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Unit III

Regulatory affairs/ regulatory requirements for drug approval

Prajakta R. Patil [1], Sachin S. Mali [2], Riya R. Patil [3], Dhanashree R. Davare [4]

[1,3,4] *Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, 416 112, India*
[2] *Department of Pharmaceutics, Bharati Vidyapeeth college of Pharmacy, Kolhapur 416 013, India*

[1] dhanashreedavare@gmail.com

Abstract: Introduction, Regulatory Affairs Historical Overview, Regulatory Authorities, Regulatory Affairs Department Role, and Regulatory Affairs Professionals' Responsibilities. Regulations needed to approve a drug: Clinical research / BE studies, Clinical Research Protocols, Biostatistics in Pharmaceutical Product Development, Data Presentation for FDA Submissions, Pharmacology, Drug Metabolism and Toxicology, Non-Clinical Drug Development, Pharmacology, Investigational New Drug (IND) Application, Investigator's Brochure (IB) and New Drug Application (NDA), and Management of Clinical Studies.

Keywords: Drug Approval, Clinical Research, Investigational New Drug (IND), New Drug Application (NDA), Biostatistics

1.1 Introduction

According to international standards, the pharmaceutical industry is currently very well-coordinated, efficient, and compliant in its production of various biological and chemical drugs (as well as medical devices, traditional herbal products, and cosmetics) for both human and veterinary use. The current well-defined and controlled regulatory framework is the result of various difficulties that the regulatory system has faced. The results of this framework lead to the methodical manufacturing and distribution of safe, efficient, and high-quality drugs. As the pharmaceutical industry has developed tremendously, regional rules have become more complicated, creating an urgent demand for regulatory specialists .Regulatory affairs are a dynamic and demanding profession created by the government to protect public health by regulating the safety and

effectiveness of products in industries such as pharmaceuticals, veterinary medications, medical devices, pesticides, agrochemicals, cosmetics, and complementary medicines.

1.2 Aspect Of History

Several catastrophes occurred throughout the 1950s, including the thalidomide, vaccination, and sulphanilamide elixir disasters, which resulted in a considerable rise in legislation limiting the efficacy, safety, and quality of pharmaceutical items. As a result, standards for Good Manufacturing Practices (GMPs) and Marketing Authorisation (MA) grow stricter.

Up to the twentieth century, India's medicinal industry was quite primitive. The majority of the medicines were imported from foreign countries.

a. **1900–1960:** The government implemented the Poisons Act of 1919 to control and prohibit the sale of low-cost drugs. This Act facilitates the sale and possession of poisonous substances. It also established the maximum number of poisons that might be sold, how they should be packed and labelled, how they should be kept safe and secure, and how vendors should inspect and test the poisons they sell throughout the year.
   The Dangerous Drugs Act of 1930, which regulated the production, possession, and trafficking of opium, came after the Poisons Act.
   The Narcotics and Psychotropic Substances Act of 1985 repealed the Dangerous Drugs Act of 1930 and the Opium Act of 1878.

These laws and rules which have been enforced during the time period include:

- **Drugs and Cosmetics Act, 1940:** It deals with the production, supply, importation and distribution of allopathic, homeopathic, unani, and siddha drugs.
- **Drugs and Cosmetics Rules, 1945:** It involves the regulation of Ayurvedic production to be sold instead of its use or for possession.
- **Pharmacy Act, 1948:** This Act was amended in 1986 generally to control and regulate the profession of pharmacists in India.
- **Drugs and Magical Remedies (Objectionable Advertisement) Rules, 1955:** These Rules regulate the advertisement of medicines in India.
- **DPCO, 1955 under the Essential Commodities Act:** DPCO was amended further in 1995. According to this rule, the government is empowered to examine and fix the maximum selling price of bulk medicines and preparations.

b. **1960–1970:** The Indian pharmaceutical sector was in its infancy, with multinational corporations controlling the vast majority of the market and relatively few Indian

producers. Because the bulk of shares rely on high-volume medication imports, medicines are scarce and expensive. Because there was no patent protection at the time, pure research and development received less attention.

c. **1970–1980:** The government took up the responsibility of drug control and enacted several laws and regulations. The Indian Patent Act 1970, which superseded the Indian Patents and Designs Act of 1911 and went into effect on April 20, 1972, is the main legislation governing patent protection in India. This Act authorised techniques and methods for creating drug compounds, but not product patents.
   - **Drug costs are capped:** The Drug Costs Control Order (DPCO) was put into place to prevent customers from paying exorbitant rates.

d. **1980–1990:**
The Indian industry has set up production infrastructure and began to invest in API process development**.**

e. **1990–2000:** The pharmaceutical industry had considerable growth in the domestic market. Businesses have begun to participate in R&D**.**

f. **2000-2010:** The years 2000–2010 are known as the Innovation and Research Era. During these years, there was innovative research, patenting of drug formulae, procedures, and indications, and firm mergers.

Patent Amendment Act 2005: To address the country's patent worries, the Indian government enacted the Patents (Amendment) Ordinance in 2004. This was later replaced by the Indian Patent (Amendment) Act of 2005. To address patent issues in the technical, chemical, and pharmaceutical industries, the new Act made numerous substantial changes to the legal structure of patent protection.

Compulsory Licenses: Compulsory permits allow pharmaceutical goods to be produced and exported "to any country having insufficient or no manufacturing capacity, for the said product, to address public health problems.

Below are a few names:

- Clinical research organisations (CROs) must register under the 2011 Drugs and Cosmetics (First Amendment) Rules before conducting clinical trials (CT).
- The Clinical Trial Registry-India (CTRI) was developed by the Indian Council of Medical Research's National Institute of Medical Statistics (NIMS).

