carmefie & V Empowered by Enforce the Act, USFDA
- TheFood and Drug Administration (FDA) National Institutes of Health (NIH) Centres for Disease Control and Prevention Department of Health and Human Services (DHHS) FedWorld US Government Information National Centre for Complementary and

AlternativeMedicine (NCCAM) National Centre for Infectious Diseases (NCID) National Library of Medicine National Science Foundation Office of Disease Prevention.

- The Food and Drug Administration (FDA) is an agency within the U.S. Department of Healthand Human Services. It consists of six product centers, one research centre, and twe offices.
- FDA's responsibilities extend to the 50 United States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, American Samoa, and other U.S. territories and possessions.

FDA HAS FOUR ROLES

1) To promote health by reviewing research and approving new products.

2) To ensure the safety and proper labeling of foods and drugs.

3) To work with other nations for reducing the burden of regulation.

4) To cooperate with scientific experts and consumers to effectively carry out these obligations. The FDA is led by the Commissioner of Food and Drugs, who is appointed by the Presidentand confirmed by the Senate

ORGANISATIONAL STRUCTURE

1) The Office of the Commissioner (OC).

2) The Centre for Drug Evaluation and Research (CDER).

3) The Centre for Biologics Evaluation and Research (CBER).

4) The Centre for Food Safety and Applied Nutrition (CFSAN).

5) The Centre for Devices and Radiological Health (CDRH).

6) The Centre for Veterinary Medicine. (CVM).

7) The National Centre for Toxicological Research (NCTR).

8) The Office of Regulatory Affairs (ORA)

RESPONSIBILITIES

Food and Drug Modernisation Act states that the Fog ne following role

1. To promote health by reviewing research and approving new products
2. To ensure the safety and proper labelling of the foods and drugs.

3. To work with other nations for reducing the burden of the regulation.
4. To cooperate with scientific experts and consumers for carrying out the obligations effectively.
5. To ensure the safety and efficacy of the medicines and medical devices
6. To ensure safety of the Cosmetic products,
7. To ensure the safety of animal foods and drugs.

It also contributes in the safety regulation of the following:

- Most types of foods
- Drugs
- Vaccines
- Blood products Medical devices
- Dietary supplements
- Biological medical products
- Radiation-emitting devices
- Veterinary products

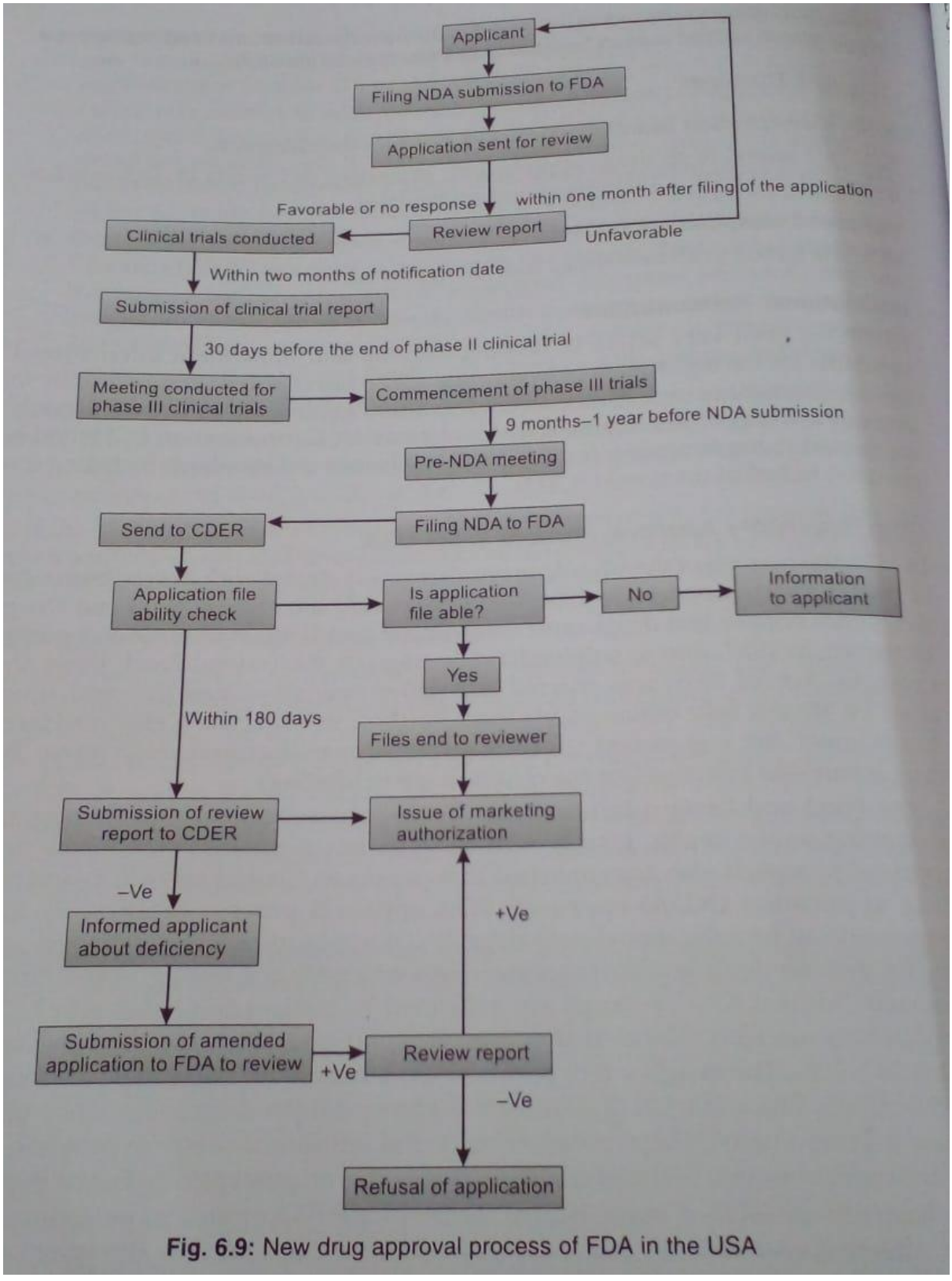


Fig. 6.9: New drug approval process of FDA in the USA

TYPES OF APPLICATIONS

1) Investigational New Drugs Application (IND): To test a new drig or biologic in human, an organisation should firstly seek permission submitting this IND application to the FDA.

2) New Drug Application (NDA): The sponsor submits a New Dr Application to FDA, once he/she is confirmed that evidence colle regarding safety and efficacy of the new drug are enough to meet FD requirements for marketing approval.

3) Abbreviated New Drug Application (ANDA): It includes data which submitted to FDA's Centre for Drug Evaluation and Research. Then office of Generic Drugs provides the review and ultimate approval in generic drug product.

Usually, Generic drug applications do not requires preclinical and cin data to establish its safety and efficacy, therefore they are also know "abbreviated".

4) Biologic License Application (BLA): A biologics license applicationincludes the submission of specific information regarding the manufac processes, chemistry pharmacology, clinical pharmacology and the me effects of the biologic product

(NDA) APPROVAL.

FDA approval process begins only after ission of investigational new drug (IND) application. The IND application Beeld provide high quality preclinical data to justify the testing of the drug in mans. Almost 85% of drugs are subjected to clinical trials, for which IND plications are filed. The next step is phase I clinical trials (1-3 years) on human cts (-100). The drug's safety profile and pharmacokinetics of drug are focused this phase. Phase II trials (2 years) are performed if the drug successfully passes phase 1. To evaluate dosage, broad efficacy and additional safety in people (0E -) the main objective of the phase II. If evidence of effectiveness is shown in phase 1 phase III studies (3-4 years) begins. These phase III concerns more about safety and effectiveness of drug from data of different populations, dosages and itcombination with other drugs in several hundred to about 3,000 peoples.

A new drug application (NDA) can be filed only when the drug successfully

passes all three phases of clinical trials and includes all animal and human data,data analyses, pharmacokinetics of drug and its manufacturinglabeling

. The preclinical, clinical reports and risk-benefit and proposes beneficial effects outweigh its possible harmful effects) are reviewed at the centerfor drug evaluation and research by a team of scientists.

Generally approval ofan NDA is granted within two years (on an average), however, this be completed from two months to several years.

The innovating company is allowed to market the drug after the approval of an NDA and is considered to be in phase IV trials.

In this phase, new areas, uses or new populations, long-termeffects, and how participants respond to different dosages are explored.

AGENCIES:

Pesticides (FDA, the US. Department of Agriculture, and the Environmental Protection

Agency regulate these).

Water (FDA regulates the labeling and safety of bottled water, while the Environmental Protection Agency develops national standards for drinking water from municipal water supplies).

FDA INSPECTION

FDA inspects manufacturers or processors of FDA-regulated products to verify that they comply with relevant regulations.

Inspection includes:

Vaccine and drug manufacturers.

Blood banks.

Food processing facilities dairy farms animal feed processors. Facilities that conduct studies in people (clinical trials).

Laboratories that conduct studies in animals or microorganisms when these studies are used to apply for FDA approval of amedical product Foreign manufacturing and processing sites for FDA-regulated products that are sold inthe United States. Imported products atthe border. * FDA conducts several types of inspections to helpprotect consumers from unsafe

Routine inspection of a regulated facility products.

Pre-approval inspection after a company submit the same application to FDA to market a new product.

For-cause inspection to investigate a specific problem that has come to FDA'S attention.FDA makes available to the public certain frequently requested records of inspections in anelectronic reading room.

Review of FDA inspectional guides

1. Investigations Operations Manual (IOM)

2. Compliance Program Guidance Manuals (CPGM)

3. Compliance Policy Guides (CPG)

Inspection Technical Guides Review of firm's Establishment Inspection Report (EIR)

Responses to FDA Form 483 etc.

4. Planning of inspections

Forms Commonly Used During FDA Inspections

fDA Form 482: Notice of inspection.

FDA Form 483: Inspectional observations.

FDA Form 484: Receipt for physical evidence (e.g., samples), but not for documentary evidence (e.g., label, copyof records).

OVERVIEW OF REGULATORY AUTHOTITIES OF EUROPEAN UNION

INTRODUCTION

The European medicines regulatory system is based on a network of around 50 regulatory authorities from the 31 EEA countries, the European Commission and EMA.

This network is what makes the EU regulatory system unique.

The network is supported by a pool of thousands of experts drawn from across Europe, allowing it to source the best possible scientific expertise for the regulation of medicines in the EU and to provide scientific advice of the highest quality.

EMA was established in 1995 and from 1995to 2004 it was known as European agency for the evaluation of medicinal product. The European Medicines Agency (EMA) is a decentralised body of the European Union, located in London Mission.

It also contributes to foster scientific excellence in evaluation and supervision of medicines. The European Medicines Agency (EMA) responsible for the scientific evaluation, supervision and safety observation is of medicines in the EU. An independent Management Board governs the EMA. The regular functioning of EMA are carried out by the EMA staff and supervised by EMA's Executive Director.

EMA is a networking organisation whose functioning involves thousands of experts all over the Europe. These experts contribute in the working of EMA's scientific committees.

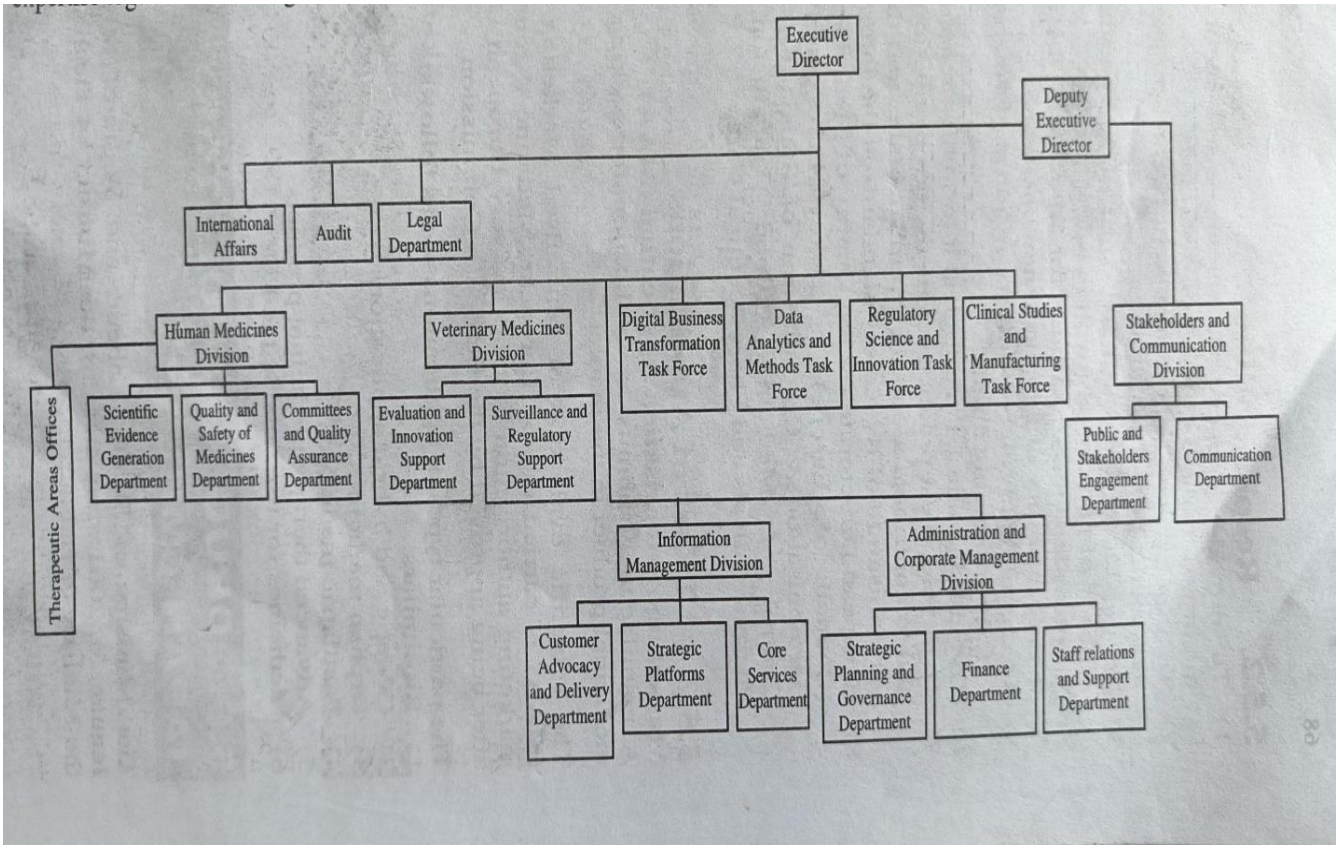
EMA is a networking organisation whose functioning involves thousands of experts all over the Europe. These experts contribute in the Working of EMA's scientific committees.

ORGANISATIONAL STRUCTURE

The EDQM (EUROPEAN DIRECTORATE FOR QUALITY MEDICINES)is an organisation that protects public health by enabling the development, supporting the implementation and monitoring the application of quality standards for medicines and their safe use. The EDQM traces its origins and statutes to a European treaty promoting the elaboration of a common pharmacopoeia in Europe. mission: to contribute to a basic human right; access to good quality medicines and healthcare.

To deliver high quality outputs for public and animal health, EMA implemented the changes in its organisational structure on 2 March 2020, for assuring that it functions as efficiently as possible. The main changes made in its organisational structure are as follows:

1) The operations are integrated in the area of humanMedicines into one human medicines division.
2) Four mission-critical task forces are established to support the human as well as veterinar medicines divisions and also to bring the expertise together for driving transformational change in high-priority areas.



RESPONSIBILITIES

1) To provide independent, science-based recommendations based on the quality, safety and efficacy of medicines.
2) To apply efficient and transparent evaluation procedures for helping in bringNew medicines in the market.
3) To implement measures for constantly supervising the quality, safety and efficacy of authorised medicines.
4) To provide scientific advice for stimulating the development and improving the accessibility of advanced new medicines.

5) To recommend safety limits for residues of veterinary medicines administeredTo food-producing animals.

6) To publish unbiased and logical information regarding medicines and its uses.

7) To develop best practice for medicines evaluation and supervision in Europe, and to contribute along the Member States and the European Commission in harmonisation of regulatory standards at the international level.

8) European Directorate for the Quality of Medicines & Health Care the EDQM (Council of Europe) is a key European Organisation involved in Harmonisation & Co-ordination of Standardisation, Regulation & Quality Control of Medicines, Blood Transfusion, Organ Transplantation,Pharmaceuticals and Pharmaceutical Care.

TYPES OF APPLICATIONS

Marketing Authorisation Application (MAA):

A manufacturer submits an application for seeking permission before bring a medicinal product in the market.The scientific evaluation of centralised Marketing Authorisation Application (MAA) is carried out by European Medicine Agency (EMA).

The centralised marketing authorisation is valid in every European Union (EU) Member States, after being approved by the European Commission.

The particular types of applications are as follows:

1) Biosimilars.
2) Generic and hybrid applications.

3) Orphan medicines.
4) Paediatric medicines.
5) Advanced therapy medicinal products.
6) Medicines for use outside the EU.
7) Marketing authorisation guidance documents
8) Compliance: marketing authorisation
9) Clinical data publication
10) Data on medicines (ISO IDMP standards): marketing authorisation
11) Fees payable to the European Medicines Agency
12) The evaluation of medicines, step-by-step

OVER VIEW OF REGULATORY AUTHORITIES OF AUSTRALIA

INTRODUCTION

- The Therapeutic Goods Administration (TGA) is a part of the Australian Government Department of Health and Ageing.
- The TGA monitor the activities of companies to ensure therapeutic goods available in Australia are of an acceptable standard.
- The Australian Community expects that medicines and medical devices in the marketplace are safe and of high quality and have equal standard in comparison of other countries.
- The TGA under regulatory framework works according to the approach of managing risk. It is designed to guarantee public health and safety.
- It also provides benefits to both consumers and industry.
- The TGA has developed a constructive partnership with industry at the similar time to free the industry from unnecessary regulatory burden, for undertaking its responsibility and minimising the cost of medicines.

Therapeutic Goods Act 1989

- Therapeutic Goods Act 1989 is a Commonwealth Act that is implemented to provide a national framework for the regulation of therapeutic goods in Australia to ensure the Quality, Safety and Efficacy of medicines and medical devices.
- A uniform national system of controls over therapeutic goods is provided by this Act.
- It also facilitates the trade between the states/territories and provides the benefits to both consumers and industry.
- The legal requirements for importing, exporting, and supplying of medicines in Australia are set by this act.
- Before the Australia essential therapeutic goods are supplied, they must be recorded in the Australian Register of Therapeutic Goods (ARTG).
- The ARTG is a computer database records containing the information about therapeutic goods approved for supply within the country or exported from Australia.
- It also contains the requirements for listing or registering medicines in the Australian Register of Therapeutic Goods.

OBJECTIVES OF THERAPEUTIC GOODS ADMINISTRATION

- To provide a national framework for the regulation of therapeutic goods in Australia to ensure the quality, safety and efficacy of medicines and ensure the quality, safety and performance of medical devices
- Essentially therapeutic goods must be entered on the Australian Register of Therapeutic Goods (ARTG) before they can be supplied in Australia.

ROLE OF THERAPEUTIC GOODS ADMINISTRATION

- The TGA carries out an overall control through five main processes
- Pre-market evaluation and approval of registered products intended for supply in Australia;
- Development, maintenance and monitoring of the systems for listing of medicines;
- Licensing of manufacturers in accordance with international standards of GMPs
- Post-market monitoring, through sampling, adverse event reporting, surveillance activities, and response to public inquiries.