- The CDSCO developed the Pharmacovigilance Program of India (PvPI) to ensure pharmaceutical safety for Indian patients.

Table No.3.1 An overview of RA's history (with significant regulatory events each year)

Year	Event	Purpose
1906	Pure Food and Drug Act	Prevent false claims
1930	FDA takes its current name	Agency is purely regulatory—no research functions
1938	Federal Food, Drug, and Cosmetic Act	Require proof of safety before marketing
1949	First publication of FDA "Guidance to Industry"	Address the appraisal of toxic chemicals in foods
1962	Kefauver–Harris Drug Amendments	Require proof of efficacy and safety before marketing
1987	Prescription Drug Marketing Act	Ensure that pharmaceutical products purchased by consumers are safe and effective, and free from counterfeit, adulterated, misbranded, subpotent, or expired drugs
2004	Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach	Emphasize risk-based approaches to development and manufacturing
2004	PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance	Achieve greater understanding of drug development and manufacturing processes. Data acquisition and multivariate analysis cited as important tools
2005	ICH Harmonized Tripartite Guideline: Pharmaceutical Development, Q8	Foster quality by design and the understanding of design space—emphasis on design of experiments to define interactions and work in multidimensions
2005	ICH Harmonized Tripartite Guideline: Quality Risk Management, Q9	Encourage the use of quality risk-management tools in all phases of a product's lifecycle
2007	ICH Harmonized Tripartite Guideline: Pharmaceutical Quality System, Q10	Enhance science- and risk-based regulatory approaches

1.3 Regulatory Authorities

The authorities that regulate:

Pharmaceuticals, medical equipment, and goods for human and animal use must be safe and effective for their intended purpose, with public health as the first priority. Several territorial regulatory organisations were formed to ensure this.

Important regulatory bodies include Health Canada (Canada), the Pharmaceuticals and Medical Devices Agency (PMDA, Japan), the Therapeutic Goods Administration (TGA, Australia), the European Medicines Agency (EMA, European Union), the World Health Organisation (WHO), the United States Food and Drug Administration (USFDA, USA), the Medicines and Healthcare Products Regulatory Agency (MHRA, UK), and the Central Drugs Standard Control Organisation (CDSCO, India). There is a need for global harmonisation since regulatory norms differ based on local demands. In 1990, the United States, Europe, and Japan formed the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The ICH has evolved over time in order to achieve more worldwide harmonisation in the

development and registration of pharmaceuticals with a higher degree of safety, efficacy, and quality. Regional regulatory authorities continue to have a significant impact on pharmaceutical approvals in the region, even though ICH has worldwide standardised drug regulatory features.

Drug Regulatory Affairs Department role:

A) During development phase:

- Ascertain adherence to legal requirements in order to establish safety, effectiveness, and quality standards.
- Development studies should seek scientific input from authorities.

Create a regulatory plan.

- Participate in multidisciplinary project teams.
- Ensure adherence to clinical trial guidelines.
- Submit application for clinical trial conduct.
- Manage regulatory filings with care.
- Cut down on time to market—every day matters.
- Proposals for a worldwide development plan.

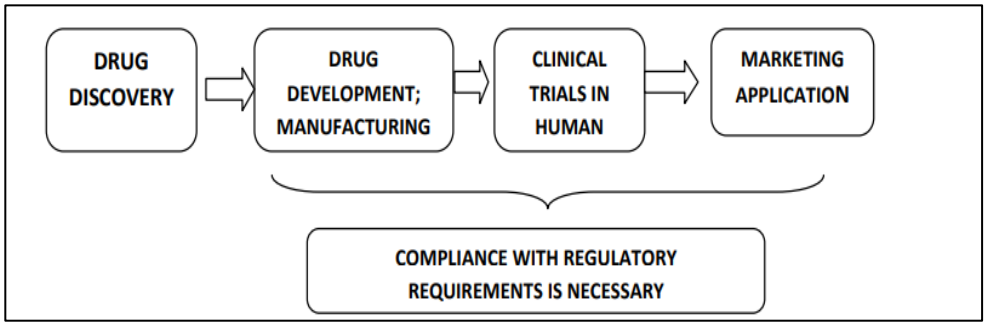


Fig. No.3.1: Drug development process

- **Improve submission tactics:**
  - preparing the dossier,
  - Reusing documents and formats.
  - Electronically submitted
  - Examining high-level documents and reports

• Involvement in the business's commercial aspects, such as reimbursement and pricing.

B) During the approval phase:

- Monitor the status of the evaluation and get ready for questions.
- Collaborate with other departments to address problems and offer solutions.

- Organize and manage agency hearings and meetings.
- Consider product information and approval with agencies.

C) During the post-approval stage:

- Compliance.
- Submit modifications or variants.
- Review product information and ensure pharmacovigilance.
- New formulations and indications.
- Renewal

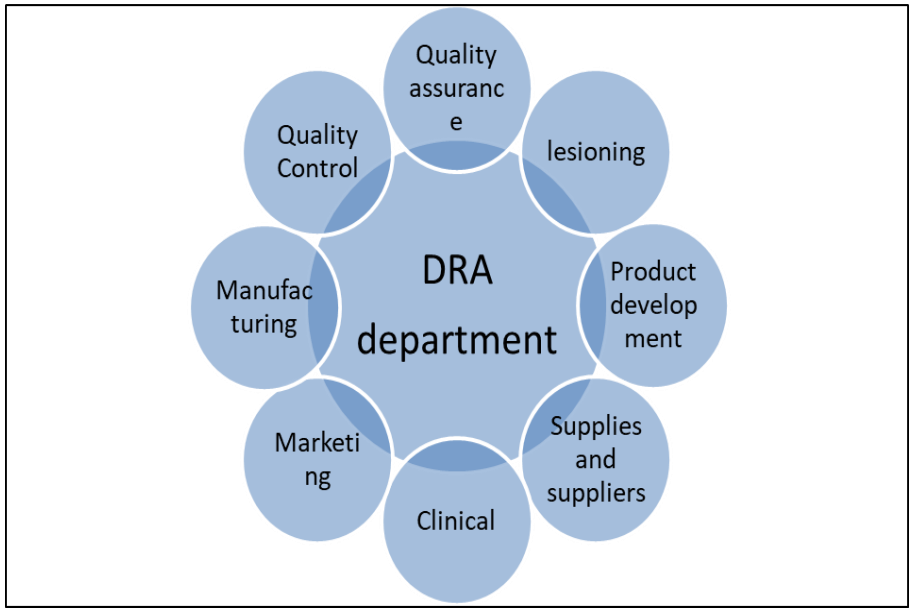


Fig. No.3.2: DRA department

Regulatory input to development plans/ Regulatory Intelligence.

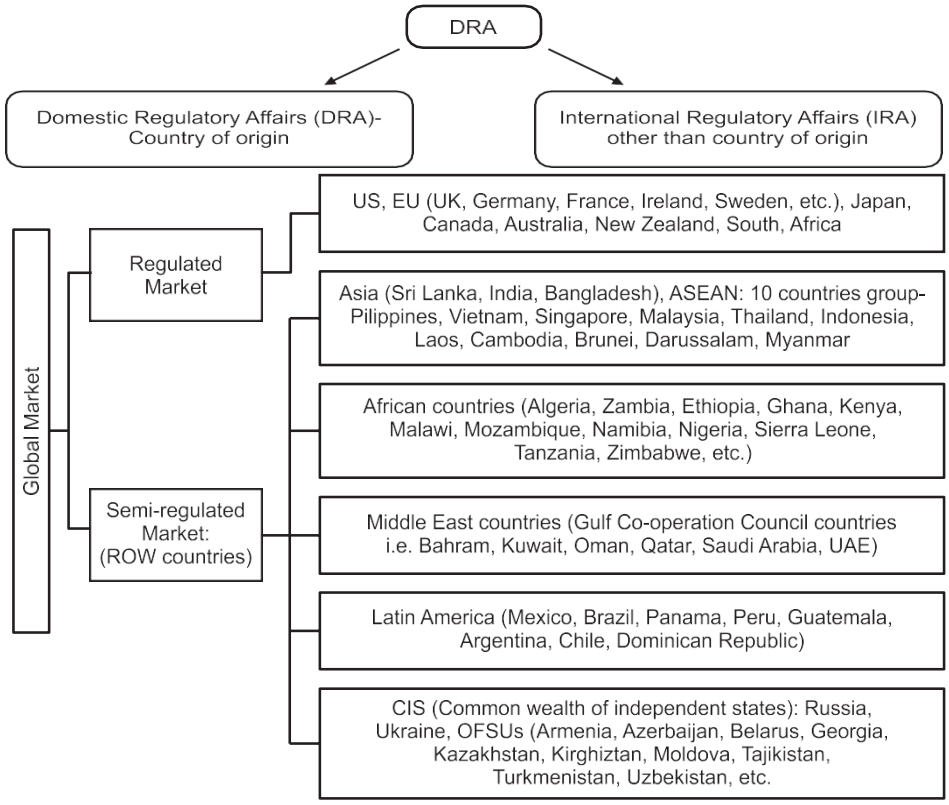


Fig. No.3.3: Various Role of Drug Regulatory Affairs Department

- A DRA specialist is necessary throughout the medication development and post-marketing process.
- Pharmaceutical corporations collect data on drug research and development for registration and marketing purposes.
- To ensure the medicine's safety and efficacy in humans, the company's RA specialists must follow a number of tight guidelines during the medication development process.
- The regulatory affairs department must authorise a drug or product's packaging and advertising before commercial use. It also contributes to medication development and marketing tactics.

1.4 Professionals In Regulatory Affairs Are Responsible:

- Ensuring compliance with relevant laws and regulations within their organisations.
- Collaborating with federal, state, and local regulatory authorities and personnel to address specific business difficulties.
- Advising businesses on environmental and regulatory implications for their operations.
- Keep up with worldwide rules, regulations, and consumer behaviour. Stay current on a company's product portfolio.
- Collect, compile, and evaluate scientific data generated by colleagues in research and development.
- Develop regulatory plans for contract, international, and domestic projects.
- Coordinate, prepare, and submit relevant paperwork (e.g., dossiers) to regulatory bodies within specified timeframes.
- Develop and review RA-related SOPs. BMR, MFR, change control, and other related works are reviewed.
- Track registration submissions' progress.
- Manage authorised applications and registration fee payments for DMF and other document submissions.
- Answer questions and ensure prompt approval and registration.
- Participate in post-marketing monitoring (ADR), pilot plant scaling up, and R&D training.
- Manage and assess customer, regulatory, and compliance inspections and audit reports.
- Provide doctors and medical specialists with accurate and thorough information about product efficacy, safety, and quality.

1.5 Drug Approval Regulatory Requirements:

Currently, different nations must follow different rules for a new drug's regulatory clearance. Understanding the legal requirements for Marketing Authorisation Applications (MAAs) in each country is critical, as it is practically impossible for all nations to follow the same regulatory approach.