ORGANISATIONAL STRUCTURE

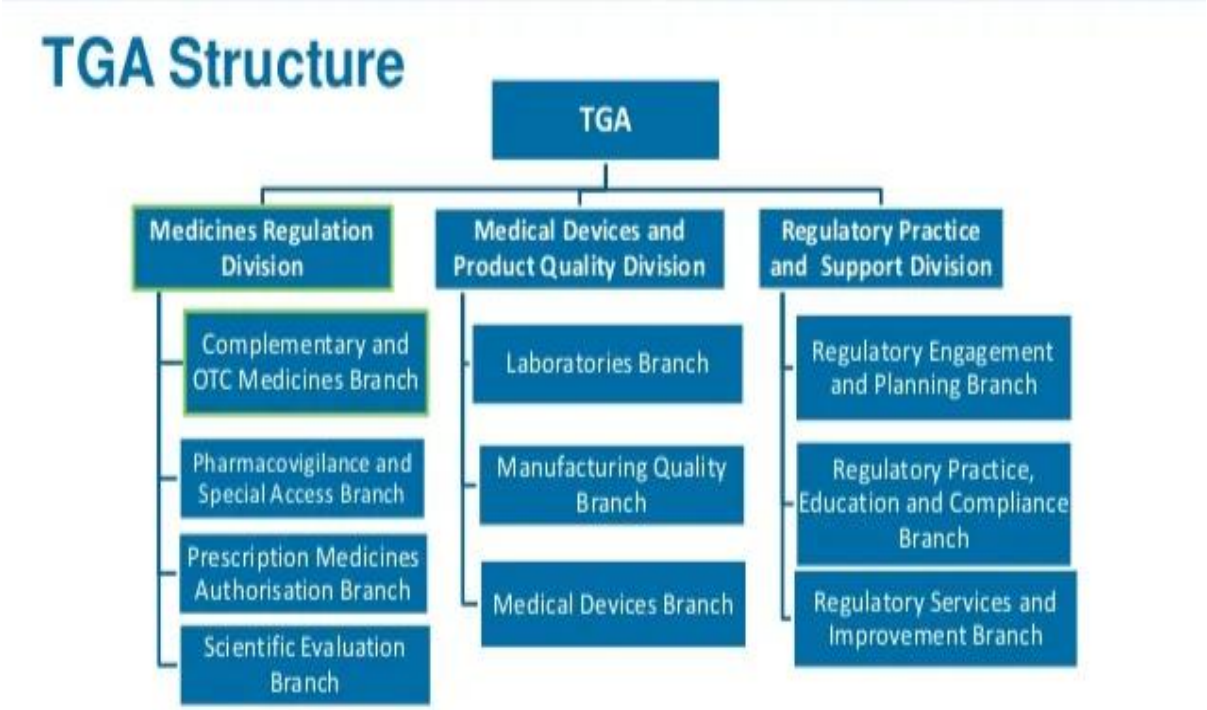
The therapeutic goods administration offices are classified into following groups:

1. Market Authorisation Group

2.Monitoring And Compliance Group

3.Regulatory Support Group

ORGANISATION STRUCTURE OF THERAPEUTIC GOODS ADMINISTRATION



REGULATION OF CLINICAL TRIALS BY THERAPEUTIC GOODS ADMINISTRATION

Clinical trials of medicines and medical devices conducted in Australia are subject to Commonwealth Government regulation administered by the Therapeutic Goods Administration (TGA).

There are two schemes to conduct clinical trials

A. Clinical Trial Exemption (CTX) Scheme: Trial sponsor notifies the TGA of their intention to conduct a clinical trial using an unapproved therapeutic good.

B. Clinical Trial Notification (CTN) Scheme: The TGA does not review any data relating to the clinical trial. The CTN Form is submitted by the investigator on behalf of the sponsor to the HREC and to the Approving Authority[3. Once the sponsor, the principal investigator, the Chairman of the HREC and the person responsible from the Approving Authority have signed the CTN Form, it is submitted by the sponsor of the trial to the TGA along with the appropriate notification fee.

REGULATORY GUIDELINES FOR DRUGS

As per therapeutic goods administration act regulations all types of goods are divided into medicines and devices. Medicines are again divided into three types

1.Prescription medicines

2.Non prescription medicines

3.Export only medicines

Prescription medicines (PM):

- High-risk medicines
- Ingredients described in Standard for the Uniform Sch of Drugs and Poisons (SUSDP) and are available by prescription only.
- The Drug Safety Evaluation Board (DSEB) evaluates the majority of prescription medicine applications. Ex: insulin for diabetics.
- Must be registered in TGA.

Non-prescription medicines (NPM)

Classified in to two categories that are,

A. OTC Medicines-The Non-prescription Medicines Branch (NPMB) is responsible for evaluating OTC medicines.

B. Complementary medicines-One or more designated active ingredients, each of which has a clearly established identity and for traditional use.

The Office of Complementary Medicines (OCM) is responsible for the evaluation of complementary medicines at the TGA

Export only medicines:

Products containing substances, quantities of substances or labels without mandatory warning statements required for listing for supply in Australia which would require registration for domestic supply will be assessed under Section 26 of the Act.

Ex:

1. Commercial export of medicines.

2. Export of medicines for donation or humanitarian purposes.

3. Export of human body fluids/ tissue.

4. Export of medical devices.

RESPONSIBILITES OF THERAPEUTIC GOODS ADMINISTRATION[TGA]

The TGA carries out an overall control through following five processes.

1. It evaluates the pre-market product and approves the registered products planned to be supplied in Australia.
2. It develops maintain and monitors the systems for listing of medicines
3. It issue licence to the manufacturers according to the international standards of good manufacturing practices
4. It performs post market monitoring with the help of sampling adverse event reporting surveillance activities and response to public inquires
5. It assesses the medicines for export.

TYPES OF APPLICATIONS

1.Investional Drug: Investigational New Drug [IND]

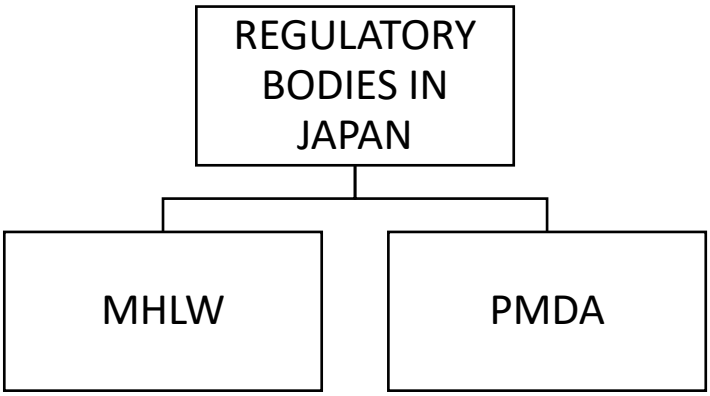
2.New Drugs: New Drug Applications [NDA]

3.Generic Drugs: Generic Drug App.

OVERVIEW OF REGULATORY AUTHORITIES OF JAPAN

INTRODUCTION

- PMDA (Pharmaceuticals and Medical Devices Agency) is Japanese regulatory agency, working together with Ministry of Health, Labour and Welfare.
- Its obligation is to protect the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices.
- It conduct scientific reviews of marketing authorization application of pharmaceuticals and medical devices, monitoring of their post-marketing safety and also responsible for providing relief compensation for sufferers from adverse drug reaction and infections by pharmaceuticals or biological products.



The Ministry of Health, Labour and welfare(MHL)

The Ministry of Health, Labour and Welfare (MHLW) is the governmental authority that

1.Issues almost all related ministerial orders

2.Administrative guidelines

3. Prepares relevant cabinet orders.

MHLW ⟹ Medicinal products

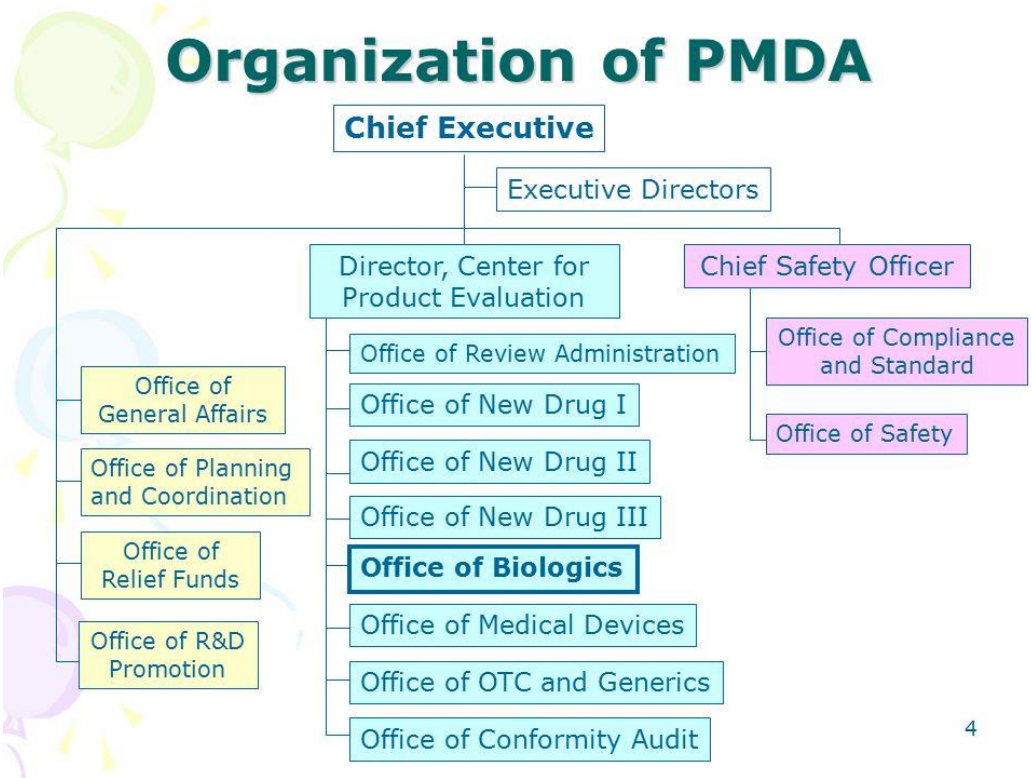
Role of MHLW

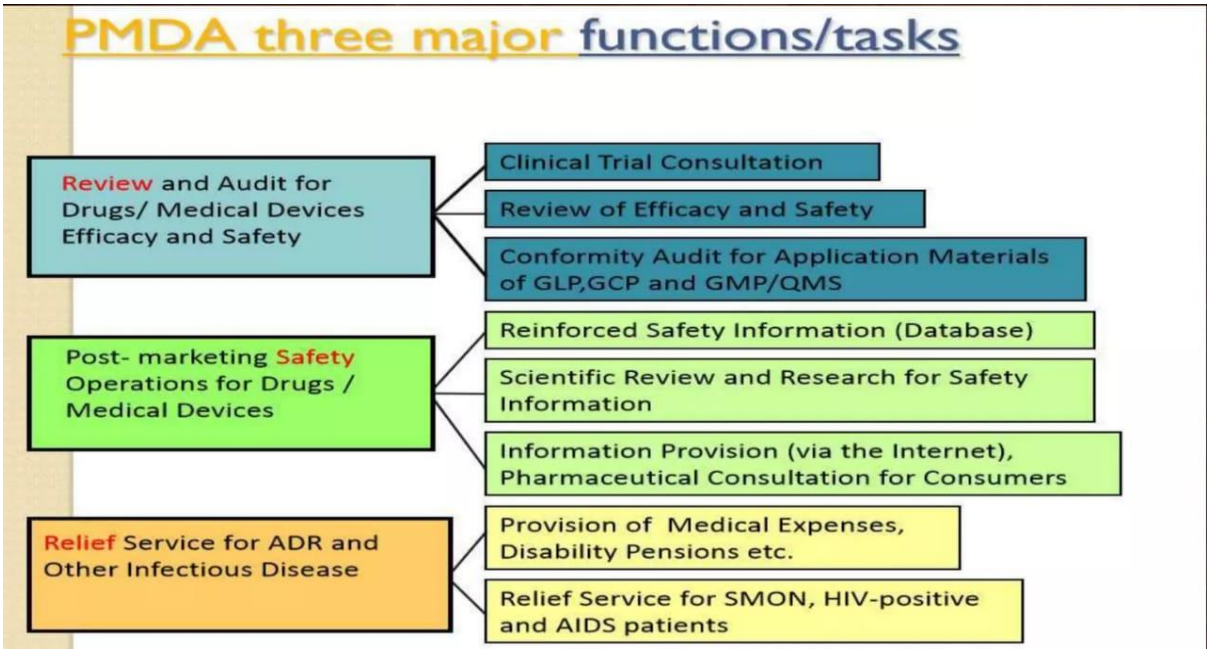
Also known as koro-sho in Japan

- Provides regulations
- In-charge of pharmaceuticals, veterinary and food safety products.
- Handles clinical studies, approval reviews and post marketing safety measure.

The Pharmaceuticals and Medical Devices Agency (PMDA)

- The main regulatory body of PMDA located in Kasumigaseki, Chiyodaku Tokyo.
- PMDA (Pharmaceuticals and Medical Devices Agency) is Japanese regulatory agency, working together with Ministry of Health, Labour and Welfare.
- Its obligation is to protect the public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices.
- It conduct scientific reviews of marketing authorization application of pharmaceuticals and medical devices, monitoring of their post-marketing safety.
- Also responsible for providing relief compensation for sufferers from adverse drug reaction and infections by pharmaceuticals or biological products.





Japan Regulatory Approval Process for Medical Devices

- Submission is preferred to be in STED.
- Pre-market submission (Todokede)
- Pre-market certification (Ninsho)
- Pre-market approval (Shonin)

MEDICAL DEVICE CLASSIFICATION

► **Class I** - General medical devices

► **Class II** - Specified Controlled medical devices

► **Class II** - Controlled medical devices

► **Class III** - Highly Controlled medical devices

► **Class IV** - Highly Controlled medical devices

- EX-x-ray film,steel, surgical,instrument in vitro diagnostics

- MRI units electronic sphygmomano meters, electronic endoscopes, ultrasonograph, equipment dental alloys

class 3

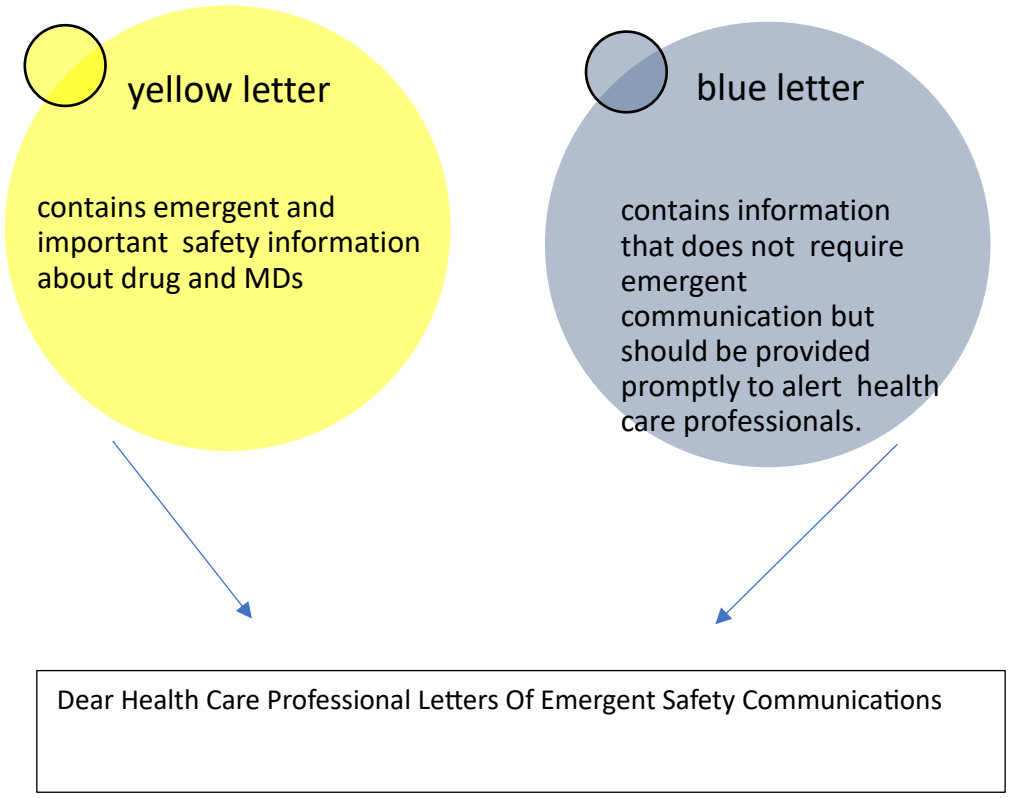
- hemodialysis, equipment, artificial bones and joints, mechanical, ventilation apparatus, ballon, catheters

class 4

- pacemakers, artificial cardiac valves, stents

RECALL

when a drugs or medical devices learn that the use of drugs or medical device that they have marketed might cause onset or spread of hazards to public health or hygiene, necessary measures shall be taken, including recall, suspension of sales, and information provision to prevent such hazards.



RESPONSIBILITIES:-

- Public Hygiene: To provide appropriate medical services for diseases & injuries assuring the safety of food, water and medical supplies. Research related to the health science in order to introduce advanced technologies for maternal and child health.
- Job Security: To provide promotion in service, employment to the elderly people and disabled people and also the management of employment insurance system should be done.
- Human Resources Development: To advance the human resources development that brings the changes in the industrial system. Encourage the initiative taken by the workers to develop their skills by their own and to develop the skilled human resources that contributes in industrial progress

APPLICATIONS:-

- Investigational New Drug Application (INDA).
- New Drug Application (NDA).
- Abbreviated New Drug Application (ANDA).

OVERVIEW OF REGULATORY AUTHORITIES OF CANADA

REGULATORY PROCESS FOR DRUG IN CANADA

The exhibit shows the steps in the regulatory process for drugs in Canada, from pre-market to post-market. The pre-market part of the process starts with pre- clinical studies. The steps are

Pre-clinical studies

Clinical trials

Regulatory product submission

Submission review

Market authorization decision

Public access

Surveillance, inspection, and investigation

The post-market part of the process begins with surveillance, inspection, and investigation when a drug has been made accessible to the public.

OVERVIEW

Canada is the second largest pharmaceutical market in North America. The Health Canada is the federal Regulatory body which is responsible to ensure the safe and effective use of drugs and health products in Canada. Strict Regulatory regime of different bodies for Food and Veterinary, Pharma and Biological drugs, makes it challenging for foreign manufacturers to enter the region. Those Regulatory bodies include:

- Health Canada's Health Products and Food Branch (HPFB) – for Food, Health and Veterinary
- Therapeutic Product Directorate (TPD) – for Pharmaceuticals and Medical Devices
- Biologics and Genetic Therapies Directorate (BGTD) – for Biological and Radiopharmaceutical drugs

Additionally, renewed guidance for Bioequivalence study for a reference listed drug (RLD) procured from countries other than Canada have made it complicated to gain approval.

To navigate new market entrants, Freyr provides comprehensive Regulatory assistance encompassing product development, review of executed data, gap analysis, dossier compilation, review of submission packages and submission of Drug Identification Number (DIN) applications, along with post-approval changes and life cycle management for various pharmaceutical products adhering to Regulatory standards. In addition, Freyr also provides qualitative and strategic support to respond to the Health Authority queries during the review process.