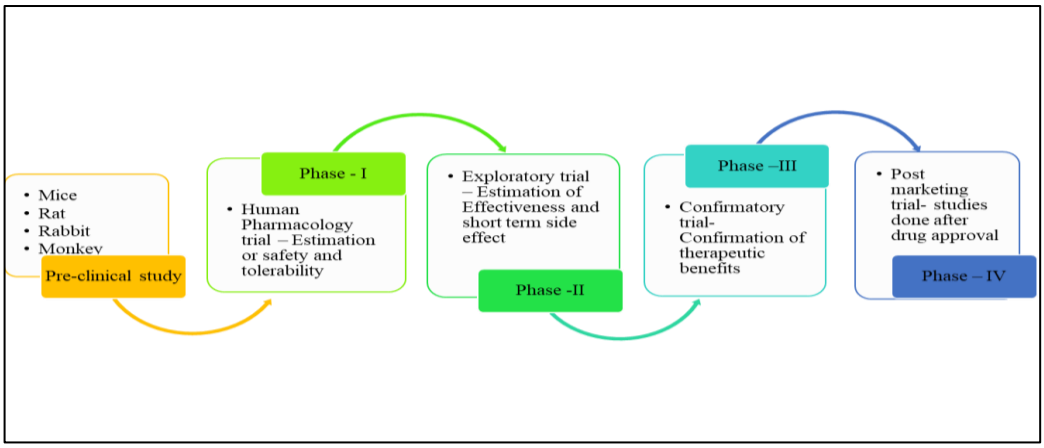


Fig. No. 3.4: Different phases of clinical trials

A novel drug Application (NDA) is a request for permission to commercialise a novel drug submitted to the relevant regulatory agency. To get this approval, a sponsor must present preclinical and clinical test results for the analysis of drug information, as well as a description of the production methods.

When the agency receives the NDA, it conducts a technical evaluation. The goal of this review step is to ensure that the essential data and supporting paperwork have been included in each component of the application form, thereby "filling" it out.

At the conclusion of the review of an NDA, there are 3 possible actions that can send to sponsor. If the action taken is either an approvable or a not approvable, then the regulator body provides applicant with an opportunity to meet with agency and discuss the deficiencies.	**NOT APPROVABLE** In this letter list of deficiencies and explain the reason.
	APPROVABLE It means that the drug can be approved, but minor deficiencies that can be corrected like-labeling changes and possible request commitment to do post-approval studies.
	APPROVAL It states that the drug is approved.

Fig. No.3.5: Possible action after the review of NDA

Drug Development Teams: Drug development project teams are used by most pharmaceutical and biotechnology businesses to direct the processes involved in the early

phases of drug discovery, through the several stages of drug development, and ultimately into the transformation of the candidate drug into a therapeutic product.

A wide range of individuals with varying perspectives and approaches to the development process comprise the drug development team. To ensure a medication's safety and effectiveness, all team members must work closely together. These project teams are responsible for the following tasks:

1. Analyse research outcomes from various scientific domains.
2. Combining data from previous studies with new results.
3. Organising research to offer further information on a possible treatment.
4. Develop a thorough drug development plan that identifies the critical path, establishes a timeline, and identifies key milestones.
5. Monitoring research project progress to ensure it adheres to the development plan's timeline and critical path. Adjusting plans as needed to reflect new information.
6. Examining research findings, development progress, and timetables for competing pharmaceutical options.
7. Conducting market research to ensure medicine development is financially viable and meets medical needs.
8. Providing management with an update on medication development progress and recommendations for the candidate's progression.

The following teams make up drug development teams:

1. The discovery and development teams consist of chemists and basic scientists responsible for developing the novel molecule. This organisation offers clinical supplies and synthesises drug molecules for pharmacology, toxicology, and "drug-screening" studies.
2. The Toxicology and Nonclinical Pharmacology Team assesses pharmaceutical safety and efficacy in animal models to identify potential issues for human use. To ensure that animal studies are applicable in therapeutic settings, the development and clinical teams must work closely with lexicologists.
3. Team for Clinical Research: Clinical research is ultimately in charge of testing pharmaceutical products on humans; it is also responsible for monitoring drug safety. Clinical trials must have clinically significant outcomes, be scientifically sound, and use suitable statistical methods. Clinical research is responsible for developing study reports with the support of regulatory affairs and biostatisticians, and it has direct interaction with the FDA. Furthermore, clinical research can provide the papers needed for any medicinal product's commercialisation.

4. The Regulatory Affairs Team: The FDA is contacted through the regulatory affairs division. They are in charge of making sure that the rules set out by the Federal Food Drug and Cosmetic Act and its amendments are adhered to.
5. The Marketing Group: Marketing team is ultimately responsible for promoting and selling the drug. They thus desire product labelling that distinguishes their medication from others on the market. Marketing must provide fresh ideas to upper management, patients, and prescribing physicians. Additionally, they must guarantee that fiscal targets are met. The marketing department typically differs from the clinical and regulatory parts, both within their own organisation and with the FDA.
6. Legal Group: Patent protection is vital for a drug's financial success. The legal staff must file patent applications on time and take all necessary precautions to stay out of possible legal action from rivals. Additionally, the legal staff makes sure that no advertising or promotional materials will be challenged by the FDA or any other organisation or business.
7. Team Management: They communicate with each team and are in responsibility of completing the project on time.

1.6 Pharmaceutical Drug Development:

1. The process of introducing a new therapeutic molecule to the market following the discovery of a lead chemical is known as pharmaceutical drug development.
2. Lead compounds are newly synthesised medicinal molecules that exhibit promising pharmacological action against a biological target specific to a disease. They are often referred to as novel chemical entities (NCEs) or new molecular entities (NMEs).
3. During the drug discovery phase, lead compounds are found by appropriate screening techniques, such high-throughput screening.
4. From lead chemical discovery to commercialization, there are several stages in the drug development process.

1.7 Pre-Clinical or Non- Clinical Phase Of Drug Development:

- Pre-clinical drug development involves the pharmacological and toxicological study of a chemical in animal models to establish the safety and effectiveness of a potential therapeutic therapy before it is provided to human volunteers during the clinical trial phase.
- Medication candidates are examined pharmacologically and toxicologically utilising in-vitro and in-vivo procedures, following GLP guidelines. The GLP guidelines may be found in 21 CFR Part 58.1: Good Laboratory Practice for Nonclinical Laboratory Studies.

- Animal models for in-vivo testing include mice, rats, guinea pigs, dogs, monkeys, & other rodents, whereas isolated tissues or cell lines are used in vitro.

Pre-clinical Drug Development involves following major type of studies:

1. Research on pharmaceuticals:

i. **Pharmacokinetic profile Study:** It focuses on ADME research. Males and females of two species, usually dogs and rats, are used in ADME tests, which are frequently repeated with different dose levels.

The main objectives of pharmacokinetic studies are to determine the optimal dosage level and provide information on the dose-effect relationship. Consequently, a number of physiological processes are investigated, and detailed information on the material's absorption, distribution, metabolism, and excretion (ADME) is generated**.**

Table No. 3.2: Proposed ADME/PK non-clinical tests

In vitro	*In vivo*	*In vivo*
1) Physical/chemical properties [lipophilicity (log P/log D), solubility, chemical stability (pKa)]	1) Pharmacokinetic profile (concentration versus time)	1) Toxicokinetic
2) Metabolic stability	- Area under the curve	- Pharmacokinetic profile (concentration versus time)
3) Hepatic clearance	- C_{max}	- Area under the curve
4) Interaction between substances (inhibition/induction of CYPs)	- T_{max}	- C_{max}
5) Physiological characteristics (plasma protein/tissue binding)	- Distribution	- T_{max}
6) Permeability	- Clearance	- Distribution
7) Plasmatic stability and total blood/plasma partition	- Half-life time	- Clearance
	2) Biodisponibility bioavailability	- Half-life time
	3) Linearity	2) Biodisponibility
	4) Metabolization	3) Metabolization
	5) Routes of excretion	4) Routes of excretion
		5) Quantification of biological fluids, organs, tissues, excrements and expired air (when necessary)

- **Study of Metabolism:**

To explain how a lead or drug candidate acts in the body, including if and to what degree the chemical is changed, drug metabolism studies are required. studies on metabolism that employ both in-vitro and in-vivo methods.

The in-vitro studies may be performed on a variety of systems, including microsomes, hepatocytes, liver slices, and CYP450 isozymes, which are the enzymes responsible for most oxidative drug metabolism. Because hepatocytes have both phase 1 (oxidative, hydrolysis, and reduction) and phase 2 (conjugation) metabolic systems and are relatively straightforward to get from both human and

animal species for pharmacology and toxicology, many researchers choose this model for their first assessment of metabolism.

For in-vivo metabolism studies in animal models, the metabolic profiles of the selected animal species are similar to those of humans. Drug metabolism tests in animal species are conducted in toxicology studies using a correctly labelled material, frequently a radioactive isotope such as carbon-14. Sometimes, an unfavourable radiolabel isotope, such 125I or 3H, is used in drug metabolism studies.
For more reliable results, the radiolabelled material should be radio chemically pure, stable, and have a particular activity high enough to be detected after dosing. The label should also be placed in a way that allows it to remain visible during phase 1 (oxidation, reduction, or cleavage) or phase 2 (conjugation) metabolism without changing the candidate's pharmacological, chemical, or physical properties.

The number of metabolites present can be estimated by subtracting the parent chemical concentration (as established by the bioanalytical test technique) from the total radioactivity in a specimen (plasma, serum, urine, or bile). The degree of metabolism is low if the change is slight and remains constant over time. A slight variation in serum or plasma samples suggests that the circulation is free of metabolites. High radioactivity levels in bile or urine samples indicate that the main component and its derivatives are mostly removed by this method. To ascertain the quantity of each putative metabolite, a study of the profile of metabolites in bile and urine was conducted.

ii. Pharmacodynamic Profile Study:

a. Primary pharmacodynamic (PD) research focusses on examining a drug's physiological effects.

b. Secondary pharmacodynamic research focusses on examining a drug's mode of action and side effects that are unrelated to its primary therapeutic goal.

To find any potential harmful pharmacodynamics effects of a drug on particular biological processes that might endanger human safety, safety pharmacology investigations are carried out. The three types of safety pharmacology research are as follows:

- **Core battery study:** Prior to human administration, safety pharmacology investigations must be conducted in accordance with GLP using the core battery of research. Since they are essential to life-sustaining functions, the

organ systems suggested by the core battery are vital to life. This includes the central nervous, cardiovascular, and respiratory systems. Therefore, the first step in examining possible pharmacological effects in various concentrations of the relevant medication on which an influence seems conceivable is to conduct in vitro investigations using segregated tissue, tissue cells, receptors, ion channels, or enzymes. The intended therapeutic route of administration should be followed for any further in vivo experiments, and it is best if the animals are not sedated.