SUBMISSION TYPE AND THEIR DESCRIPTION

Cosmetic

All cosmetics sold in Canada must be safe to use and must not pose any health risk. They must meet the requirements of the Food and Drugs Act and the Cosmetic Regulations. Under the Food and Drugs Act, a cosmetic includes "any substance or mixture of substances, manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth and includes deodorants and perfumes." This includes cosmetics used by professional esthetic services, bulk institutional products (such as hand soap in school rest rooms), as well as "handmade" cosmetics sold at craft sales or home- based businesses.

The Cosmetic Regulations and the Food and Drugs Act require that cosmetics sold in Canada be manufactured, prepared, preserved, packed and stored under sanitary conditions. The manufacturer and importer must notify Health Canada that it is selling the product and provide a list of the product's ingredients.

DEFINITIONS

1. Cosmetic (Section 2 Of The Food And Drugs Act)

Any substance or mixture of substances manufactured, sold or represented for use in cleaning, improving or altering the complexion, skin, hair or teeth, and includes deodorants and perfumes.

2. Drug (Section 2 Of The Food And Drugs Act)

Includes any substance or mixture of substances manufactured, sold or represented for use in

a) The diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,

b) Restoring, correcting or modifying organic functions in human beings or animals, or

c) Disinfection in premises in which food is manufactured, prepared or kept;

3. Natural Health Product (Section 1 Of The Natural Health Products

Regulations Pursuant to the Food and Drugs Act)

A subset of drugs pertaining to medicinal ingredients of natural origin, defined in the Natural Health Products Regulations as "a substance set out in Schedule 1 or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1, a homeopathic medicine or a traditional medicine, that is manufactured, sold or represented for use in

a) The diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;

(b) Restoring or correcting organic functions in humans; or

(c) Modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

4. Personal Care Product (PCP):

For the purposes of this document, defined as a substance or mixture of substances which is generally recognized by the public for use in daily cleansing or grooming. Personal care products may fall into one of three regulatory categories in Canada: cosmetics, drugs or natural health products.

5. Product At The Cosmetic-Drug Interface (PCDI):

A subset of personal care products, which are not easily distinguished as either a drug or cosmetic, as defined in the Food and Drugs Act.

Information on label

❖ This guide covers three aspects of information appearing on the labels of cosmetic products:

❖ The classification of cosmetic products (see section 3).

❖ Required declarations that must appear on a label. These include:

❖ Product identity (see section 4),

❖ Net quantity (see section 5),

❖ Name and address of the manufacturer (see definition) (see section 6),

❖ Avoidable hazards and cautions (see section 7), and

❖ Ingredients (see section 8).

❖ Sources of additional information concerning labelling requirements

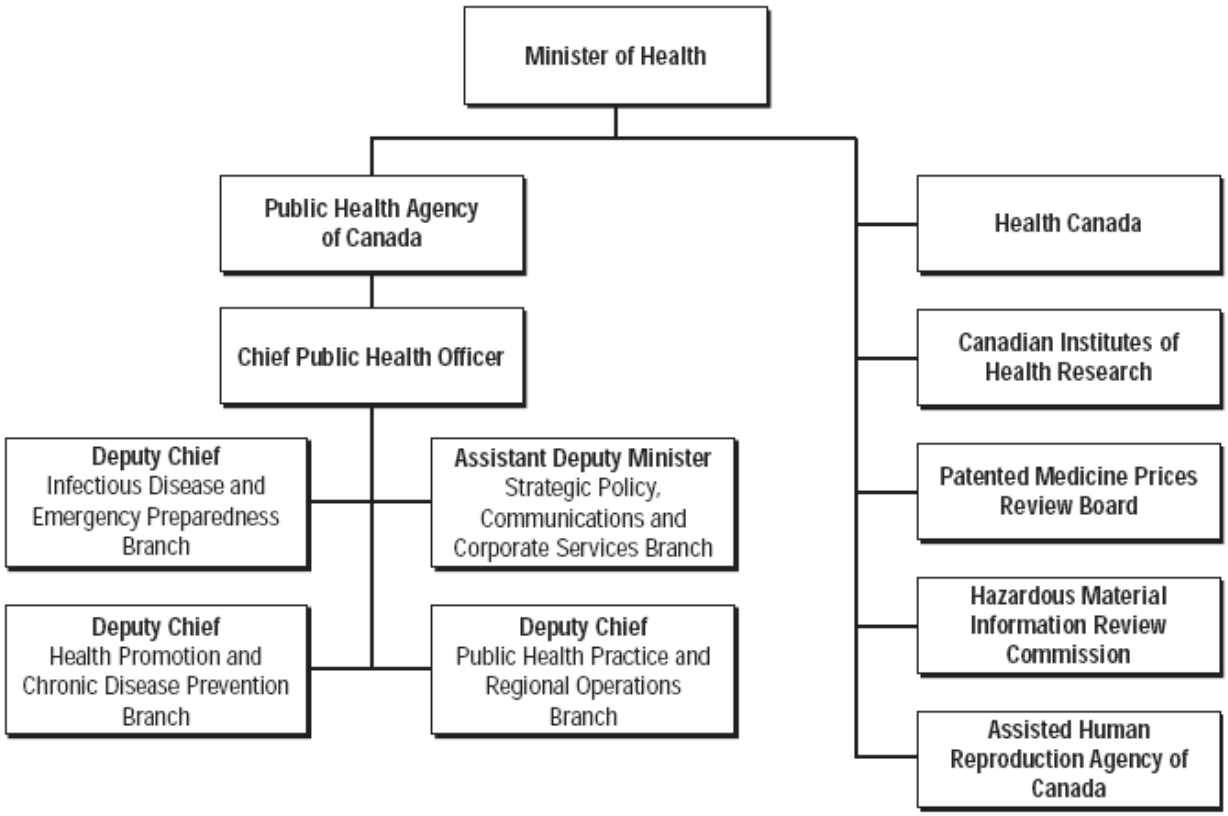
Natural health products

Natural health products (NHPs) are naturally occurring substances that are used to restore or maintain good health. They are often made from plants, but can also be made from animals, microorganisms and marine sources. They come in a wide variety of forms like tablets, capsules, tinctures, solutions, creams, ointments and drops.

Natural health products, often called “complementary” or “alternative” medicines, include:

vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines like traditional Chinese and Ayurvedic (East Indian) medicines, Probiotics, other products like amino acids and essential fatty acids.

ORGANISATIONAL STRUCTURE



TYPES OF APPLICATIONS:-

New Drugs

1) NDS (New Drug Submission**)**

2) SNDS(Supplemental New Drug Submissio)

1) NDS

Health Canada's New Drug Submission (NDS) is the process through which new drugs are approved and controlled by the Canadian Health Authority before entering the Canadian market. In Canada, new drugs are regulated under Part C, Division 8 of Food and Drugs Regulations.

2) SNDS

Health Canada's New Drug Submission (NDS) is the process through which new drugs are approved and controlled by the Canadian Health Authority before entering the Canadian market. In Canada, new drugs are regulated under Part C, Division 8 of Food and Drugs Regulations**.**

Generic Drugs

1) ANDS(Abbreviated New Drug Submission)

2) SANDS(Supplemental Abbreviated New Drug Submission)

1) ANDS:-

An Abbreviated New Drug Submission is used to obtain approval for generic drugs. This is in contrast to a New Drug Submission (NDS), which is used to obtain approval for a new brand name drug. An ANDS lists the related drug's brand name, chemical name, manufacturer name, dosage form(s), and strength(s). It states whether the drug has already been approved for marketing in the United States, the European Union, Switzerland, Singapore, and/or Australia. It also addresses questions about drug impurities and drug stability.

2) SANDS:-

SANDS (Supplement to Abbreviated New Drug Submission) and SNDS (Supplement to a New Drug Submission) are types of submission towards Health Canada which stand as important resources to ANDS (Abbreviated New Drug Submission) and NDS (New Drug Submission).

Unit III Registration of Indian drug product in overseas market

Procedure for export of pharmaceutical products, Technical documentation, Drug Master Files (DMF), Common Technical Document (CTD), electronic Common Technical Document (eCTD), ASEAN Common Technical Document (ACTD)research.

Registration of Indian Drug Products in overseas market for export of Pharmaceutical Products

Introduction:

1. Indian Pharmaceutical Market:

The Indian Pharmaceutical industry has acquired a noteworthy position in the global pharmacy sector and has been achieving significant growth in recent years. India is among the top six global pharmaceutical producers in the world. Presently there are 10,500 manufacturing units and over 3,000 pharmacy companies in India, growing exceptionally. India has about 1,400 WHO GMP-approved manufacturing units. India has been accredited with approximately 1,105 CEPs (Certificate of Suitability) more than 950 TGA approvals and 584 sites approved by the USFDA.

2. Structure of the Indian Pharmaceutical Sector:

Indian Pharmaceutical sector can be divided into two major segments namely, Active Pharmaceutical Ingredients (API) or bulk drugs and formulations. The API can be branded or generic and these ingredients will be a part of formulations, which will be used to treat Acute or chronic diseases.

Export:

Export is selling drugs, pharmaceuticals, medical devices, etc. to other countries crossing the geographical frontiers of the country.

A good example is India selling the drugs to U.S.A. and England.

Export earns a country lot of foreign exchange and helps in tilting the balance of payment.

PROCEDURE FOR EXPORT OF PHARMACEUTICAL PRODUCTS AND MEDICINES FROM INDIA:

- Make a company or firm that will manufacture or market the pharmaceutical products
- Get the IEC Number or Import Export Code Number
- Appoint distributors or agents, or you need to register an office in the country to export

UNIT -3

- Get the particulars, and terms and conditions signed off by the agent or distributor
- Register your product in the country you are exporting
- Get the approval for export from DCGI
- Formulize the shipping method, payment mode, and delivery terms
- Receive Purchase Order
- Send a pro-forma invoice with details such as the type of packing, rate, freight details, etc.
- Prepare commercial invoice against Letter of Credit or Purchase Order
- Sign a contract with the freight forwarding agency to ship the material to the respective country
- Send products to custom clearance
- After getting clearance, the material will be shipped
- In the importing country also customs clearance is required

GETTING IMPORT EXPORT CODE OR IEC NUMBER

When you are an exporter, it is mandatory to get registered at the website of the Director General of Foreign Trade.

When you get registered, a 10-character alphanumeric code will be allotted. This number is required for importing or exporting any item.

To apply for an IEC number you need to apply to the Regional office of Director General of Foreign Trade located in the jurisdiction range of your company.

If the application is digital, then it has to be digitally signed by applicants. Upload all necessary documents (soft copy) to the website and make payment online.

The Regional Authority of DGFT checks the application form and processes it further. If the application form is complete and fulfills all required norms, then the applicant receives a digitally signed E-IEC.

If the application gets rejected due to some reason, then the applicant gets information. The reason for rejection is informed to the applicant.

UNIT -3

DOCUMENTS TO BE UPLOADED

- Passport Size Photo of the Proprietor or Partners or Directors or authorized person
- PAN Copy of the applicant
- Proof of Address
- Proof of ownership or lease of the manufacturing unit or rent agreement
- Company association documents or partnership deed
- Bank Certificate or Cancelled cheque with details of firm/company and account number mentioned
- Any other document asked by the DGFT department

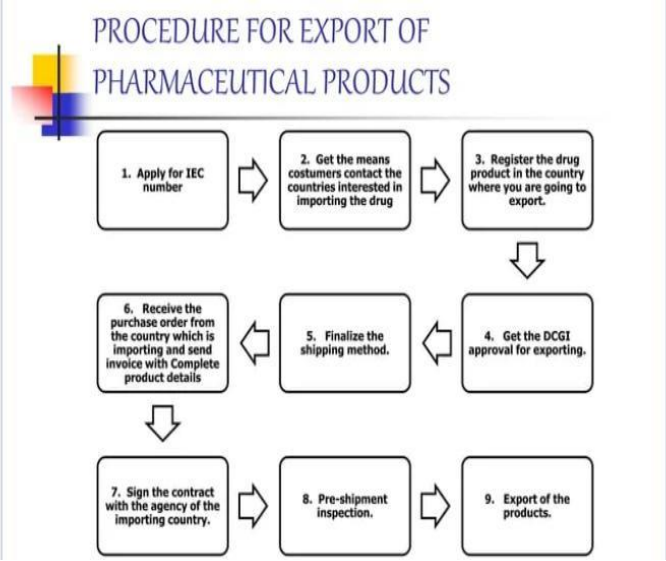
CUSTOM CLEARANCE

Customs clearance is another important document that should be mandatorily obtained when you want to export medicines abroad.

You can do it personally or hire a customs clearance agent. Generate online shipping bills electronically. Thus, the material is moved to the shipping area where custom experts inspect it.

- This is the procedure that you need to follow for the exporting of pharmaceutical medicines and products from India.

FLOW CHART



Advantages Of Exporting Pharmaceuticals From India:

- Since the past ten years, the demand for Indian pharmaceutical exports has increased significantly around the globe.
- Trade agreements with foreign countries for the convenience of doing business aid in the simplicity of the export process Several initiatives have been taken by the government the ease of doing business and export procedures from India.

*The lowest price range of the domestically manufactured pharmaceuticals products in the world.

India makes it easily reachable to the lowest section of the world and is highly growing.

TECHNICAL DOCUMENTATION

Technical documentation is refers to the collection of documents that provide all the necessary information for regulatory agencies to grant marketing authorization clearances for newly developed medicinal products and/or generics. These documents are organized in a standardized format known as the Common Technical Document (CTD) format, which is internationally agreed upon and used by regulatory authorities such as the FDA in the US and the EMA in the EU for the registration and approval of new drugs and for post-approval regulatory submissions.

The CTD format is not the only format used in drug regulatory affairs, and other formats such as the FDA's Common Technical Document (eCTD) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M4 guideline are also used.

Additionally, for medical devices, the Technical Documentation (also known as Technical File) is a collection of documents that manufacturers must prepare and submit to regulatory authorities to demonstrate compliance with regulatory requirements. The Technical Documentation is used for selected premarket and postmarket conformity assessment activities and typically includes information on the device description and specification, manufacturing information, general safety and performance requirements, benefit-risk analysis and risk management, product verification and validation, and clinical evidence.

The Technical Documentation is often extensive and sections of it may be held in different locations, but it should be controlled in the manufacturer's quality management system (QMS) and updated to reflect any changes made during the lifecycle of the device.

1.A. COMMON TECHNICAL DOCUMENT

- Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing of new drug by the applicant by Central Drugs Standard Control Organization (CDSCO)
- The regulations under Drugs and Cosmetics Rules 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacture of new drug for marketing
- Substantial documentation and data are required in these types of submissions, resulting in large, complex applications.
- Till date, applicants have used many different approaches in organizing the information and the differences in organization of data in each application has made reviewing more difficult and can also lead to omission of critical data or analyses.
- Such omissions can result in unnecessary delays in approvals. Thus, a common format of submission will help in overcoming these hurdles.
- Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance's have been developed for Japan, European Union, and United States.
- CTD is a joint effort of 3 Regulatory Agencies:✓ European Medicines Agency (EMEA, Europe),

✓ Food and Drug Administration (FDA, USA) and

✓ Ministry of Health, Labour and Welfare (MHLW,Japan).

- Through the ICH process, considerable harmonization has been achieved among the three

regions in the technical requirements for the registration of pharmaceuticals for human use. However, until now, there has been no harmonization of the organization of the registration documents.

- Each region has its own requirements for the organization of the technical reports in the submission and for the preparation of the summaries and tables.

✓InJapan, the applicants must prepare the GAIYO, which organizes and presents a summary of the technical information.

✓InEurope, Expert Reports and tabulated summaries are required, and written summaries are recommended.

✓TheU.S. FDA has guidance regarding the format and content of the New Drug Application.

- To avoid the need to generate and compile different registration dossiers, this guideline describes a format for the Common Technical Document that will be acceptable in all three regions.
- Most countries have adopted the CTD format. Hence, CDSCO has also decided to adopt CTD format for technical requirements for registration of pharmaceutical products for human use.
- The same is already in use for biological products since 2009 and now this guidance document describes the format for preparation of CTD for marketing approval of pharmaceuticals for human use other than biological products (vaccines, biotechnology products, stem cell products, etc).
- It is apparent that this structured application with comprehensive and rational contents will help the CDSCO to review and take necessary actions in a better way and would also ease the preparation of electronic submissions, which may happen in the near future at CDSCO.
- The regulations under Drugs and Cosmetics Rules 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacture of new drug for marketing.

1.B. CTD REGULATORY SOURCES

- Notice to Applicants, Eudralex Vol. 2B:"NTA Guidance" June 2006 http://ec.europa.eu/enterprise/pharmaceuticals/cudralex/vol-2/b/ctd_06-2006.pdf

- Q&A Document:-http://www.ich.org/LOB/media/MEDIA620.pdf
- Location issues (Quality) - see CPMP/ICH/4680/02
- ICH Updates:- http://www.ich.org

1.C. CDSCO GUIDELINES BASED ON CTD

- It is apparent that this structured application with comprehensive and rational contents will help the CDSCO to review and take necessary actions in a better way and would also ease the preparation of electronic submissions, which may happen in the near future at CDSCO.
- This guidance is developed by CDSCO based on

✓ The ICH Harmonized Tripartite Guideline on "Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use". M4, Step 4 version dated January 13, 2004, and

✓ Drugs & Cosmetics Act 1940 and Rules made there under.

1.D. SCOPE OF CTD GUIDELINES

This guideline applies to import/manufacture and marketing approval of new drugs including new chemical entity, new indication, new dosage forms, modified release form, new route of administration etc. under the definition of new drug under Rule 122E of Drugs & Cosmetics rules as a finished pharmaceutical product.

- This guideline is not intended to advice on the design of studies that are required for product registration, but, indicates an appropriate format for submission of the data that have been acquired

1.E. OBJECTIVE OF CTD

> A common format for the technical documentation will significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions.

> Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.

> In addition, exchange of regulatory information between Regulatory Authorities will be

simplified.

1.F. GENERAL ASPECTS-CTD

>The CTD is only a format for submission of information to CDSCO. It does not define the content.

>Although adherence to overall CTD structure is necessary, it should be noted that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore applicants can modify the format at some of the subsection levels, if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation.

>Clear and unequivocal information should be provided.

> Text and tables should be prepared using margins that allow the document to be printed clearly without losing any information and the left-hand margin should be sufficiently large so that information is not obscured by the method of binding.

> Documents printed on both sides of a page can be submitted, however, one should take care that the information is not obscured when the page is placed in a binder.

> Font sizes for text and tables should be of a style and size that are large enough to be easily readable. Times New Roman, 12-pointfont is recommended for descriptive text and Times New Roman, 9 to10-point font for table contents and text

* Document Pagination and segregation:

✔ Entire submission should never be numbered consecutively by page. Page numbering should be at the document level and not at the volume or module level.

✓ Every document should be numbered starting at page one, except for individual literature references, where the existing journal page numbering is considered sufficient.

✓ All pages of a document should include a unique header or footer that briefly identifies its subject matter. Alternatively, a similar identifier should be used on a tab that precedes the document, to facilitate finding that document within the dossier.

✔ If a section contains more than one document, a specific table of contents for that section can be included in the tab to identify the chronology and titles of the documents contained therein.

- All abbreviations should be defined at the first instance they are used and listed at the end of the dossier.
- References should be cited in accordance with the current edition of the uniform requirements for manuscripts submitted to biomedical journals, International committee of medical journal editors (JCMJE)

SUBMISSION REQUIRMENTS/METHODOLOGY

✓ Please submit ONE hard copy and THREE soft copies i.e. Compact Disc (CD) (PDF format) of the dossier.

- If there are multiple CDs for one submission dossier, then the numbering as mentioned above should be followed. Scanned copies of only signed documents like test reports, signature pages will be acceptable and rest of the document has to be in PDF format with optical character recognition (OCR).

✓ The table of contents under each head should be linked to the files (s) or relevant document for easy tracking in CD's.