- **Follow-Up research:** A more thorough grasp of kinetic circumstances and possible repeat dosage administrations on an appropriate animal species may be obtained from the follow-up studies for the core battery.
- **Supplemental investigation:** Organ systems that are not covered by the core battery are examined in extra safety pharmacology studies. Interestingly, this is carried out in tandem with other critical organ systems, such as the immunological, renal, or gastrointestinal systems.

2. **Toxicological Studies:** The preclinical stage of the safety evaluation during drug development is defined by toxicology. Toxicological tests are used to identify potential dangers and hazards.

i. **Studies on acute (one dosage) and chronic (repeated dose) toxicity:**
To assess acute toxicity, rats are usually administered a single, high dosage of the test drug. Mice and rats of both sexes are typically used.
At least two techniques are used to provide the single dose, one of which ought to be the one advised for human use. After up to two weeks of observation for overt effects and mortality, a degree of trust of 95% is used to calculate the LD50 value. At least two species, one of which shouldn't be rats, should be used in repeated-dose toxicity experiments. Small dosages of the medication are given every day for six to nine months during a repeated-dose toxicity trial.

ii. **Reproductive toxicity studies:** These evaluate the potential teratogenicity of the drug candidate as well as maternal and infant care, parturition, embryo and foetal death, and male and female fertility.
Three different research types often referred to as segment I, segment II, and segment III have previously assessed these reproductive factors.
Rats' fertility and overall reproductive function are assessed in Segment I.
Segment II evaluates the teratogenic effects or embryo toxicity of the drug candidate and is commonly performed on rats and rabbits.
Segment III, referred to as the perinatal and postnatal study, usually exclusively involves rats. It evaluates how the medication candidate affects breastfeeding, labour and delivery, late foetal development, neonatal viability, and infant

growth. The reproductive toxicity of medication candidates has been assessed in a variety of rodent and nonrodent species, including mice, guinea pigs, minipigs, ferrets, hamsters, dogs, and nonhuman primates.

Male fertility in Segment I is assessed by continuing to take medicine for at least four weeks prior to mating season and during the mating season. Effects on spermatogenesis are shown by the histopathology or sperm analysis of these tests. A minimum for 14 days of premating treatment & continuous dosing during the mating season are necessary to evaluate female fertility.

Teratology investigations, sometimes referred to as Segment II, are carried out in both rodent and nonrodent species to determine whether a medication candidate has the potential to produce teratogenic effects or embryotoxicity.

During the organogenesis phase, which is generally understood to be gestation days 6 to 15 for mice and rats and 6 to 18 for rabbits, the medication candidate is given. Foetuses are delivered via caesarean sections one or two days before to the anticipated period of parturition. Rat foetuses are tested for skeletal abnormalities in half of them and visceral changes in the other half. All rabbit foetuses may be inspected for skeletal and soft tissue anomalies using microdissection methods for soft tissue changes. Segment III studies, often limited to rats, seek to assess the impact on the function of the mother and the prenatal and postnatal development of the pups. From the moment for implantation until the conclusion of nursing, the mothers get the medication candidate. In order to evaluate reproductive potential, one male and one female pup are usually chosen from each litter at the time of weaning to be raised to adulthood and mated.

iii. Mutagenicity/Genotoxicity Study:

The purpose of a genotoxicity/mutagenicity research is to ascertain if a proposed medication might damage DNA by altering chromosomal structure or nucleotide base sequence .Mutagenicity investigations frequently include both in vitro and in vivo techniques. ICH recommends a standard battery of tests that includes an in vitro test of chromosomal damage or mouse lymphoma thymidine kinase (TK) assay, an in vivo test of chromosomal damage using rat haematopoietic cells, and a gene mutation assay in bacteria.

Table No.3.3: Standard Genetic Toxicology Test Battery (ICH)

Genetic toxicology test	Purpose
Ames bacterial mutation assay	Gene mutation in bacteria
Mouse lymphoma assay (MLA) Chinese hamster ovary (CHO) chromosomal aberration assay	In vitro evaluation of chromosomal damage
Micronucleus test (MNT)	Evaluation of in vivo chromosomal damage in bone marrow polychromatic erythrocytes

iv. Carcinogenicity Study:

When a medicine is taken for more than six months, extensive carcinogenicity studies takes place. Animals used in this kind study have their tumour progression tracked. Over the course of two years, carcinogenicity investigations are carried out among two mice species, namely mice and rats. Maximum Tolerated Dosage (MTD) and 25-fold AUC ratio (25:1 exposure ratio of rodent to human plasma AUC of the parent chemical) are the two dosage categories utilised in the investigation.

v. Immunotoxicity Study:

In this study, ability of a pharmaceutical ingredient to trigger a sensitivity or immunological response is examined. Repeated dose toxicity studies can be used to examine immunotoxicity. One of the negative immune-system consequences of medications, according to the article, is immunosuppression, which can lead to autoimmune reactions to self-antigens, hypersensitivity, infectious diseases, or malignancies. To determine potential immunological reactions, a number of metrics are employed, including lymph node weight, lymphoid cell shape analysis, and antibody (IgM, IgE, IgG, etc.) measurement.

vi. Toxicokinetic Studies:

These might be conducted either as an independent, additional research or as an essential component for nonclinical toxicity studies. In general, toxicokinetic studies must be conducted in accordance with GLP regulations in addition to drug safety studies. The primary objective of toxicokinetics studies is to ascertain systemic exposure in animals and its relationship to the toxicity study's length and dose level. By linking exposure to toxicological outcomes, kinetic studies also assist in determining the significance of these results in terms of clinical security. The chosen matrix (blood, plasma, excreta, or tissues) need to be retrieved often

enough in toxicokinetic experiments to allow exposure estimate without disrupting research procedures or subjecting the animals to unnecessary physiological stress.

1.8 Investigational New Drug Application

- Before filing an Investigational New Drug (IND) application with an appropriate regulatory body, including the FDA in the US or CDSCO in India, among others, a drug researcher / sponsor must first successfully complete preclinical research.
- The official procedure via whereby a sponsor obtains permission to perform human drug testing is an IND application.

The following must be included in the IND application:

- Data from previous human research;
- Data from animal studies and toxicity data;
- Manufacturing details;
- Clinical procedures (study plans) for planned trials;
- Investigator details;
- Any other data

Once the IND was submitted, after reviewing all the information, the appropriate regulatory body authorised the sponsor to start the clinical study. After an IND is filed, the FDA will take 30 to 60 days to approve a clinical investigation. Before the medicine's marketing application is accepted, any pharmaceutical corporation can seek for approval under the Investigational New medicine (IND) program to start human clinical studies and export an experimental drug across state boundaries, generally to clinical investigators.

Presenting proof that human testing for a novel medicine is suitable is the goal of an investigational new drug (IND) application.

Current federal law states that until a pharmaceutical has been the focus of an approved marketing application, it cannot be transported or sold over state lines (Clinical Investigators).

Given the likelihood that it may want to ship the experimental medication to clinical investigators across many states, a sponsor must ask for an exception from that legal requirement.

Through the IND application, the sponsor formally obtains this exemption from the FDA.

In the early preclinical phases of a novel drug's development, the sponsor's primary goal is to determine if the molecule has pharmacological action that justifies commercial development and whether the product is reasonably safe for initial human use.

Once a product has been identified as a suitable candidate for further development, the sponsor subsequently focusses on obtaining the information and data necessary to demonstrate that using it in tiny, early-stage clinical trials won't put patients at unnecessarily high risk.

When a drug's sponsor, usually the manufacturer or a potential marketer, wants to test the medication's therapeutic or diagnostic potential in humans after evaluating it for pharmacological activity and acute toxicity potential in animals, the FDA becomes engaged in the development of the new medicine.

The molecule subsequently changes its legal position under the Federal Food, Drug, and Cosmetic Act, becoming a new drug subject to certain requirements of the drug regulatory system.

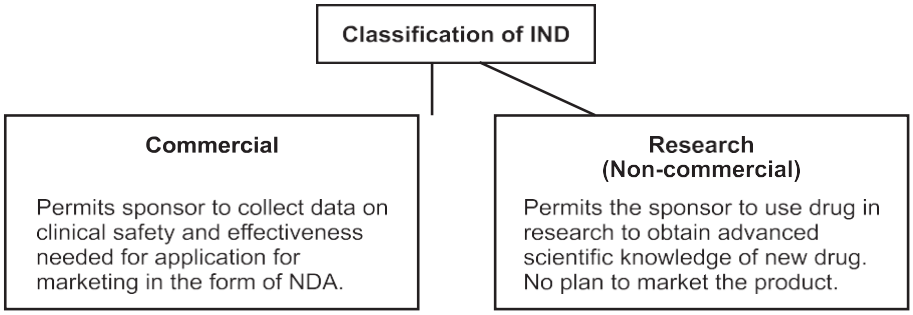


Fig. No.3.6: IND Classification

IND APPLICATION TYPES

1. IND applications for emergency users and investigators
2.The Treatment IND application
3. Looking at the application for IND

1. Investigator IND Application:

This kind of application is submitted by a physician who both initiates and directs an investigation and oversees the administration or distribution of the experimental drug. A physician may submit an application for a research IND to recommend investigating:

- An unapproved medication,
- A product that has been authorized for a new indication or a new patient group.

2. **Emergency Use IND Application:**

This application allows the FDA to authorise the use of an experimental drug in an emergency situation where there isn't enough time to file an IND application, in accordance with 21 CFR, Sec. 312.23 or Sec. 312.20. It is also used when there is no documented study procedure or for patients who do not meet its standards. In this case, before an IND application is filed, the FDA may authorise the drug's shipment for a specified purpose.

3. **Treatment IND Application**:

1. This application is submitted for investigational medications that exhibit promise in clinical testing for serious or immediately life-threatening disorders during the FDA assessment and final clinical work.
2. During phase III studies or after all clinical trials are completed, a medication may normally be made available for use as a therapy for a serious illness.
3. Similarly, a drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no satisfactory alternative medication or other therapy is available.
4. In the case of an immediately deadly illness, a drug may be authorised for use in therapy before to phase III, although usually not.

4. **Screening IND Application:**

It is submitted for a number of closely related compounds in order to identify the required compounds or formulations. The requested chemical can be produced under a separate IND. It may also be used to screen for different salts, esters, and other drug derivatives that differ chemically yet have comparable pharmacodynamics.

Review and Report on IND:

During this time, the FDA has the opportunity to review the IND application for safety to make sure research participants won't be put in unnecessary danger. Safety, statistical analysis, pharmacology/toxicology, chemistry, and medical reviews are among the factors evaluated in the study.