✓ Applicant should preserve a duplicate copy of the submitted dossier for any future reference and should be able to submit multiple copies, if required by CDSCO.

- All sentences in blue italic fonts are instructions to the applicant and the same when present in the templates has to be deleted before finalizing the documents.
- During cross-referencing from one module to other modules ,please mention the volume CTD module tab identifier and page number of the other referring document/section.

1.G. MERITS AND DEMERITS OF CTD

MERITS

- Enables the ease and fast submission.
- Easily approachable and loadable from the industry to regulatory agency.
- Available in various formats like pdf, xml and word files.
- Most frequently it is being adopted by the pharmaceutical industries and research on a large scale.
- It is multidisciplinary so widely acceptable.
- The labelling based on the SPL (structured product labelling) format makes easy, clear, and

readable fast according to the particular sections.Granularity in the whole document is increased.

- Easy navigation by the XML (extensible markup Language) index throughout the document.
- In case of any discrepancies in particular page of any section, only that page can be replaced in spite of replacing the complete section.
- STF makes the filing very easy.
- The electronic software helps in creating the STFs (Study Tagging Files) in order to correlate the case report forms with the study files.

DEMERITS

- It is far easier to prepare paper submission (CTD) than to build electronic submissions (eCTD) expertise in-house Since it is fully electronic, it requires full skills and knowledge about the software and other technologies.
- Extensive retraining of staff is usually needed: It is based on the XML format; therefore the person involved in the eCTD compilation must be trained.
- The eCTD requires more attention as a single minor mistake can create a deficiency in the whole application. Therefore it is not fully mandatory in the world. It is mandatory in USA whereas in EU it is accepted along with the paper submission.

1.J. BENEFITS OF eCTD

1) Complete and Efficient review process online in less time

2) Regulators used computer based tools, i.e., searching, copying, pasting, etc.

3) Streamliness review process for multiple reviewers.

4) Increase efficient ability to organise, manage and prepare submissiom5) Reduce storage cost with producing and storing paper dossiers.

6) Streamliness work flow in development, regulatory and marketing dept. while increasing collaborations with team.

7) no actucal increase in EU and /or Japanese application size/review time.

DRUG MASTER FILE(DMF)

INTRODUCTION:

1)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.

2) The submission of a DMF is not required by law or FDA regulation and a DMF is submitted solely at the direction of the holder (a person who owns a DMF)

3) The information contained in the DMF may be used to support an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these.

4) But a DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application

5) DMF are provided for in 21 CFR 314.420.

6) This guideline is intended to provide DMF holders with procedures acceptable to the agency for preparing and submitting a DMF.

7) The guideline discusses types of DMF's, the information needed in each type, the format of submissions to a DMF, the administrative procedures governing review of DMF's, and the obligations of the DMF holder.

8) DMF's are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file.

9) When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or ANDA directly rather than establishing a new Drug master file.

TYPES OF DMF:

1) Type I

Manufacturing Site, Facilities, Operating Procedures, and Personnel:

i) A Type I DMF is recommended for a person outside of the United States to assist FDA in conducting onsite inspections of their manufacturing facilities. The DMF should describe the manufacturing site, equipment capabilities, and operational layout.

ii) A Type I DMF is normally not needed to describe domestic facilities, except in special cases, such as when a person is not registered and not routinely inspected.

iii) The description of the site should include actual site address, and a map showing its location with respect to the nearest city. An aerial photograph and a diagram of the site may be helpful.

iv) A diagram of major production and processing areas is helpful for understanding the operational layout. Major equipment should be described in terms of capabilities, application, and location. Make and model would not normally be needed unless the equipment is new or unique.

v) A diagram of major corporate organisational elements, with key manufacturing, quality control, and quality assurance positions highlighted, at both the manufacturing site and corporate headquarters, is also helpful.

2) Type II;

i. Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product: A Type II DMF should, in general, be limited to a single drug intermediate, drug substance, drug product, or type of material used in their preparation.
ii. Drug Substance Intermediates, Drug Substances, and Material Used in Their Preparation:
   a) Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.
   b) Guideline for the Format and Content of the Chemistry. Manufacturing, and Controls Section of an Application.

3) Type III:

Packaging Material

i) Each packaging material should be identified by the intended use, components, composition, and controls for its release. The names of the suppliers or fabricators of the components used in preparing the packaging material and the acceptance specifications should also be given.

Data supporting the acceptability of the packaging material for its intended use should also be submitted as outlined in the

ii) "Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics."

iii) Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross reference to another document

4) Type IV

Excipient, Colorant, Essence, or Material Used in Their Preparation:

i) Each additive should be identified and characterised by its method of manufacture, release specifications, and testing methods.

ii) Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross reference to another document.

iii) Usually, the official compendia and FDA regulations for color additives (21 CFR Parts 70 through 82), direct food additives (21 CFR Parts 170 through 173), indirect food additives (21 CFR Parts 174 through 178). and food substances (21 CFR Parts 181 through 186) may be used as sources for release tests, specifications, and safety.

iv) Guidelines suggested for a Type II DMF may be helpful for preparing a Type IV DMF.

5) Type V

FDA Accepted Reference Information:

i) FDA discourages the use of Type V DMF's for miscellaneous information, duplicate information, or information that should be included in one of the other types of DMF's.

ii) If any holder wishes to submit information and supporting data in a DMF that is not covered by Types I through IV, a holder must first submit a letter of intent to the Drug Master File Staff FDA will then contact the holder to discuss the proposed submission.

Content of Drug Master Files Submission:

Each DMF submission should contain a transmittal letter, administrative information about the submission, and the specific information to be included in the DMF as described in this section. The DMF must be in the English language. Whenever a submission contains information in another language, an accurate certified English translation must also be included. Each page of

each copy of the DMF should be dated and consecutively numbered. An updated table of contents should be included with each submission.

1) Transmittal Letters: The following should be included:

i) Original Submissions:

a) Identification of Submission: Original, the type of DMF as classified in Section III, and its subject.

b) Identification of the application, if known that the DMF is intended to support, including the name and address of each sponsor, applicant, or holder, and all relevant document members.

c) Signature of the holder or the authorized representative.

d) Type written name and title of the signer.

ii) Amendments: Administrative information should include the following:

a) Identification of Submission: Amendment, the DMF number, type of DMF, and the subject of the amendment.

b) A description of the purpose of submission, e.g., update, revised formula, or revised process.

c) Signature of the holder or the authorised representative.

d) Typewritten name and title of the signer.

2) Administrative Information:

i) Original Submissions:

a) Names and addresses of the following:

- Corporate headquarters.
- Manufacturing/processing facility.
- Contact for FDA correspondence.

b) The specific responsibilities of each person listed in any of the categories.

c) Statement of Commitment: A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.

ii) Amendments:

a) Name of DMF holder.

b) DMF number.

c) Name and address for correspondence.

d) Affected section and/or page numbers of the DMF.

e) The name and address of each person whose IND, NDA, ANDA, DMF. or Export Application relies on the subject of the amendment for support.

f) The number of each IND, NDA, ANDA, DMF, and Export Application that relies on the subject of the amendment for supp ort, if known.

g) Particular items within the IND, NDA, ANDA, DMF, and Export Application that are affected, if known.

General Information and Suggestions to Prepare DMF

1) Environmental Assessment: Type II, Type III, and Type IV DMF's should contain a commitment by the firm that its facilities will be operated in compliance with applicable environmental laws.

2) Stability: Stability study design, data, interpretation, and other information should be submitted, when applicable, as outlined in the "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics."

3) Format, Assembly, and Delivery:

a) the Original and Duplicate Copies Must be Collected and Fully Assembled: Each volume of a DMF should, in general, be no more than 2 inches thick. For multivolume submissions, number each volume. For example, for a 3volume submission, the volumes would be numbered 1 of 3, 2 of 3, and 3 of 3.

b) U.S. Standard Paper Size (8-1/2 by 11 inches) is Preferred: Paper length should not be less than 10 inches nor more than 12 inches. However, it may occasionally be necessary to use individual pages larger than standard paper size to present a floor plan, synthesis diagram, batch formula, or manufacturing instructions. Those pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.

c) Delivery to FDA[3]

Authorisation to Refer a Drug Master File:

Letter of Authorisation to FDA:

1) Before FDA can review DMF information in support of an application, the DMF holder must submit in duplicate to the DMF a letter of authorisation permitting FDA to refer the DMF.

2) If the holder cross refers its own DMF, the holder should supply in a letter of authorisation the information designated by items 3, 5, 6, 7, and 8 of this section. The holder does not need to send a transmittal letter with its letter of authorization.

The letter of authorisation should include the following:

1) The date.

2) Name of DMF holder.

3) DMF number.

4) Name of persons authorised to incorporate information in the DMF by reference.

5) Specific products covered by the DMF.

6) Submission dates

7) Section numbers and/or page numbers to be referenced.

8) Statement of commitment that the DMF is current and that the DMF holder will comply with the statements made in it.

9) Signature of authorising official.

10) Typed name and title of official authorising reference to the DMF.

Processing and Reviewing Policies:

1) Policies Related to Processing Drug Master Files

2) Public availability of the information and data in a DMF is determined under 21 CFR Part 20, 21 CFR 314.420(e), and 21 CFR 314.430.

3) An original DMF submission will be examined on receipt to determine whether it meets minimum requirements for format and content. If the submission is administratively acceptable, FDA will acknowledge its receipt and assign it a DMF number.

4) If the submission is administratively incomplete or inadequate, it will be returned to the submitter with a letter of explanation from the Drug Master File Staff, and it will not be assigned a DMF number.

Drug Master File Review:

A DMF is Never Approved or Disapproved

The agency will review information in a DMF only when an IND sponsor, an applicant for an NDA, ANDA, or Export Application, or another DMF holder incorporates material in the DMF by reference. As noted, the incorporation by reference must be accompanied by a copy of the DMF holder's letter of authorisation.

If FDA reviewers find deficiencies in the information provided in a DMF, a letter describing the deficiencies is sent to the DMF holder. At the same time, FDA will notify the person who relies on the information in the deficient DMF that additional information is needed in the supporting DMF. The general subject of the deficiency is identified, but details of the deficiency are disclosed only to the DMF holder.

When the holder submits the requested information to the DMF in response to the agency's deficiency letter, the holder should also send a copy of the accompanying transmittal letter to the affected persons relying on the DMF and to the FDA reviewing division that identified the deficiencies.

Holder obligation:

Any change or addition, including a change in authorisation related to specific customers, should be submitted in duplicate and adequately cross referenced to previous submission. The reference should include the date, volume, section, and/or page number affected.

1) Notice Required for Changes to a Drug Master File: A holder must notify each affected applicant or sponsor who has referenced its DMF of any pertinent change in the DMF (21 CFR 314. 420(c)). Notice should be provided well before making the change in order to permit the sponsor/applicant to supplement or amend any affected application(s) as needed.

2) Listing of Persons Authorised to Refer to a Drug Master File:

UNIT -3

i) A DMF is required to contain a complete list of persons authorised to incorporate information in the DMF by reference [21 CFR 314.420(d)].

ii) The holder should update the list in the annual update. The updated list should contain the holder's name, DMF number, and the date of the update. The update should identify by name (or code) the information that each person is authorised to incorporate and give the location of that information by date, volume, and page number.

3) Annual Update:

i) The holder should provide an annual report on the anniversary date of the original submission.

ii) If the subject matter of the DMF is unchanged, the DMF holder should provide a statement that the subject matter of the DMF is current.

iii) Failure to update or to assure FDA annually that previously submitted material and lists in the DMF remain current can cause delays in FDA review of a pending IND, NDA, ANDA, Export Application, or any amendment or supplement to such application; and FDA can initiate procedures for closure.

4) Appointment of an Agent:

i) When an agent is appointed, the holder should submit a signed letter of appointment to the DMF giving the agent's name, address, and scope of responsibility (administrative and/or scientific).

ii) Domestic DMF holders do not need to appoint an agent or representative.

5) Transfer of Ownership: To transfer ownership of a DMF to another party, the holder should so notify FDA and authorised persons in writing. The letter should include the following:

i) Name of transferee

ii) Address of transferee

iii) Name of responsible official of transferee

iv) Effective date of transfer

v) Signature of the transferring official

vi) Typewritten name and title of the transferring official. The new holder should submit;

a) A letter of acceptance of the transfer

b) An update of the information contained in the DMF, where appropriate.

c) Any change relating to the new ownership (e.g., plant location and methods) should be included.

Closure of a Drug Master File:

A holder who wishes to close a DMF should submit a request to the Drug Master File Staff stating the reason for the closure. The request should include a statement that the holder's obligations. The Agency may close a DMF that does not contain an annual update of persons authorised to incorporate information in the DMF by reference and a list of changes made since the previous annual report. The holder will be notified of FDA's intent to close the DMF.

Common Technical Document (CTD)

Introduction:

The Common Technical Document (CTD) is a set of specifications for a dossier for the registration of medicines.

The CTD was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and adopted by the Therapeutic Goods Administration (TGA) in 2004.

CTD is an internationally agreed "well structured common format" for the organization of the technical requirements that is to be submitted to the regulatory authority as an application for the registration of pharmaceuticals for human use in all three ICH regions (U.S.A., Europe and Japan).

Prior to the advent of the CTD, regulatory reviewers received an application from one company and spent a year or more engaged in its review.

When the review was completed, reviewers received the next application-most likely in a different format and had to learn the structure of the new application.

1996- Industry proposed CTD but ICH regulators were hesitant

↓

disruptive to the review process

↓

Regulators asked industry to do a feasibility study.

Benefits of CTD:

1) Resources savings in building the dossier
2) Single summaries
3) Facilitation of regulatory information exchange
4) Facilitation of response to questions
5) Harmonised format allowing electronic transmission
6) Partially identical data package
7) No actual increase in EU and/or Japanese application size/review time.

Organisation of the Common Technical Document

- Module 1-Administrative Information and Prescribing Information:
  i. This module should contain documents specific to each region.
  ii. Example: Application forms regarding the prescribing information,proposed label
  iii. . This module is not part of the CTD.
  iv. The content & format of this module can be specified by the relevant regulatory authorities.
- Module 2- Common Technical Document Summaries:
  i. It should begin with a general introduction to the pharmaceutical. including its pharmacological class, mode of action& proposed clinical use. In general, the information should not exceed one page.
  ii. Module-2 should contain 7 sections in the following order:
    a) CTD table of contents.
    b) CTD introduction.
    c) Quality& overall summery.
    d) Non-clinical overview.
- Module 3: Quality

  Module 3 describes the format and organisation of the chemical, pharmaceutical and biological data relevant to the application.

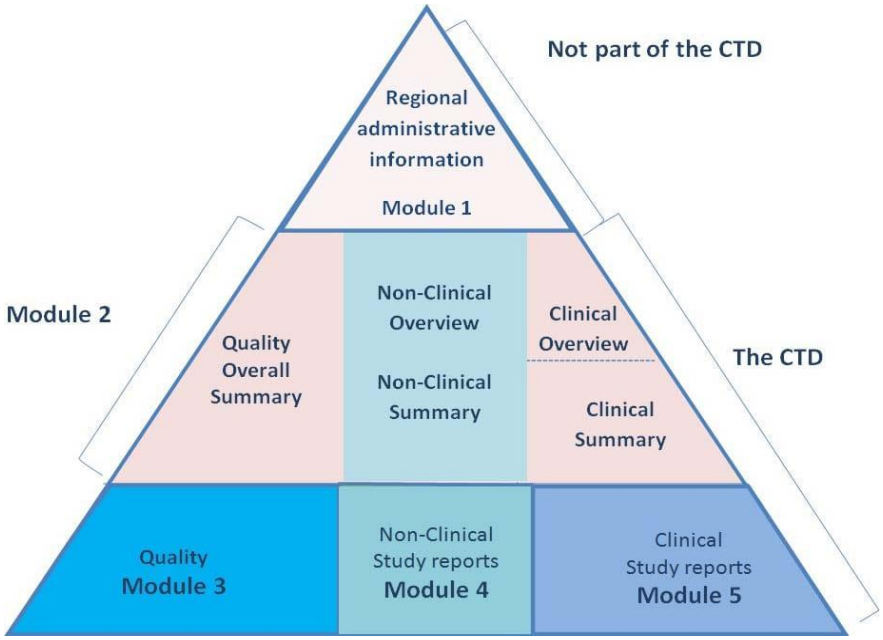
This module is an EU CTD document adopted in Australia

- Module 4: Safety (nonclinical study reports)

  Module 4 describes the format and organisation of the nonclinical (pharmaco-toxicological) data relevant to the application. This module is an EU CTD document adopted in Australia.

- Module 5: Efficacy (clinical study reports)

  Module 5 describes the format and organisation of the clinical data relevant to the application. This module is an EU CTD document adopted in Australia.



ORGANISATION OF THE COMMON TECHNICAL DOCUMENT

REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Module 1: Administrative Information and Prescribing Information

1.1) Table of Contents of the Submission Including Module 1

1.2) Documents Specific to Each Region (for example, application for information)

Module 2: Common Technical Document Summaries

2.1 Common Technical Document Table of Contents (Modules 2-5)

2.2 CTD Introduction

2.3 Quality Overall Summary

2.4 Nonclinical Overview

2.5 Clinical Overview

UNIT -3

2.6 Nonclinical Written and Tabulated Summaries

Pharmacology

Pharmacokinetics

Toxicology

2.7 Clinical Summary

Biopharmaceutic Studies and Associated Analytical Methods

Clinical Pharmacology Studies

Clinical Efficacy

Clinical Safety

Module 3: Quality

3.1 Table of Contents of Module 3

3.2 Body of Data

3.3 Literature References

Module 4: Nonclinical Study Reports

4.1 Table of Contents of Module 4

4.2 Study Reports

4.3 Literature References

Module 5: Clinical Study Reports

5.1 Table of Contents of Module 5

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

5.4 Literature References

ELECTRONIC COMMON TECHNICAL DOCUMENT (ECTD)

eCTD (electronic Common Technical Document) is a standard format of submitting Regulatory information (such as applications, supplements, and reports) to the concerned Health Authorities (Has). It provides a harmonized solution to implement the Common Technical Document (CTD) electronically. An eCTD consists of individual documents in PDF format which are arranged in a hierarchical form as per the CTD structure. It also has an XML backbone which cross-links required documents and provides information

regarding the submission. The purpose of introducing eCTD was to reduce the burden on the reviewers of the Has. It also simplifies the process of submission as all the Regulatory authorities use it as a standard format.

.Electronic Common Technical Document, Common format for Quality, Safety, and Efficacy information. The eCTD is the electronic equivalent to the CTD. [CTD = eCTD].An interface for industry to agency transfer of regulatory information.

eCTD in Simple Words: The eCTD backbone is an XML file representing the structure of the submission, it includes links to files and other metadata such as check sum.

ORGANISATION OF e-CTD

Modules of e-CTD

The e-CTD has five modules in two categories. There are:

1) Regional Module which Includes only Module 1: Administrative information and prescribing information that is not harmonized and different for each region, i.e., country, defined by each of the ICH regions (USA, Europe and Japan).
2) Common Modules: Which includes module 2-5 (Harmonized-common to all the regions)

i) Module 2: Common technical document summaries

ii) Module 3: Quality

iii) Module 4: Nonclinical study reports

iv) Module 5: Clinical study reports.

The specification for the e-CTD is based upon content defined within the CTD issued by the ICH M4 EWG. The CTD describes the organization of Modules, sections and documents. The structure and level of detail specified In the CTD have been used as the basis for defining the e-CTD structure and Content but where appropriate, additional details have been developed within The e- CTD specification.

The ICH website includes an empty e-CTD folder template as an example of an e-CTD submission folder structure. It shows all of the possible modules 2-5 folders and can be populated with the applicant data and edited as appropriate (i.e., adding additional folders or

removing unnecessary folders). The applicant should still add the relevant regional module 1 folders and content, add the appropriate utility folders and content, and create the XML.

1) Module 1- Administrative Information and Prescribing Information:

   The name of the folder for module 1 should be ml. This module contains administrative information, i.e., unique for each region. The e-CTD backbone was developed to allow the transfer of the regional information included in a regulatory dossier. Regional guidance will provide the specific instructions on how to provide the administrative formats and detailed prescribing information.
   Each region provides specific guidance on the format and content of the regional requirements of each Module.

2) Module 2- Common Technical Document Summaries:

   This module contains overall summaries of quality, non-clinical and clinical. The files in this module should be provided as PDF (Portable Document Format) text with exception of a few embedded images, when needed. The name of the folder for module 2 should be m2. The folder in this module 2 should be named as follows but can be further reduced or omitted to minimize path length issues.

3) Module 3- Quality:

   This module contains Quality aspects of the intended drug or medicinal product. The name of the folder for module 3 should be M3. The folders in the module 3 should be named as follows but can be further reduced or omitted to minimize path length issues.

4) Module 4- Nonclinical Study Reports:

   This module contains details of nonclinical studies. The name of the folder for module 4 should be m45. The folders in module 4 should be named as follows but can be further reduced or omitted to minimize path length issues.

5) Module 5- Clinical Study Reports:

   This module contains details of clinical studies. The name of the folder for module 5 should be m5. The folders in the module 5 should be named as follows but can be further reduced or omitted to minimize path length issues.

COMPONENTS OF e-CTD

1. Folder or tree structure

2. Set of files (Portable Document Format (.pdf), Microsoft® Word files (.doc) or Rich Text Format (.rtf) and picture files like jpeg, or png, etc.)
3. The eCTD backbone is an XML file (Extensible Markup Language) representing the structure of the submission, it includes links to files and other metadata such as check sum information. The schema for the XML is very rigid
4. PDF hyperlinks
5. The common formats that can be included in an eCTD submission are:Narrative: Portable Document Format (PDF)
6. Structured: Extensible Markup Language (XML)
7. Graphie: Whenever possible, use PDF. When appropriate or when PDF is not possible, use Joint Photographic Experts Group (JPEG), Portable Network Graphics (PNG), Scalable Vector Graphics (SVG), and Graphics Interchange Format (GIF). Special formats for very high resolutions could be appropriate on a case-by-case basis.

eCTD submissions are accepted for the following applications

1. Investigational New Drug (INDs)
2. New Drug Applications (NDAS)
3. Abbreviated New Drug Applications (ANDAS)
4. Biologics License Applications (BLAs)
5. All the applications following the Submission of the above-stated applications

All the Master Files (MFs) which are part of any above-mentioned applications
Major countries, such as the US, Europe, Australia, Canada, South Africa, Thailand, and Japan, are using eCTD as a standard format for submissions of documents because of numerous advantages that it offers over the traditional submission method. Some of which are:

Allows agencies to upload sequences automatically with the help of XML backbone Automatically with the help of XMLBackbone

1. Reviewers can refer information easily with the help of hyperlinks
2. No need to scan, copy or store paper documents
3. Changes and updates made to the dossiers can be easily identified
4. Easy product lifecycle tracking

BENEFITS OF e-CTD

✓ Make the reviewing of each application more easy.
✓ Avoid omission of critical data or analyses.
✓ Save time.
✓ Better information management.
✓ Support of Life Cycle Management.
✓ Immediate access to complete and up-to- information.
✓ Reduced workload.
✓ Better use of resources.
✓ Simplified business process.
✓ Better communication with industry.

ASEAN COMMON TECHNICAL DOSSIER (ACTD)

DOSSIER

It s a complete set of document. A collection of papers giving detailed information about a particular person or subject.

The ASEAN Common Technical Dossier (ACTD) is a format for applications submitted to ASEAN regulatory authorities to register pharmaceuticals for human use**.**

Although the current ASEAN Common Technical Requirements (ACTR) has not included specific requirements for biosimilar products, the ACTD format is also applicable for biosimilar products.

ORGANIZATION OF ACTD

ACTD documents comprises following parts;

➤ PART I: Table of contents, Administrative Data & Product Information(Applicable)

UNIT -3

➤ PART II: Quality Documents (Applicable)

➤ PART III: Non Clinical Documents (Not Applicable for generic products)

➤ PART IV: Clinical Documents (Not Applicable for generic products some exception may apply)4

Part 1: Table of Content Administrative Information and Prescribing Information

Section A: Introduction

Section B: Overall ASEAN Common Technical Dossier Table of Contents

Section C: Documents required for registration (for example, application forms, Labeling, Product Data Sheet, prescribing information)

Part II: Quality Document

Section A: Table of Contents

Section B: Quality Overall Summary

Section C: Body of Data

Part III: Nonclinical Document

Section A: Table of Contents

Section B: Nonclinical Overview

Section C: Nonclinical Written and Tabulated Summaries

1. Table of Contents
2. Pharmacology
3. Pharmacokinetics
4. Toxicology

Section D: Nonclinical Study Reports

1. Table of Contents
2. Pharmacology
3. Pharmacokinetics

UNIT -3

4. Toxicology

Part IV: Clinical Document

Section A: Table of Contents

Section B: Clinical Overview

Section C: Clinical Summary

Summary of Biopharmaceutics and Associated Analytical Methods

Summary of Clinical Pharmacology Studies

Summary of Clinical Efficacy

Summary of Clinical Safety

Synopses of Individual Studies

Section D: Tabular Listing of All Clinical Studies

Section E: Clinical Study Reports

Section F: List of Key Literature References

List of Documents Required

List of documents required for Part I Administrative

Section writing:

1 Application form (details to be filed in)

2 Letter of Authorization

3 Certifications

I. Manufacturing license
II. Certificate of Pharmaceutical Product
III. GMP certificate of the Manufacturer
IV. Site Master File of manufacturer

4.Labeling

I. Mock-up for Inner Carton

UNIT -3

II. Mock-up for outer carton

III. Mock-up for Label

5.Product Information

I. Package Insert

II. Summary of Product Characteristics (Product Data Sheet)

- Summary of Product Characteristics is required for NCE and Biotechnology products.

III. Patient Information

- PIL is required for Ov Information

List of documents required for Part II Quality section

Writing:

1. DMF of API
2. BMR Finished product
3. BPR Finished product
4. Critical manufacturing steps and justifications
5. Process validation protocol and report
6. Flow chart (Detailed and simple)
7. Process development report
8. Impurity profile with justifications
9. Excipient details:
    I. Specification and testing method
    II. COA
    III. TSE/BSE declaration from supplier/manufacturer.
10. Specification and method of Analysis (MOA)
    I. Intermediates and in-process specification & MOA
    II. Finished product release specification & MOA
    III. Finished product Stability specification & MOA
    IV. API specification & MOA from finished product manufacturer.
    V. Packaging material (primary, secondary and tertiary)
11. Analytical method validations at release and stability (if different methods are used)
    I. Assay
    II. Related substance

III. Dissolution (if applicable)
IV. Preservative content (if applicable)
V. Sterility (if applicable)
VI. Endotoxin (if applicable)
VII. MLT
VIII. Forced degradation

12. COA's
    I. API (3 consecutive batches) from FP manufacturer
    II. All the raw material (excipients and coating Materials)
    III. Reference and working standards
    IV. Impurity standards
    V. Packaging material (primary, secondary and tertiary)
13. IR spectra of PVC/PVDC sheets and aluminum foil if used
14. Soft copy of labels (PDF)
15. Food grade certificate from primary packaging material manufacturer for its primary packaging
16. Preparation of reference standard in brief
17. Stability protocol
18. Stability data and Photo stability data (if applicable)
19. Bioequivalence study

Unit IV Clinical trials

Developing clinical trial protocols, Institutional Review Board / Independent Ethics committee - formation and working procedures, Informed consent process and procedures, GCP obligations of Investigators, sponsors & Monitors, Managing and Monitoring clinical trials, Pharmacovigilance - safetymonitoring in clinical trials

UNIT -4

DEVELOPING CLINICAL TRAIL PROTOCOL

CLINICAL TRAILS

Definition:- A clinical trial is a research study conducted with human volunteers to evaluate the safety and effectiveness of a medical intervention, such as a new drug, medical device, treatment, or procedure.

- These trials are designed to answer specific questions about the intervention's effects on participants and are essential for advancing medical knowledge and improving healthcare.

PARTS OF THE PROTOCOL

According to ICH good clinical practice guidelines, a protocol / a study summery should include the following topics:-

1. Title page
2. Signature page
3. Content page
4. List of abbreviations
5. Introduction/abstract
6. Objectives
7. Background/rationale
8. Eligibility criteria
9. Study design/methods (including drug / device info)
10. Safety/adverse events
11. Regulatory guidance
12. Statistical section (including analysis and monitoring)
13. Human subjects protection/informed consent

Developing Clinical Trail Protocol

Protocol development and complexity depends greatly upon the type of clinical study being conducted. For instance, interventional, multi-site, greater than minimal risk studies require more protocol content than minimal risk and single site. When developing a successful study design and writing a protocol, the researcher must address various essential components-

including the types of data being collected, (e.g. safety, laboratory), data handling and record keeping. Outcome measures, how monitoring and reporting will occur, and data analysis.

• A research protocol is a document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project.

Background information/significance:-

1. Name and description of the investigational product, and is one of t reviews, justification for the chart and medical Second reviews
2. Summary of results from prior clinical studies and decal data to do
3. Human subject a risks and benefits
4. Description of the population to be studied.
5. Description and justification for the dosing regimen and treatment period
6. A paragraph stating that the clinical study will be conducted in compliance with the protocol, SOP's and the federal, state and local regulations
7. Citations from the references and data relevant to the study that also provides background for trail.

General Information

1. Protocol title, protocol identifying number, and date any amendment should also bear the amendment number and date.
2. Name and address of the sponsor and monitor (if other than the sponsor).
3. Name and title of the person authorised to sign the protocol and the protocol amendment for the sponsor
4. Name, title, address, and telephone number of the sponsor's medical expert (or dentist when appropriate) for the trial.
5. Name and title of the investigator who is responsible for conducting the trial, and the address and telephone number of the trial site.
6. Name, title, address, and telephone number of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
7. Name and address of the clinical laboratory and other medical and/or technical department and/or institutions involved in the trial.

Members involve in protocol development

1. A chemist
2. A pharmacologist/ toxicologist
3. A medical monitors
4. A data management person
5. Potential investigators
6. Capable program manager

INSTITUTIONAL REVIEW BOARD (IRB)/ INDEPENDENT ETHICAL COMMITTEES (IEC)

Institutional Review Board (IRB) is an independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Objective of IRB/IEEC

1) Before a site is allowed to start enrolling patients in a clinical trial, the IRB/IEC must review all study-related materials in an initial review. The IRB/IEC also performs periodic reviews- called continuing reviews- throughout the trial's duration. Continuing reviews may take place at least once a year and include the entire trial, not just changes.

2) The IRB/IEC may also ask for additional information regarding payments and compensation to study participants, as well as the informed consent process.

3) The objective of IEC is to facilitate the use of Central review process (use of single central IEC) for the Fortis Network group of Hospitals involved in clinical research activities.

4) Independent Ethics committee at Fortis Escorts Heart Institute will conduct the central review process based on the ethical guidelines for biomedical research on human subjects by Indian Council of Medical Research (ICMR) and Code of federal regulation 56.114.

5) This document shall put in place a consistent ethical review mechanism for health and biomedical research for all research proposals received by the Committee.

6) It will ensure that quality and consistency of an ethical review mechanism is put in place.

UNIT -4

Formation of the IRB/IEC

IRB/IEC members should be collectively qualified to review the scientific, medical and ethical aspects of the trial. As per the FDA, an IRB/IEC should have:

1) At least five members.

2) Members with varying backgrounds.

3) At least one member who represents a non-scientific area (a lay member).

4) At least one member who is not affiliated with the institution or the trial site (an independent member).

5) Competent members who are able to review and evaluate the science, medical aspects and ethics of the proposed trial.

Working Procedures

- Only those IRB members who are independent of the clinical trial and the Sponsor of the trial should vote / provide opinion in matters related to the study
- Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advice.
- The IRB should perform its functions according to written standard operating The IRB shoshd hd maintain written records of the viable minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement.
- The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB or in the vote/opinion of the IRB.
- The IRB should establish, document in writing, and follow its procedures,

which should include:

i) Determining its composition (names and qualifications of the members) and the authority under which it is established.

ii) Scheduling, notifying its members of, and conducting its meetings.

iii) Conducting initial and continuing review of trials.

iv) Determining the frequency of continuing review, as appropriate.

- Specifying that no subject should be admitted to a trial before the IRB issues its written approval / favourable opinion of the trial.
- Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB approval / favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistical or administrative aspects of the trial.
- Specifying that the investigator should promptly report to the IRB about:

  i) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects.

  ii) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial.

  iii) All adverse drug reactions (ADRs) that are both serious and unexpected

  iv) New information that may affect adversely the safety of the subjects of the conduct of the trial.
- Ensuring that the IRB promptly notify in writing the investigator/institution concerning:

  1) Its trial-related decisions/opinions.

  ii) The reasons for its decisions/opinions.

  iii) Procedures for appeal of its decisions/opinions.
- Records: The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3-years after completion of the trial and make them available upon request from the regulatory authority (ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists

Responsibilities of IRB/IEC

1) An IRB should safeguard the rights, safety, and well-being of all trial subjects.

2) The IRB should obtain the following documents:

i) Trial protocol/amendment.

ii) Written informed consent form.

iii) Subject recruitment procedures (e.g.: Advertise).

iv) Written information to be provided to subjects.

v) Investigator's Brochure (IB).

vi) Available safety information.

vii) Information about payments and compensation.

viii) Investigator's current curriculum vitae.

ix) Any other may need to fulfil its responsibilities.

3) The IRB should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

i) Approval/favourable opinion

ii) Modifications required prior to its approval / favourable opinion;

iii) Disapproval/ negative opinion

iv) Termination/suspension of any prior approval / favourable opinion

4) The IRB should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and / or by any other relevant documentation the IRB requests.

5) The IRB/IEC should conduct continuing review of each on going trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

6) The IRB may request more information than is given to study subjects when, in the judgement of the IRB the additional information would add meaning to the protection of the rights, safety and/or well-being of the subjects.

7) When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative, the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

8) Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible, the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

9) The IRB should review both the amount and method of payment to subjects to assure neither compulsion nor undue influence on the trial subjects.

10) Payments to a subject should be prorated (day basis) and not wholly contingent on completion of the trial by the subject.

11) The IRB should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects.

INFORMED CONSENT PROCESS AND PROCEDURES

Definition:

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate.

Informed consent is documented by means of a written, signed and dated informed consent form.

The goal of the informed consent process is to provide people with sufficient information so that they can make informed choices about whether to begin or continue participation in clinical research.

UNIT -4

Informed consent guidelines:

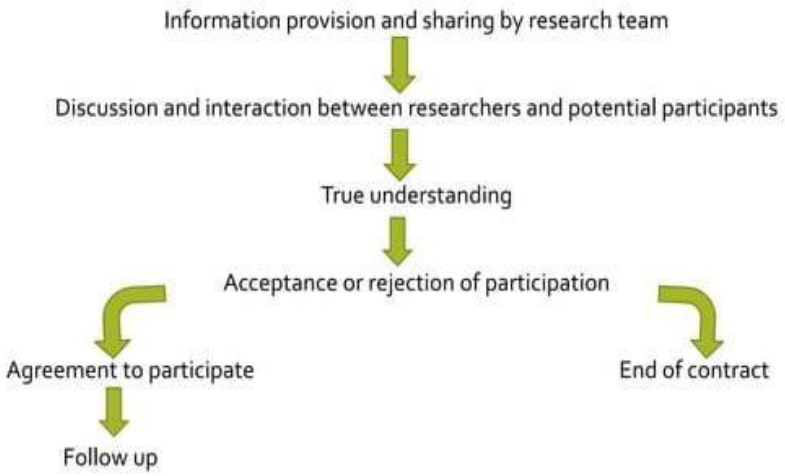
1. ICMR (Indian Council of Medical Research) "Ethical Guidelines for Biomedical Research on human subjects." Published in 2000 and revised in 2006

2. ICH

ICH Guidelines E6 section 4.8 under GLP (Good Clinical Practices)

The Process of Consent

- Choose the right environment and location to obtain consent.
- Involve multiple health care personnel as necessary.
- Include family members in the process as warranted.
- Ensure that the subject or Legally Authorized Representative is competent.
- Ensure the subject or LAR has sufficient understanding.
- Continue the process of consent throughout the study.
- Identify obstacles to participation in study and ways to overcome obstacles
- Identify words subject may not understand
- Compile "Frequently Asked Question" list
- Decide who will do consent discussion
- Decide where consent discussion will be held
- Provide adequate time to explain study to subject.
- Provide adequate time for subject to read and consider and for questions to be answered.



Who can sign the Informed Consent Form?

1. Subject or Legally Acceptable Representative (LAR)
2. Person conducting review of consent.
3. Impartial witness

Elements of Informed Consent Form:

Process:

To be valid, informed consent must be based on the following:

1)Capacity to Give Informed Consent

- A person who has a court-appointed legal guardian or who has been determined by a court to be legally incompetent cannot sign an Informed Consent Form even if he or she has the capacity to make a decision.
- This determination is made by the legal system and not by clinicians.

2**) Disclosure of all Relevant Information**

This information generally includes:

- The purpose of the study.

UNIT -4

- The nature of the procedure or intervention that is being studied.
- The potential risks and benefits as well as the uncertainties of study participation.
- Reasonable alternatives to participation in the study.
- The participants obligations for the duration of the study.

3)Comprehension by the Participant

- The potential participant must understand the information disclosed to him or her about the research study.
- The participant is free to ask questions to the study team as well as take additional time to make a decision regarding participation.

4) Voluntary Agreement by the Participant

- The participant must agree to participate in the research study and his or her agreement must be voluntary and free from coercion or undue influence.

5)Right to Withdraw

- The participant must be informed that he or she has a right to withdraw from the study at any time and for any reason, without penalty or loss of benefits that he or she would otherwise be entitled to receive.

Additional elements

- Withdrawal criteria.
- Additional costs to subjects.
- Statement that there may be risks which are unforeseeable.
- Approximate number of subjects in study.
- Statement that will be told of new findings.

Authoring the Informed Consent Form

UNIT -4

Components of ICF (according to ICMR guidelines, 2006)

a) Important Information about the Research Study.
b) What is the study about and why are we doing it?
c) Benefits of taking part in the study.
d) Possible risks that might result from being in the study.
e) Certificate of Confidentiality.
f) What will happen to the information collected after study period is over.
g) Compensation for being part of the study.
h) Possible expenditures to a subject to be part of study.
i) Who can profit from study results.
j) Choices to a subject if they don't wish to take part in the study.
k) Voluntariness
l) Contact information of subject.
m) Contact information of study team.
n) Consent: Name, Signature and Date
o) Parent or LAR: Name, Signature and Date

UNIT -4

GOOD CLINICAL PRACTICES OBLIGATIONS OF INVESTIGATORS

- GCP is a standard for the design; conduct performance, monitoring, auditing, Recording, analyses, and reporting of clinical trials. Certain functions of GCP are follows:
- It provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of study subjects are protected
- It sets minimum quality standards for the conduct of clinical research Compliance with GCP.
- It ensures that the rights, safety, and well-being of study participants are protected.
- It ensures the integrity of the data submitted for approval.
- It sets standards for a system of mutual accountability among sponsors, regulatory authorities, investigators, and IRBs.

PRINCIPAL INVESTIGATOR:

While studies have a Lead Investigator with primary responsibility over the entire trial, this individual is often the Principal Investigator (PI) at the lead research site and has responsibility over the conduct of a clinical study at that site. For multicentre trials, there is a number of research sites, each with its own Principal Investigator with oversight responsibility and staff involved in the conduct of a study.

1) The PI retains ultimate oversight responsibility even when specific tasks are delegated to other site research staff. additionally. Pl responsibilities include

2) Documenting the delegation of study responsibilities to qualified and adequately trained research staff.

3) Supervising study performance and overseeing the performance of study staff at the research sites.

4) Ensuring that:

- Participants' well-being and safety are protected.
- All study procedures are conducted at the research sites in accordance with the protocol and GCP.
- Preparing a communication plan for all staff involved in the study.
- Overseeing Investigational product accountability.

- Of note, the PI must sign the protocol signature page in that capacity. If the study is being conducted under an Investigational New Drug (IND) application, the PI must also sign Form FDA 1572.

QUALIFICATIONS AND EXPERIENCE (ICH GCP 4.1):

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the study.
- If the study involves the use of an investigational product, be thoroughly familiar with the appropriate use of that product as described in the study protocol.
- Beaware of and remain in compliance with GCP and applicable regulatory Requirements.
- Maintain a list of qualified persons to whom he or she delegates significant study-related duties.

ADEQUATE RESOURCES (ICH GCP 4.2):

- Ability to recruit in sufficient numbers and on time
- Sufficient time to complete the study
- Adequate number of qualified staff and adequate facilities to complete the study
- Staff who are well informed about the protocol, the IP, and their study responsibilities.

Medical Care of Study Participants (ICH GCP 4.3)

- All study participants should receive appropriate medical care both for study-related adverse events and for all medical conditions unrelated to study participation.
- A qualified physician or, where appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) who is an investigator or a sub-investigator for the trial should have the overall responsibility for trial-related medical care and decisions.
- Other appropriately qualified healthcare professionals may be involved in the medical care of trial participants, in line with their normal activities and in accordance with local regulatory requirements.

- During and following participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial.

Communication with Institutional Review Board (ICH GCP 4.4)

- The PI is identified to the designated IRB. Before and during a study, the PI must comply with all requirements of the designated Institutional Review Boards (IRBs).
- A study may not begin prior to obtaining IRB approval.

Compliance with the Protocol (ICH GCP 4.5)

- The PI is responsible for ensuring that the study is conducted in compliance with the research protocol.
- He or she should ensure that all protocol violations are identified, documented, and reported in accordance with sponsor and IRB requirements.
- Repeated protocol violations may indicate that protocol amendments, procedural changes, or additional training are needed.

Use of Investigational Products (ICH GCP 4.6)

- Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.
- Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.
- The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused products.
- These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

- The investigational products should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
- The investigator should ensure that the investigational products are used only in accordance with the approved protocol.
- The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational products to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

Randomisation and Blinding (ICH GCP 4.7)

The investigator should follow the trial's Randomisation procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, then the investigator should promptly document and explain to the sponsor about any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

Informed Consent (ICH GCP 4.8)

The Pl is responsible for ensuring that procedures for obtaining and documenting informed consent comply with GCP and with the ethical principles originating in then Declaration of Helsinki.

Records and Reports (ICH GCP 4.9)

- The Pl is responsible for ensuring the accuracy, completeness, legibility, and timeliness of all study data that are reported to the Sponsor.
- The PI should provide written reports on the status of the study to the Sponsor and IRB when and as often as required to do so at each institution where the study is conducted.
- All serious adverse events must be reported immediately to the Sponsor. The Pl must also comply with regulatory requirements to report serious adverse events to the IRB and regulatory authorities.

Progress Reports (ICH GCP 4.10)

- The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

- The investigator should promptly provide written reports to the sponsor, the IRB/IEC and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

Safety Reporting (ICH GCP 4.11)

- All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB/IEC.
- Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
- For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information.

Premature Suspension or Termination of Study (ICH GCP 4.12)

If the study is suspended or stopped early for any reason, the PI is responsible for:

- Promptly informing all study participants.
- Ensuring that all participants receive appropriate therapy and follow-up.
- Complying with all requirements to inform regulatory authorities.

Final Study Reports (ICH GCP 4.13)

On completion of the study, the PI is responsible for providing:

- All required reports to the Sponsor and regulatory authorities.
- A summary of the study outcome to the Institutional Review Board.
- Records and reports are discussed in greater detail in the Documentation
- Record keeping module. Serious adverse events are discussed in the Participant.

1. Safety and Adverse Events module.
    a. Upon completion of trail, the investigator where applicable should inform the institution. the investigator/institution should provide the IRB/IEC with a summary of the trails outcome and the regulatory authority with any reports required.

GCP OBLIGATIONS

❖ **Introduction:**

Definition:

- GCP (Good clinical practice) is a standard for the design, conduct, performance, motoring, auditing, recording, analysing and reporting of clinical trials that assurance that the data and reported results are credible and accurate and the rights integrity and confidentiality of trial subjects are protected.
- GCP is a standard for the design; conduct performance, monitoring, auditing, recording, analyses, and reporting of clinical trials. Certain functions of GCP are as follows:

1) It provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of study subjects are protected.

2) It sets minimum quality standards for the conduct of clinical research Compliance with GCP.

3) It ensures that the rights, safety, and well-being of study participants are protected.

4) It ensures the integrity of the data submitted for approval.

5) It sets standards for a system of mutual accountability among sponsors, regulatory authorities, investigators, and IRBs.

❖ **INVESTIGATORS:**

While studies have a Lead often the Principal Investigational study the lead entire trial, this responsibility over the conduct of clinical study at that research site and has there is a number of research sites, each with its own site. For multicenter trials, with oversight responsibility and staff involved in the conduct of a study.

1) The Pl retains ultimate oversight responsibility even when specific tasks are delegated to other site research staff. Additionally, PI responsibilities include:

2) Documenting the delegation of study responsibilities to qualified and 3 adequately trained research staff.

3)Supervising study performance and overseeing the performance of study staff at the research sites.

4) Ensuring that:

i) Participants' well-being and safety are protected.

ii) All study procedures are conducted at the research sites in accordance with the protocol and GCP.

iii) Preparing a communication plan for all staff involved in the study.

iv) Overseeing Investigational product accountability.

v) Of note, the PI must sign the protocol signature page in that capacity. If the study is being conducted under an Investigational New Drug (IND) application, the PI must also sign Form FDA 1572.

- Qualifications and Experience (ICH GCP 4.1),

The PI must have following qualifications and Experience:

1) Be qualified by education, training, and experience to assume responsibility for the proper conduct of the study.

2) If the study involves the use of an investigational product, be thoroughly familiar with the appropriate use of that product as described in the study protocol.

3) Be aware of and remain in compliance with GCP and applicable regulatory requirements.

4) Maintain a list of qualified persons to whom he or she delegates significant study-related duties.

- Adequate Resources (ICH GCP 4.2),

1) The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within

the agreed recruitment period.

2) The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

3) The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4) The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

- Premature Suspension or Termination of Study,

The study is suspended or stopped early for the PI is responsible for

i) Promptly informing all study participants.

ii)Ensuring with all participants receive appropriate therapy and follow-up.

iii)Complying to inform regulatory authorities.

- Final Study Reports (ICH GCP 4.13),

On completion of the study, the PI is responsible for providing: All required reports to the Sponsor and regulatory authorities. 2) A summary of the study outcome to the Institutional Review Board.

Records and reports are discussed in greater detail in the Documentation and Record keeping module. Serious adverse events are discussed in the Participant. 5)Safety and Adverse Events module.

❖ **Sponsors:**

In the conduct of a clinical trial, a sponsor is an individual, institution, company or organization (for example, a contract research organization) that takes the responsibility to initiate, manage or finance the clinical trial, but does not actually conduct the investigation. The Sponsor may transfer any or all of the Sponsor's trial-related duties and functions to a Contract Research Organisation (CRO). However, the ultimate responsibility for the quality and integrity of the trial data always resides with the Sponsor. Any trial-related duties and functions that are transferred to and assumed by a CRO are specified in writing.

UNIT -4

- Quality Management (ICH GCP 5.0),

The sponsor should implement a system to manage quality throughout all stages of the trial process. Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision-making. The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below:

1) Critical Process and Data Identification: During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

2) Risk Identification: The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g, standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

3) Risk Evaluation: The sponsor should evaluate the identified risks, against existing risk controls by considering:

i) The likelihood of errors occurring.

ii) The extent to which such errors would be detectable.

iii) The impact of such errors on human subject protection and reliability of trial results.

4) Risk Control: The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5) Risk Communication: The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

6) Risk Review: The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

7) Risk Reporting: The sponsor should describe the quality management approach implemented in the trial and summarise important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

- Quality Assurance and Quality Control (ICH GCP 5.1),

1)The Sponsor is responsible for implementing and maintaining quality assurance and quality control with the protocol ensure that studies are conducted and do assurance in compliance with the protocol, GCP, and regulatory requirements.

2)The sponsor is responsible for securing agreement from all involved to ensure direct access to all trial related sites, source data/documents parties reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

3)Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly ha Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

- Contract Research Organisation (CRO) (ICH GCP 5.2),

UNIT -4

1)A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

2)Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

3)The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

4) Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5) All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

- Medical Expertise (ICH GCP 5.3),

The Sponsor is responsible for designating appropriately qualified medical personnel to advise on trial-related medical questions or problems.

- Trial Design (ICH GCP 5.4),

The sponsor should utilise qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analysing and preparing interim and final clinical trial reports. For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

- Trial Management, Data Handling, and Record Keeping (ICH GCP 5.5),

1) The sponsor should utilise appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

2) The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a

trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

❖ **Monitors:**

Monitoring of the Integrated Addendum to ICH E6 (R1) that is guideline for Good Clinical Practice E6 (R2). e.g., contains the E6 (R2) Addenda, and provides an overview of the scope of, requirements to clinical trial monitoring process, as well as responsibilities of all participants.

- Selection and Qualifications of Monitors,

1) Monitors should be appointed by the sponsor.

2) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

3) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

- Monitor's Responsibilities,

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

1) Acting as the main line of communication between the sponsor and the investigator.

2) Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

3) Verifying, for the investigational product(s):

i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

iii) That subjects are provided with necessary instruction on properly using. handling, storing, and returning the investigational product(s).

iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

4) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

5) Verifying that written informed consent was obtained before each subject's participation in the trial.

6) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

7) Ensuring that the investigator and the investigators trial staff are adequately informed about the trial.

8) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorised individuals.

9) Verifying that the investigator is enrolling only eligible subjects.

10) Reporting the subject recruitment rate.

11) Verifying that source documents and other trial records are accurate. complete, kept up-to-date and maintained.

12) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

13) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

ii) Any dose and/or therapy modifications are well documented for each of the trial subjects. iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs. iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

14) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

15) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

16) Determining whether the investigator is maintaining the essential documents.

17) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

Managing and Monitoring Clinical Trial

- Trial monitoring is an Integral Component of trial quality assurance process, and critical for GCP fulfilment. E6-GCP defines monitoring as, "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted,
- Recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)".

So the monitor is a person who is responsible to perform all the above-mentioned activities.

- According to the U.S. Food and Drug Administration's Center of Drug Evaluation and Research, the top five deficiency categories for site inspections caught by clinical monitors as reported in the 2001 Report to the Nation are:
    - Failure to follow investigation protocol (the procedures and treatment subjects must undergo, as well as the schedule of assessments).
    - Failure to keep adequate and accurate records.
    - Problems with the informed consent form.
    - Failure to report adverse events.
    - Failure to account for the disposition of study drugs.

Purpose:

The purposes of trial monitoring are to verify that:

1) The rights and well-being of human subjects are protected.

2) The reported trial data are accurate, complete, and verifiable from source documents.

3) The conduct of the trial is in compliance with the currently approved protocol/amendment, with GCP, and with the applicable regulatory requirements

Monitor's Responsibilities:

The monitor(s) in accordance with the sponsor's requirements should ensure that t trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial

Trail site:

Acting as the main line of communication between the sponsc and the investigator. Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including laboratories, equipment and staff, are adequate to safely and properly conduct the trial and remain' adequate throughout the trial period.

Verifying ,for the investigational products:

- That storage times and conditions are acceptable and that supplies are sufficient throughout the trial.

- That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
- That subjects are provided with necessary instruction on properly using, handling, storing and returning the investigational product(s). properly using, handling, storing and returning the investigational product(s).
- That the receipt, use and return of the investigational product(s) at the trial sites are controlled and documented adequately.
- That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is accordance with the sponsor.
- Verifying that the investigator follows the approved protocol and a approved amendment(s), if any.
- Verifying that written informed consent was obtained before each subject's participation in the trial.
- Ensuring that the investigator receives the current Investigator's Brochure, all documents and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
- Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial
- Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution and have not delegated these functions to unauthorized individuals.
- Verifying that the investigator is enrolling only eligible subjects.
- Reporting the subject recruitment rate.
- Verifying that source documents and other trial records a accurate, complete, kept up-to-date and maintained.
- Verifying that the investigator provides all the required reports,notifications, applications and submissions and that these documer are accurate, complete, timely, legible, dated and identify the trial.
- Checking the accuracy and completeness of the CRF entries, sour documents and other trial-related records against each other.

4 Types of monitoring in clinical trials:

UNIT -4

1. On-site monitoring:

- On-site monitoring is the process of evaluating clinical trial procedures at the investigation site. Monitoring is carried out in person by the sponsor or their representatives, overseeing trial processes at sites where the research is taking place.
- On-site monitoring is the most traditional form of clinical monitoring, and is used commonly across site-based clinical trials. This is sometimes referred to as clinical site monitoring.
- This type of clinical monitoring is most appropriate for trials that take place at a centralised investigation site. However, on-site monitoring is less practical for clinical trials that are spread across multiple investigation sites - especially if sites are not located nearby.

2. Remote monitoring:

- Remote monitoring oversees clinical trial research, evaluating the study off-site. Monitoring is carried out away from the investigational site where the research is taking place.
- This type of clinical monitoring became much more common during the COVID-19 pandemic, when on-site visits were limited due to restrictions and safety measures. On-site monitoring became impossible, and so remote monitoring became the most effective solution.
- Even now, after many COVID-19 restrictions have ended, remote monitoring remains an effective way to observe and track clinical trials. As a method that requires no face-to-face interaction with patients or site personnel, remote monitoring comes both with less risk to patients and a lower cost for the study.

3. Centralised monitoring:

- Centralised monitoring is carried out away from the investigational site at a separate central location.
- This centralised approach is similar to remote monitoring, since both involve clinical evaluation away from the study site. The main difference is that centralised monitoring takes place in a central location and can result in an efficient monitoring process that could simultaneously save development budget.
- The process of reviewing data that has been centrally submitted can also help the study monitors to identify and address data gaps or inconsistencies and take mitigating steps

to rectify immediately. For example, it may be that instrumentation at one particular site is incorrectly calibrated.

- This could potentially be detected when the data from that facility is inconsistent with the other sites participating in the trial. The study monitor would be able to flag this with the on-site team.

4. Risk-based monitoring (RBM):

- Risk based monitoring (RBM) is used in clinical trials to assess the risks involved with the clinical study. This assesses the risks to investigation quality, human subjects, data integrity, as well as lower-impact risks that are less likely to occur.

  RBM is a critical part of clinical monitoring, and is normally used to determine which type of monitoring is the most appropriate for the study.
- The risk-based monitoring process works by:

  1 Identifying any potential risks

  2 Designing a clinical monitoring plan.

Monitoring Report:

- Submitted to sponsor
- Reports should include:
- I. Date
- II. Site
- III. Name of the monitor
- IV. Name of the investigator or other individuals contacted during study
- V. Summary of monitor review, statements concerning significant findings, deficiencies deviations, actions to be taken or taken or actions recommended to secure compliance.

Pharmacovigilance safety monitoring in clinical trails

Introduction:

Pharmacovigilance, sometimes shortened to "PV," is the science of collecting. monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications and biologics.

As such, pharmacovigilance heavily focuses on adverse drug reactions, or ADRs. which are defined as any response to a drug which is noxious and unintended. including lack of efficacy. Medication errors such as overdose, and misuse and abuse of a drug as well as drug exposure during pregnancy and breastfeeding are also of interest, even without an adverse event, because they may result in an adverse drug reaction.

Good Clinical Practices (GLP):

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and the rights, integrity, and confidentiality of trial subjects are protected.

According to the Principles of ICH GDP Guidelines

The right, safety, and well-being of the trial subjects are the most important considerations.

Stakeholders in Safety Monitoring.

What is Pharmacovigilance?

The World Health Organization defines pharmacovigilance (PV) as "It is a pharmacological science which deals with safety of drugs and activity which concern to assess, detect, understand and prevent adverse effects or the drug-related problem." The aim of PV are to reinforce patient safety concerning medicine use by providing a system to collect, evaluate, and distribute drug safety data. PV activities consist of monitoring approved drugs and investigational medicinal products (IMPs) to: Determine previously unknown adverse effects. Acknowledge changes in the severity of known adverse effects. Assess a drugs risk/benefit to ascertain if action is required to improve safety Guarantee the accuracy of data communicated to health care professionals and patients, and to make sure information contained in patient information leaflets (PILs) is up so far.

Safety monitoring in done by:

- Monitoring patients safety during clinical trials is a critical component throughout the drug development life cycle.

UNIT -4

- Pharmaceutical sponsors must work proactively and collaboratively with all stakeholders to ensure a systematic approach to safety monitoring.
- Since clinical trials are experiments in human, they must be conducted following established standard in order to protect the rights, safety and well-being of the participants.

1. Sponsor
2. Subjects
3. Investigators
4. Institutional review board/Ethics Committee
5. Data and Safety Monitoring Board
6. Regulatory Authorities
7. Medical Community and patients

1) Sponsors:

- Clinical trials sponsors, usually pharmaceutical companies, are responsible for developing the clinical trials protocol. The protocol describes every aspect of the research, including the rationale for the experiment.
- The protocol also details the safety reporting procedures, specifically on the requirements for expedited reporting of serious adverse events.

❖ ICF

- The informed consent form is used to disclose current information about the investigational drug and about the procedure, risk and benefits for subject who participate in clinical trials.

❖ CRF

- Case report form are designed by the sponsor as data collection tools. This tool is based on electronic data capture module via internet rather than the traditional based route.

2) Subjects:

- Subjects are Patients or healthy volunteers who agree to participate in a clinical trials and have signed ICF.

3) Investigator:

- Investigators are qualified individuals who are trained and experience to provide medical care to the subject enrolled in the trails.

4) **Institutional Review Board / Ethics committee:**
   - The institutional Review Board (IRB) also known as Ethics Committee, is charged with protecting the rights and welfare of human subject recruited to participate in research protocol.
   - The IRB review all the Clinical trials protocol involving human subjects that the particular institution is involved with has authority to approve, disapprove or require modifications in the protocol.
5) **Data and Safety Monitoring Board:**
   - The Data and Safety Monitoring Board (DSMB), also called as Data Monitoring Committee (DMC) is an expert committee, chartered for one or more clinical trials. [2]
   - The DSBM is to review on the regular basis the accumulating data of the clinical trials to ensure the continuing safety of current participants and those who have yet to be enrolled.
6) **Regulatory Authority:**
   - Prior to the initiation of a first human in clinical trials, pharmaceutics sponsors must submit as Investigational New Drug (IND) application to the FDA has require by the law. The FDA reviews the IND (within the 30 calendar day) for safety to ensure that research subjects will not be subjected to unreasonable risk.
7) **Medical Community and Patients:**
   - Clinical trials generate data that contribute to the body of knowledge about the treatment and the disease that benefit the broader medical community and, ultimately, the patients. Safety information of one product may be informative to other practitioners using similar class of agent.

Communicating Safety Information among Stakeholders:

Timely communication among the various stakeholders is critical to ensure subject safety in clinical trials. Sponsors of clinical trials are accountable for monitoring the subjects appropriately, including the requirement of long-term follow up as appropriate. The protocol (including the ICF) specifies the details of the assessments, the frequency and the length of follow-up. In addition, most pharmaceutical sponsors have Standard Operating Procedures (SOPs) in place to collect, process, review, evaluate, report and communicate accumulating safety data to ensure a systematic approach for safety surveillance and monitoring. In general, safety information, including adverse events and laboratory findings are reported to a sponsor by investigators conducting the clinical trial. However, safety information may come from

sources outside the immediate clinical trial. The sponsor is required to promptly review all information relevant to the safety of the drug and to update subjects, investigators, IRBs and regulatory authorities of any new risks associated with the use of the investigational drug that arise from the clinical trial or from other sources.

Statistical Methods in Safety Monitoring:

- Methods for Single Arm Trials.
- Methods for Randomized, Controlled Trials.
- A Hypothetical Clinical Trial Example.

Unit V Regulatory Concepts

Basic terminology, guidance, guidelines, regulations, Laws and Acts, Orange book, Federal Register, Code of Federal Regulatory, Purple book

UNIT -5

BASIC TERMINOLOGIES IN REGULATORY CONCEPTS

INTRODUCTION:

Pharmaceutical regulations are defined as the combination of legal, administrative, and technical measures that governments take to ensure the safety, efficacy, and quality of medicines, as well as the relevance and accuracy of product information".

Its main task is to ensure the quality, safety and efficacy of drugs, and the accuracy of product information. This is done by making certain that the manufacture, procurement, import, export, distribution, supply and sale of drugs, product promotion and advertising, and clinical trials are carried out according to specified standards. Several of these functions also contribute to efforts to promote rational drug use" (WHO, 2001).

Pharmaceutical regulations have striven toward two goals simultaneously:

1) The development and production for market of new and effective therapeutics, and

2) The protection of the patient from unsafe and/or misbranded products**.**

BASIC TERMINOLOGIES

1. **Legislation:** It refers specifically to "the creation of laws that are usually written in fairly general terms to meet present and possible future needs. They have language that enables the government to issue regulations based on the law. Passing new laws requires a lengthy process and involves a country's legislative body".

2. **Regulations:** They are "the rules established by an agency that interprets the laws to facilitate their practical implementation". The drug regulatory authority is "the agency that develops and implements most of the legislation and regulations on pharmaceuticals.

3. **Regulatory Affairs:** Regulatory Affairs in a Pharmaceutical industry, is a profession which acts as the interface between the Pharmaceutical Industry and Drug Regulatory Authorities across the world. It is mainly involved in the registration of the drug products in respective countries prior to their marketing".

4. **Investigational New Drug (IND) Application:** It is an application which is tiled with FDA to get approval for legally testing an experimental drug on human subjects in the USA.

UNIT -5

5. **New Drug Application (NDA):** The NDA is vehicle through which drug sponsors formally propose that the approve a new pharmaceutical for sale and marketing in the US. The data gathered during the animal studies and human clinical trials of an investigational new drug become part of the NDA. In simple words, "It is an application which is tiled with FDA to market a new Pharmaceutical for sale in USA."

6. **Abbreviated New Drug Application (ANDA):** It is an application tiled with FDA, for a U. S. generic drug approval for an existing licensed medication or approved drug. In simple words, "It is an application for the approval of Generic Drugs."

7. **Generic Drug Product:** A generic drug product is the one the comparable to an innovator drug product in dosage form, strength, route administration, quality, performance characteristics and intended use.

8. **Marketing Authorization Application (MAA):** It is an application filed with the relevant authority in the Europe (typically, the UK's MHRA or the EMA's Committee for Medicinal Products for Human Use (CHMP) to market a drug or medicine. As per UK's MHRA: Applications for new active substances are described as 'full applications'. Applications for medicines containing existing active substances are described as 'abbreviated' or 'abridged applications'.

9. **Active Substance Master File (ASMF):** Active substance master file is a submission which is made to EMA, MHRA or any Drug Regulatory Authority in Europe to provide confidential intellectual property or 'know how' of the manufacturer of the active substance. In simple words, "It is a submission made to European Drug regulatory agencies on the confidential information of Active Substance or Active Pharmaceutical Ingredient (API)".

10. **International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH):** It is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.

UNIT -5

11. Common Technical Document (CTD): It is a set of specification for application dossier, for the registration of Medicines and designed to be used across Europe, Japan and the United States. Quality, Safety and Efficacy information is assembled in a common format through CTD. The CTD is maintained by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). CTD format for submission of drug registration applications/dossiers is widely accepted by regulatory authorities of other countries too like Canada, Australia, etc**.**

Orange Book

It is the publication of "Approved Drug Products With Therapeutic Evaluations by the Food and Drug Administration." It is prepared by the orange book staff, Centre for drug evaluation and research. It identified drug products on the basis of safety and effectiveness by the food and drug administration under the Federal Food, drug and Cosmetic Act. The list of independent of any current regulatory action against a drug product.

Objectives

- To review of patterns of access and usage.
- To allow discovery of use of unusual privileges.
- To allow discovery of repeated attempts to bypass protections.
- To serve as a deterrent by its existence.
- To supply an additional form of user assurance

Contents of "THE ORANGE BOOK":

The Orange Book is composed of four parts:

1. approved prescription drug products with therapeutic equivalence evaluations;
2. approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs or ANDAs because they are not covered under existing OTC monographs;
3. drug products with approval under Section 505 of the FD and C Act administered by the Center for Biologics Evaluation and Research; and
4. a cumulative list of approved products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing and we have not determined that they were withdrawn from sale for safety or effectiveness reasons

or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing.

This publication also includes indices of prescription and OTC drug products by proprietary name (brand name or trade name) or, if no proprietary name exists, established name of the active ingredient and by applicant name, which have been abbreviated for this publication. Established names for active ingredients generally conform to compendial names or UNITED STATES ADOPTED NAMES (USAN) as described in 21 CFR 299.4(e**).**

Hatch-Waxman Act

It is the popular name for Drug Price Competition and Patent Term Restoration Act, 1984. It is considered as the landmark legislation which established the modern system of generic drugs in USA. Hatch- Waxman amendment of the federal food, drug and cosmetics act established the process by which, would be marketers of generic drugs can file Abbreviated New Drug Application (ANDA) to seek FDA approval of generic drugs. Paragraph IV of the act, allows 180-day exclusivity to companies that are the "first-to-file" an ANDA against holders of patents for branded counterparts.

In simple words "Hatch-Waxman act is the amendment to Federal, Food, Drug and Cosmetics act which established the modern system of approval of generics". Patent Certifications under Hatch-Waxman Act: As per the Hatch and Waxman act, generic drug and 505 (b) (2) applicants should include certifications in their applications for each patent listed in the "Orange Book" for the innovator drug.

12. **Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP):** It is the certificate which is issued by Certification of Substances division of European Directorate for the Quality of Medicines (EDQM), when the manufacturer of substance provides proof that the quality of the substance is suitably controlled by the relevant monographs of the European Pharmacopoeia.

13. **Current Good Manufacturing Practice (cGMP):** It is practice and the systems required to be adapted in pharmaceutical manufacturing, quality control, quality system covering the manufacture and testing of pharmaceutical or drugs including; active pharmaceutical ingredients, diagnostics, foods, pharmaceutical products and medical devices.

14. **Good Clinical Practice (GCP):** It is an international quality standard that is provided by international council for Harmonization (ICH) that defines standards, which governments can transpose into regulations for clinical trials involving human subjects.

Good Laboratory Practice (GLP): It specifically refers to a quality system of management controls for research laboratories and organizations to try to ensure the uniformity, consistency, reliability, reproducibility, quality and integrity of chemical (including pharmaceuticals) safety and efficacy tests**.**

REGULATORY GUIDANCE AND GUIDELINES

- The FDA also is empowered to issue other documents which do not have the force of law and are not obligatory. The main document in this situation is the "Guidance". This represents FDA's current thinking on the issue in question. It is not a law and is not obligatory. As the FDA states on the first page of every guidance.
- Guidances "do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both."
- Guidances may be issued as drafts for comment or directly as final guidance's. FDA has no obligation to finalize draft guidance and it may simply be left as a draft.
- It is generally felt in the industry that following FDA guidance's is a wise course of action. However, a company is not obliged to follow guidance and will not be cited in an FDA inspection as failing to follow guidance. For example, the concept of Clinical Trial Data Monitoring Committees (DMCs) was issued as a guidance in March 2006 with an expiration date which has continually been extended and is now due to expire December 31, 2018. So DMCs are not obligations. In practice DMCs are very well accepted and their use is widespread. However, technically, they are not obligatory.
- FDA may issue other documents such as FAQs (frequently asked questions), white papers. comments and presentations from the Commissioner or other senior FDA officials. These documents may give opinions on FDA's thinking and thus are not obligatory unless they clearly reference laws or regulations. Careful attention must be paid.

- After a regulation is issued, the FDA may determine that it needs to provide industry, academia and other stakeholders with more information on how the FDA intends to exert (or decline to exercise , as the case may be) its regulatory authority.

INDIAN REGULATIONS AND GUDILINES

CDSCO	**Central drug standard control organisation(CDSCO),** ministry of health and family welfare, government of India provide general information about drug regulatory requirements in India.
NPPA	**Drugs (Price Control) Order 1995** and other orders enforced by **National Pharmaceutical Pricing Authority (NPPA)**, Government of India.
D&C Act 1940	**The Drugs & Cosmetics Act, 1940** regulates the import, manufacture, distribution and sale of drugs in India.
Schedule M	**Schedule M** of the D&C Act specifies the general and specific requirements for factory premises and materials, plant and equipment and minimum recommended areas for basic installation for certain categories of drugs.
Schedule T	**Schedule T** of the D&C Act prescribes GMP specifications for manufacture of Ayurvedic, siddha and unani medicines.
GCP guidelines	**The Ministry of Health, along with Drugs Controller General of India (DCGI) and Indian Council for Medical Research (ICMR)** has come out with draft guidelines for research in human subjects. These GCP guidelines are essentially based on Declaration of Helsinki, WHO guidelines and ICH requirements for good clinical practice.
The Pharmacy Act 1948	**The Pharmacy Act, 1948** is meant to regulate the profession of Pharmacy in India.
The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954	**The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954** provides to control the advertisements regarding drugs; it prohibits the advertising of remedies alleged to possess magic qualities.

UNIT -5

REGULATIONS

The FDA develops regulations based on the laws that are set forth in the FD and C Act as well as the other laws under which the FDA operates. Regulations issued by the FDA are federal laws and are modified in the Code of Federal Regulations. When issuing regulations, the FDA follows the procedures set forth in the Administrative Procedure Act (APA).

Broadly speaking, the APA sets for a Notice and Comment Rule Making process, which requires that regulatory agencies issue a proposed regulation, allow time for public input and then issue a final regulation.

Regulations" are the rules established by an agency that interprets the laws to facilitate their practical implementation. They can be passed more quickly and simply than laws. For example, the United States Food and Drug Administration (US FDA) has the rule-making responsibility for the "Food, Drug, and Cosmetic Act" of 1938 in the United States (US).

Regulations have a way of expanding far beyond the size of the enabling law. For example, the "Food, Drug, and Cosmetic Act" consisted of a mere 19 pages. Today, Code of Federal Regulations Title 21, which enforces the law, requires nine volumes containing over 4,000 pages.

Many laws then charge other US government agencies to create and issue regulations which have the force of law ("regulatory law"). In the case of DS & PV, this duty falls upon the FDA. These regulations do not have to be approved by the Congress or signed by the President.

A regulation is a rule or directive made and maintained by an authority or the or process of regulating or being regulated. A regulation, as it is published, is word for word and immediately the law.

UNIT -5

Regulations hold the force of law and must be obeyed in the country. The primary legislation refers to treaties and agreements at a very high level in the country. Ten there is secondary legislation that derives from primary legislation.

A proposed new or amended regulation is published in the Federal Register and a time period is usually defined for the public to comment. After review, the final regulation is published by the FDA in the Federal Register and in the Code of Federal Regulations. The time period for review may be very long. Sometimes a proposed regulation is withdrawn or never put into effect.

REGULATORY LAWS AND ACTS

Laws:

A law is defined as an assemblage of rules and regulations that are indispensable and must be followed. Law holds its single purview over the larger picture. It ensures that people will strictly follow the defined rules and regulations. It is more generic in its nature of operations and is not that complicated to comprehend. Law can be enforced as it has been established by the regulatory procedures. It is defined to stop malpractices, maintain public order, and most importantly to protect fundamental rights.

A law is an established phenomenon under regulation by government authority and holds sovereignty in it. Law includes Act, Rules, and Regulations, circulars, policies governing a particular subject or sphere of activity. In fact, it also includes customs and traditions, judicial pronouncements known as case law or precedent. Law is a broad term in which the whole range of provisions in which both procedural and substantive aspects are included. Law is a

living thing that evolves over a period of time that means the law is not complete once an Act is passed. The Act is only a guiding factor, following which the entire law is developed.

A law is written statute, requirement, ordinance passed by a legislature and signed into law by the executive (where required) at federal, state and local levels. One of the primar laws establishing the framework within which FDA operates the Federal Food, Drug and Cosmetic Act (FD and C Act). The FD a d C Act is amended by Congress from time to time. Some of the more significant amendments include the Orphan Drug Act of 1983, Food Quality Protection Act of 1996 and the FDA Food Safety Modernization Act 2011.

A law on medicine must, first and foremost and clearly define what all the parties- manufacturers, doctors and pharmacists are required to do, so that no serious misunderstanding is possible. Medicine registration law and regulations,

for example, make clear what a manufacturer needs to do to obtain licence to sell a product. They define how a registration agency should assess both the manufacturer and the product to determine if they meet society's needs.

A good law also creates administration bodies to put rules into practise, for example, a national drug regulatory authority with broad competence, or separate organs to deal with the various aspects of pharmaceuticals regulation such as practise of pharmacy, inspections of factories and advertising of medicines. When a law is approved, regulations are developed to guide the implementation of the law.

Regulatory law refers to secondary legislation, including regulations, promulgated by an executive branch agency under a delegation from a legislature; as well as legal issues related to regulatory compliance. It contrasts with statutory law promulgated by the legislative branch, and common law or case law promulgated by the judicial branch.

Regulatory law also refers to the law that governs conduct of administrative agencies (both promulgation of regulations, and adjudication of applications or disputes), and judicial review of agency decisions, usually called administrative law. Administrative law is promulgated by the legislature (and refined by judicial common law) for governing agencies.

The administrative agencies create procedures to regulate applications, licenses, appeals and decision making. In the United States, the Administrative Procedure Act is responsible for all federal agency policies.

UNIT -5

ACTS :

The Act was one of the earliest British statutes on the control of medicines and it established the appointment of four inspectors of Apothecary Wares, Drugs, and Stuffs. An Act is a decree that is approved by the respective legislature, for example in India it is the State Legislative Assembly or Parliament of India. An act is legislation passed by a competent legislature outlining the broad aspects of the activity intended to be regulated. The Act provides for the making of rules regulations and procedures. Therefore, an Act is a subset of Law. It is the foundation on which the law is erected. An Act is employed in specific situations meaning establishing regulations and rules in specified domains. For example, the Indian Companies Act, which regulates the formation and functioning of companies or corporations in India. Acts are conditional and specific depending on the domains they have been applied for. An Act is represented by the bill it is passed for and will not be enforced until it becomes law. Acts are made to make people aware of certain rules and regulations that are in place. For example, in India, an Act is originally a bill which is proposed by the Parliament first and when it gets approval from the Lok Sabha and Rajya Sabha and the President, it becomes an Act. Acts are provisions enacted by a legislative body or the government for the people to understand the meaning of specific circumstances.

Introduction :

The Orange Book: Reclaiming Liberalism, by members of the British Liberal Democrat party. Approved Drug Products with Therapeutic Equivalence Evaluations, published by the FDA's Center for Drug Evaluation and Research. The IUPAC Compendium of Analytical Nomenclature informally known as the Orange Book. One of the compact disc standards

collections in the Rainbow Books series. Orange-Book-Standard, issued in 2009 by the German Federal Court of Justice on the interaction between patent law and standards. Orange Book, a local area networking protocol based on the Cambridge Ring and one of the UK Coloured Book protocols.

Orange Book is a list of drugs and pharmaceuticals that the U.S. Food and Drug Administration (FDA) have approved as both safe and effective. Although it is commonly called the Orange Book, its formal name is Approved Drug Products with Therapeutic Equivalence Evaluations.

The Orange Book does not include drugs only approved as safe; they must also have been proven to be effective. Drugs whose safety or efficacy approval has been withdrawn are excluded from the Orange Book. However, a Drug that is currently subject to regulatory action may still appear in the Orange Book.

The main criterion for the inclusion of any product is that the product is the subject of an application with an approval that has not been withdrawn for safety or efficacy reasons. Inclusion of products in the Orange Book is independent of any current regulatory action being taken administratively or judicially against a drug product. It is the publication of "Approved Drug Products with Therapeutic Equivalence Evaluations" by the Food and Drug Administration. It is prepared by The Orange Book Staff, Center for Drug Evaluation and Research. It identified drug products on the basis of safety and effectiveness by the Food and Drug Administration under the Federal Food, Drug, and Cosmetics Act.

Drugs marketed only on the basis of safety or pre-1938 drugs. The list is independent of any current regulatory action against a drug product. The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons. The FDA does not recommend substituting drugs that have not been determined to be bioequivalent. Drugs that are not listed as bioequivalent should not be substituted for each other.

The main criterion for the inclusion of any product is that the product is the subject of an application with an approval that has not been withdrawn for safety or efficacy reasons. Inclusion of products in the Orange Book is independent of any current regulatory action being taken administratively or judicially against a drug product.

In addition, the Orange Book contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations have been prepared to serve as

public information and advice to state health agencies prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs, Therapeutic equivalence evaluations in this publication are not official FDA actions affecting the legal status of products under the FD&C Act.

History

YEAR	ACTION
May 31, 1978	The Commissioner of the Food and Drug Administration sent a letter to officials of each state stating FDA's intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multi-source prescription products.
January, 1979	The list was distributed (included only currently marketed prescription drug products approved by FDA through NDAs and ANDAs under the provision of section 505 of the Act)
January 12, 1979	A complete discussion of the background and basis of FDA's therapeutic equivalence evaluation policy was published in the Federal Register (44 FR 2932)
October 31, 1980	The final rule (includes FDA's response to the public comments on the proposal) was published in the Federal Register (45 FR 72582). The list incorporated appropriate corrections and additions.

On May 31. 1978, the Commissioner of the Food and Drug administration sent a letter to officials of each state announcing FDA'S intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.

The Orange Book was distributed as a proposal in January 1979. It included only currently marketed prescription drug products approved by FDA through new drug applications (NDAs) and abbreviated new drug applications (ANDAs) under the provisions of Section 505 of the FD&C Act and FDA regulations at that time.

The final rule, which includes FDA's responses to the public comments on the proposal, was published in the Federal Register on October 31, 1980. The first publication of the Orange Book in October 1980, concurrent with finalisation of the rule, incorporated appropriate

UNIT -5

corrections and additions Each subsequent edition has included new approvals and made appropriate changes in India.

Objectives :

To review of patterns of access and usage.

To allow discovery of the use of unusual privileges.

To allow discovery of repeated attempts to by pass protections.

To serve an deterrent by its existence.

To supply an additional form of user assurance.

Content :

1)Content And Exclusion :

1.Approved prescription drug products with therapeutic equivalence evaluations.

2. Approved over-the-counter (OTC) drug products for those drugs that may not be marketed.
3.Drug products with approval under Section 505 of the FD&C Act administered by the Centre for Biologics Evaluation and Research.

4.A cumulative list of approved products that have never been marketed, are for exportation, are for military use, have been discontinued from the market.

2) Therapeutic Equivalences:

1.**Pharmaceutical Equivalents:** Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient. Products that have identical strength or concentration. They may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients, expiration date/time, and, within certain limits. Labelling.

2.**Pharmaceutical Alternatives:** Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety. Different dosage forms and strengths.

3.**Therapeutic Equivalents:** Approved drug products are considered to be therapeutic equivalents if they are pharmaceutical equivalents for which bioequivalence has been demonstrated, and they can be expected to have the same clinical effect and safety profile when administered to patients.Under the conditions specified in the labelling.

4.**Bioavailability**: For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action.

5.**Bioequivalence**: Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

3) Further Guidance on Bioequivalence:FDA's regulations and guidance documents provide additional information regarding bioequivalence and bioavailability, including methodologies and statistical criteria used to establish the bioequivalence of drug products.

4) Reference Listed Drug: A reference listed drug is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. A reference standard is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval.

5) General Policies and Legal Status: The Orange Book contains public information and advice. It does not mandate the drug products that arePurchased, prescribed, dispensed, or substituted for one another, nor does it.Conversely, mandate the products that should be avoided. To the extent the Orange Book sets forth FDA's evaluations of the therapeutic equivaletes of drug products that have been approved, it contains FDA's advice to the public, to practitioners, and to the states regarding drug product selection.These evaluations do not constitute determinations that any product is preferable to any other.

6) Practitioner/User Responsibilities:

1.Professional care and judgment should be exercised in using the orange Book.

2.Multisource and single source drug products.

3.Products in the Orange Book are identified by the names of the holden of approved applications (applicants) who may not necessarily beManufacturer of the product.

4.Professional care and judgment should be exercised in using the Orange Book.

5.Multisource and single source drug products.

UNIT -5

6.Products in the Orange Book are identified by the names of the holden Proapproved applications (applicants) who may not necessarily be the manufacturer of the product.

7.Every product in the Orange Book is subject at all times to regulatory action.

7) Therapeutic Equivalence Evaluations Codes: The coding system for therapeutic equivalence evaluations is designed to allow users to determine quickly whether the Agency has evaluated a particular approved product.leg a particular strength of an approved drug) as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter).

1. A CODES: A products are those for which there are no known tr suspected bioequivalence problems or for which actual or potential bioequivalence problems have been resolved with adequate in vive and/or in vitro evidence supporting bioequivalence. A Drug product the FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products, i.e., drug products for which:

a) AN Solutions and powders for aeroionisation

b) AO Injectable oil solutions

c) AP Injectable aqueous solutions and, in certain instances intravenous non-aqueous solutions

d) AT Topical products

2.B CODES: B products, for which actual or potential bioequivalence. Problems have not been resolved by adequate evidence f bioequivalence, often have a problem with specific dosage forms rather than with the active ingredients.

B Drug products that FDA at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products, i.e.:

a) BC Extended-release dosage forms (capsules, injectable and tablets)

b) BD Active ingredients and dosage forms with documentel bioequivalence problems

c) BE Delayed release oral dosage forms

d) BN Products in aerosol-nebulizer drug delivery systems

e) BP Active ingredients and dosage forms with potential f) bioequivalence problems

f)BR Suppositories or enemas that deliver drugs for systemic absorption

UNIT -5

g) BS Products having drug standard deficiencies

h) BT Topical products with bioequivalence issues

i) BX Drug products for which the data are insufficient to determine therapeutic equivalence.

8) Description of Certain Special Situations: Amino Acid and Protein Hydrolysate Injections. These products differ in the amount and kinds of amino acids they contain and, therefore, are not considered pharmaceutical equivalents.

9) Therapeutic Equivalence Code Change for a Category of Multisource Drug Products: Such changes will generally occur when the Agency becomes aware of new scientific information affecting the therapeutic equivalence of an entire category of multisource drug products in the Orange Book (e.g., information concerning the active ingredient or the dosage form). Rather than information concerning a single drug product within the category. These procedures will be used when a change in therapeutic equivalence code is under consideration for all drug products found in the Prescription Drug Product List under a specific active ingredient and dosage form.

10) Discontinued Section: Those drug products in the discontinued section of the Orange Book (Discontinued Drug Product List) for which a determination has been made that the products were not withdrawn for safety or effectiveness reasons have been annotated with a footnote following the product strength.

Uses of orange book :

1.To search for innovators drugs and approved corresponding generic drug information.

2. It's helps in a taking important decision / strategies for pharmaceutical complain wheather to go into the market for sale or any modification can be done to existing drugs products it by filling a patents.

3. To retrive information such as drug application date, approval date and liot of releated patent to find out wheather the patent claim drug substance such as active pharmaceutical ingredients (API) and polymorph or drug product such as method of training, dosages, compositions, and formulations and also to find out the expiry dates and corresponding patents.

UNIT -5

FEDERAL REGISTER

Published by the Office of the Federal Register, National Archives and Records Administration (NARA), the Federal Register is the official daily publication for rules, proposed rules, and notices of Federal agencies and organizations , as well as executive orders and other presidential documents. Federal regulations are published in two venues. First, content related to rulemaking is published in the Federal Register in chronological order.

The Federal Register is published each business day by the federal government and includes presidential proclamations and executive orders, regulations, proposed regulations and notices. It often Code of Federal Regulations, which makes the Federal Register an invaluable resource contains background information about regulatory changes, not otherwise available in the for understanding regulations and the policies behind them. Additionally, the Federal Register can serve as a compliance officer's crystal ball, providing advanced notice of regulations (proposed regulations) that might affect one's compliance program inthe near future.

The Federal Register's notice proposal rule making includes the following points:

1) Step 1: Agency drafts rule in consultation with interested parties

2) Step 2: Proposed rule is published in Federal Register

3) Step 3: Interested parties may file written comments on written draft of rule,

usually within 30 days of publication in Federal Register

4) Step 4: First draft of rule, accompanied by statement of purpose and cost-benefit analysis, is published in Federal Register 30 days before it takes effect.

5) Step 5: During 30 day Period agency receives feedback from interested parties and decides if final drafts should be rewritten, if not, the rule becomes law.

CODE OF FEDERAL REGULATIONS (CFR)

The Code of Federal Regulations (CFR) annual edition is the codification of the general and permanent rules published in the Federal Register by the departments and agencies of the Federal Government. The online CFR is a joint project authorised by the publisher, the National Archives and Records Administration's (NARA) Office of the Federal Register (OFR), and the Government Publishing Office (GPO) to provide the public with enhanced access to Government information.

UNIT -5

CLASSIFICATION

The CFR is divided into 50 titles that represent broad areas subject to Federal regulation. Each title is divided into chapters, which usually bear the name of the issuing agency. Each chapter is further subdivided into parts that cover specific regulatory areas. Large parts may be subdivided into subparts. All parts are organised in sections, and most citations to the CFR refer to material at the section level.

The 50 subject matter titles contain one or more individual volumes, which are updated once each calendar year, on a staggered basis. The annual update cycle is as follows:

1) Titles 1-16 are revised as of January 1

2) Titles 17-27 are revised as of April 2

3) Titles 28-41 are revised as of July 3

4) Titles 42-50 are revised as of October 4

CONTENT

1) It currently contains the titles from 1996 to the present. CFR volumes are added concurrent with the release of the paper editions. When revised CFR volumes are added, the prior editions remain on govinfo as a historical set.

2) Bulk data downloads of Code of Federal Regulations XML files are available to the general public via Data.gov and GPO's Bulk Data Repository. Information on the legal status, authenticity, and schema of the Code of Federal Regulations XML renditions can be found in the User Guide Document - Code of Federal Register XML Rendition.

3) To see more recently updated titles of the CFR, visit the electronic Code of Federal Regulations (e-CFR), a regularly updated, unofficial editorial compilation of CFR material and Federal Register amendments. The eCFR is updated on a daily basis.

4) To see a cumulative list of CFR sections that have been changed at any time since each CFR title was last updated, view the List of CFR Sections Affected (LSA)

5) To find final and proposed rules that affect the CFR and have been published in the Federal Register within the past 24 hours, week, month, or within a specific date range, browse the CFR Parts Affected from the Federal Register.

STRUCTURE OF ORGANISATION

The following describes how information is contained in a CFR citation:

1) Title: The numeric value to the left of "CFR"

2) Part: The numeric value to the right of "CFR" and preceding the period (".")

3) Section/Subpart: The numeric value to the right of the period (".") A subpart is a letter of the alphabet (A-Z) that is used to retrieve an entire subpart of the CFR rather than many individual sections. For example: Subpart E.

4) Revision Year: Four digit year from the "Revised as of" text represents the year being cited. The revision year is not always available when the CFR is cited.

5) Example: 21 CFR 310.502 Revised as of April 1, 1997.

i) Title: 21

ii) Part: 310

iii) Section: 502

iv) Year: 1997

CODE OF FEDERAL REGULATIONS (CFR)

DEFINATION-CFR

The code of federal regulations (CFR) is “the codification of the general and permanent rules by the department and agencies of the federal government.” this is a historical collection of the code of federal regulations dating from 1938-1995. To access the code of regulations from 1996- present.

The C.F.R. has 50 titles, with each title focusing on a subject area. The titles are in turn broken down into chapters, which are often named for the agency that issued the rules included, subchapters, parts, and occasionally subparts, before coming down to individual rules or “sections” some titles are brief, spanning only a single slim volume, while others may fill twenty volumes.

UNIT -5

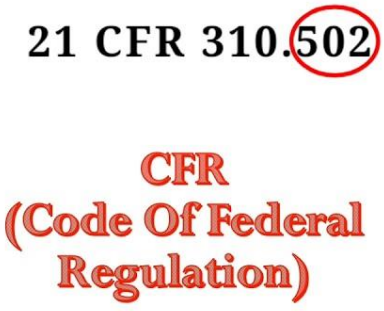
PUBLICATION PROCEDURE

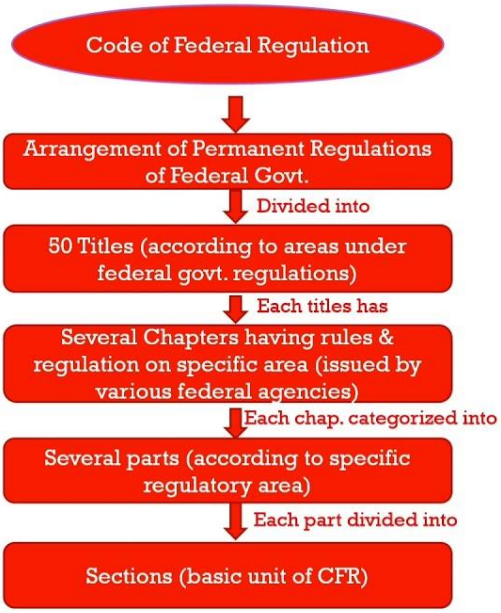
The rules and regulation are first promulgated or published in the federal register. The CFR is structured into 50 subject matter titles. Agencies are assigned chapters within these titles. The titles are broken down into chapters, parts, sections and paragraphs. For example, 42 C.F.R. 260.11(a)(1) would indicate "title 42, part 260, section 11, paragraph (a)(1)."

While new regulations are continually becoming effective, the printed volumes of the CFR are issued once each calendar year, on this schedule:

- Titles 1-16 are updated as of January 1
- Titles 17- 27 are updated as of April 1
- Titles 28- 41 are updated as of July 1
- Titles 42- 50 are updated as of October 1

The office of the federal register also keeps an unofficial, online version of the CFR, the e-CFR, which is normally updated within two days after changes that have been published in the federal register become effective. The parallel table of authorities and rules lists rulemaking authority for regulations codified in the CFR.





HISTORY OF CFR

UNIT -5

- Franklin D. Roosevelt – 32nd president of the US.
- 1935 – instrumental in passing the federal register act – empowered the national archives of the US to form an administrative committee publish the federal register.
- The federal register act – amended in 1937 to provide a "codification" of all regulations every five years – known as code of federal regulations.
- The first edition of the CFR was published in 1938 and included all finalised regulations that were published in the federal register from march 14, 1936 to June 1, 1938.
- Beginning in 1963 for some titles and for all titles in 1967, the office of the federal register began publishing yearly revisions.
- Beginning in 1972 – published revisions were conducted in staggered quarters.

CFR TITLE 21

- Title 21 of the CFR is reserved for rules of the food and drug administration.
- Governs food and drugs within the united states for the FDA, DEA, and the ONDCP.
- In all, 21 CFR consists of 1499 parts.
- It is divided into three chapters:
- Chapter 1 – food and drug administration
- Chapter 2 – drug enforcement administration
- Chapter 3 – office of national drug control policy

CHAPTER 1

- Most of the chapter 1 regulations are based on the federal food, drug and cosmetic act.
- 11 electronic records and electronic signature related.
- 50 protection of human subjects in clinical trials.
- 56 institutional review boards that oversee clinical trials.
- 58 good laboratory practices (GLP) for nonclinical studies.
- The 100 series are regulations pertaining to food.
- The 200 and 300 series are regulations pertaining to pharmaceuticals the 500 series are regulations for animal feeds and animal medications.
- The 600 series covers biological products.
- The 700 sreies includes the limited regulations on cosmetics.

UNIT -5

- The 800 series are for medical devices.
- The 900 series covers mammography quality requirements enforced by CEDRH.
- The 1000 series covers radiation – emitting device.
- The 1100 series includes updated rules with regards to tobacco products.
- The 1200 series consists of rules primarily based in laws other than the food, drug, and cosmetic act.

CHAPTER 2

- Notable sections:
- 1308 – schedules of controlled substances
- 1308.03(a) – administrative controlled substances code number
- 1308.11 – list of schedule 1 drugs
- 1308.12 – list of schedule 2 drugs
- 1308.13 – list of schedule 3 drugs
- 1308.14 – list of schedule 4 drugs
- 1308.15 – list of schedule 5 drugs

The list of schedule drugs, as a part of the controlled substances act, falls under the policy of the united states government. The following findings are required for drugs to be placed in the aforementioned schedules.

LIST OF CODE OF FEDERAL REGULATIONS

- Title 1: general provisions
- Title 2: grants and agreements
- Title 3: the president, compilation and reports
- Title 4: accounts
- Title 5: administrative personnel
- Title 6: homeland security
- Title 7: agriculture
- Title 8: aliens and nationality
- Title 9: animals and animal products
- Title 10: energy

UNIT -5

- Title 11: federal elections
- Title 12: banks and banking
- Title 13: business credit and assistance
- Title 14: aeronautics and space
- Title 15: commerce and foreign trade
- Title 16: commercial practices
- Title 17: commodity and securities exchanges
- Title 18: conservation of power and water resources
- Title 19: customs duties
- Title 20: employee benefits
- Title 21: 2009 only food and drugs
- Title 22: foreign relations
- Title 23: highways
- Title 24: housing and urban development
- Title 25: Indians
- Title 26: internal revenue
- Title27: alcohol tobacco products and firearms
- Title 28: judicial administration
- Title 29: labor
- Title 30: mineral resources
- Title 31: money and finance
- Title 32: national defence
- Title 33: navigation and navigable waters
- Title 34: education
- Title 35: Panama canal
- Title 36: parks, and public property
- Title 37: patents, trademark and copyrights
- Title 38: pensions, bonuses and veterans relief
- Title 39: postal health
- Title 40: protection of the environment
- Title 41: public contracts and property management
- Title 42: public health

- Title 43: public lands
- Title 44: emergency management and assistance
- Title 45: public welfare
- Title 46: shipping
- Title 47: telecommunications
- Title 48: federal acquisition regulations system
- Title 49: transportation
- Title 50: wildlife and fisheries.

CONCLUSION

The federal register and the code of federal regulations replaced the existing system of dual set of regulations and legislations that were in place.

Although not perfect, the federal register and the CFR appear to have met their original purpose of providing the public with a comprehensive publication vehicle for all the regulations issued by federal agencies and the president.

PURPLE BOOK

The Purple Book is an electronic record of all FDA licensed biological products that is managed by the CDER and acts as a record of licensed biological products and their reference products including bio similar and interchangeable products. The Purple Book also includes data on all the FDA-licensed allergenic, cellular and gene therapy, hematologic and vaccines regulated by CBER.

That is why the nickname “Purple Book” is so easy to remember. How a colour is used for the nickname of the list can be explained referring to the fact that at FDA the nickname ‘The Orange Book’ was used for ‘Approved Drug Products with Therapeutic Equivalence Evaluations’. For this reason, health care professionals and other people with interest in Orange Book favor this longer but official title. FDA, thus, sought a likewise non-intimidating term for a reference that included biologics, bio similar, and interchangeable products. This can be said, for example, if one time during a meeting a staff member remarked, “how about purple?” Ever since, people started calling it the “Purple Book. ”

UNIT -5

Purpose

The primary purpose of the Purple Book is two-fold: to allow a user to determine whether a biological product which was licensed under section 351(k) of the PHS Act has been found by the FDA to be therapeutically equivalent or interchangeable to a reference biological product; which is an already licensed innovator biological product approved under section 351(a) of the PHS Act and to also give information on any existing reference product exclusivity for protecting a reference biological product.

Content

Some of the information you can find in the Purple Book include:Some of the information you can find in the Purple Book include:

1) The date a biological product was approved under section 351(a) or 351(k) of the PHS Act.
2) whether a biological product licensed under section 351(k) of the PHS Act

has been approved by the FDA as to be therapeutically equivalent to the reference biologic product (an already FDA licensed biological product).

3) The date on which the exclusivity applicable under section 351(k)(7) of the PHS act if FDA has the biological product for reference product exclusivity or under section 351(k)(6) of the PHS act for the first interchangeable biological product.

4) As for the information for multiple users (e. g. . patients, the general public, the manufacturers, researchers, and healthcare providers), all of them are welcome to read the User Guide to know how to use the Simple Search and the Advanced Search. such as how to get to the labelling of a product.

Biologics Price Competition and Innovation Act of 2009 (BPCI Act)

1) To understand the Purple Book, let's review the key statutory definitions and concepts related to biological products brought about by the passage of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act).

2) The BPCI Act created both the licensure pathway for biologics allowing for the licensure of bio similar and interchangeable biologics, and for the first time created an exclusivity period for certain qualifying innovator biological products.

3) Until the passage of the BPCI Act, applications for biological products had to contain a full complement of product-specific preclinical and clirical data. These "soup to nuts" applications were approved under section 351(a) of the PHS Act.

4) The BPCI Act, however, amended the PHS Act to create section 351(k) that describes the abbreviated regulatory approval pathway established for biological products. 5) Products evaluated under this pathway can be approved based on less than full compleinent of product-specific preclinical and clinical data because of reliance on what is previously known about the reference product (publicly-available information), including FDA's previous finding of safety and effectiveness of the reference product.

6) There are two types of biological products under the 351(k) pathway: biosimilar products and interchangeable biological products. 201 7) Bio similarity and inter changeability are assessed with respect to a reference product.

8) A reference product is the single biological product licensed by FDA under section 351(a) of the PHS Act against which a proposed biological product is evaluated in an application submitted under section 351(k).