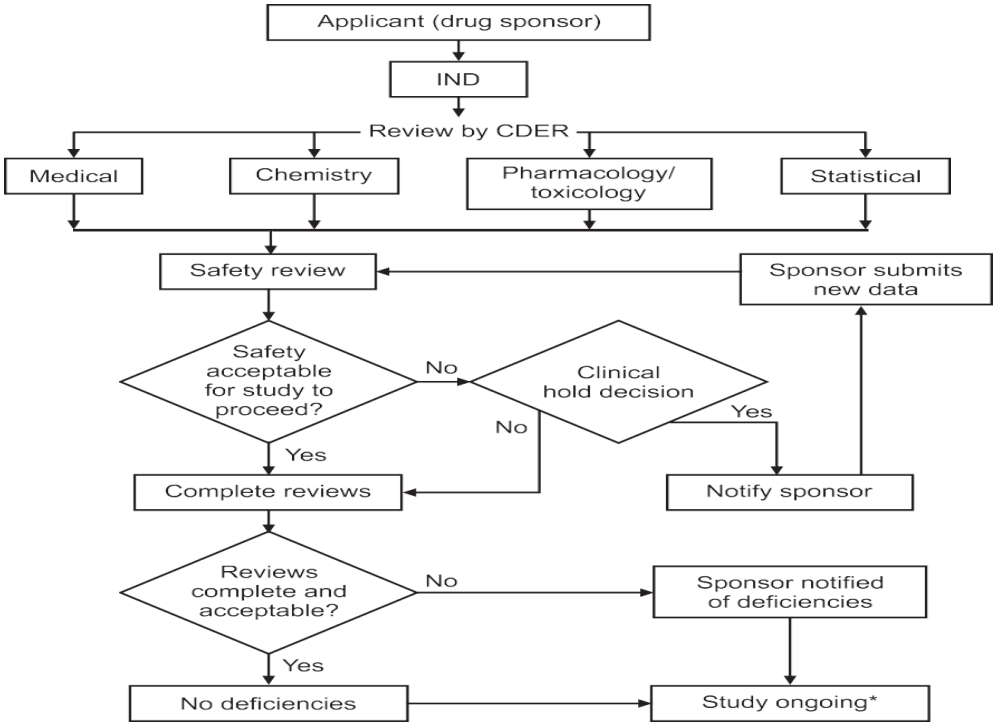


Fig. No.3.7: Layout chart for IND Application

1.9 The Investigator's Brochure:

- In addition to being produced for presentation to prospective clinical investigators and, eventually, an investigator's IRB (Institutional Review Board or Independent Review Board), a Investigator's Brochure (IB) is a crucial document that must be included in the IND.
- Clinical and nonclinical information investigational product which is pertinent to the product's research in human subjects is gathered by the IB.
- Its goal is to make it easier for trial investigators and other participants to understand and adhere to many of the protocol's essential elements, including dosage, frequency and spacing of doses, administration techniques, and safety monitoring standards.
- In order to help with the medical care for study participants during clinical research, the IB also offers recommendations. A physician or prospective researcher should be able to comprehend the material & do an independent risk-

benefit analysis of the suitability of the proposed study if it is provided in an uncomplicated, straightforward, objective, and nonpromotional manner.

- •. In view of this, an IB must typically be updated by a medical practitioner, but the disciplines that produced the data should accept the IB's content.
- The IB should be reviewed and revised as necessary to comply with the sponsor's stated procedures at least once a year.

Presenting the most recent IB to the appropriate IRBs is often the investigators' responsibility, and the sponsor's job is to make sure that the study participant or investigators have access to the most recent IB. The information that has to be in the IB is listed below:

1. **Title Page:**

   The sponsor's name, the date of release, and, if allowed by law and requested by the sponsor, the identification of every experimental product (including the trade name(s), chemical or authorised generic name, and research number) should also be included. Furthermore, mentioning the edition number and the date it replaces, as well as the edition number itself, is advised.

INVESTIGATOR'S BROCHURE TITLE PAGE (Example)

- Name of Sponsor: Research Number for Product: Name(s): Generic (if authorized), Chemical
- Trade Name or names (if allowed by law and preferred by the sponsor) Number of Edition:
- Date of Release:
- The previous edition number of the substitutes
- Date:

2. **Confidentiality Statement:**

   The sponsor may want to include a provision directing the investigator and receivers to safeguard IB's confidentially and to use it just for their team's and the IRB/IEC's information.

3. **Information in the Investigator's Brochure:**

   IB should have the following sections, each of which includes references to pertinent literature:

   1. Contents Table

2. Synopsis
3. Overview
4. Formulation and Physical, Chemical, and Pharmaceutical Properties
5. Nonclinical Research
5.1. Pharmacological Nonclinical
5.2. Animal Product Metabolism and Pharmacokinetics
5.3. The study of toxicology
6. Impact on People
6.1 Pharmacokinetics and Human Product Metabolism
6.2. Effectiveness and Safety
6.3. Experience in Marketing
7. Data Synopsis and Investigator Guidance
8. Publications
9. Reports and Appendices (if any): these sources should be located at the conclusion of every chapter.

Clinical Phase of Drug Development: Preclinical research provides a basic idea of a drug's safety in animal models, but it does not take the role of human subjects. Studies or trials that employ human subjects to ascertain a drug's efficacy and safety are known as "clinical research."

There are four stages to clinical trials:

- **Phase I:** Research Participants: 20–100 individuals in good health
  Study Period: a few months to a year
  Goal: Dose range and safety
- **Phase II:** Study Participants: 100–300 unwell participants.
  Study Period: Up to Two Years
  Goal: Safety and Efficacy
- **Phase III:** Research Participants: 300–3,000 individuals with the illness of interest
  Study period: one to four years
  Goal: Verify long-term safety and efficacy while keeping an eye out for negative responses.

1.10 Application For New Drugs (Nda)

Sponsors of pharmaceuticals can submit a New Drug Application (NDA) to the appropriate regulatory agency with the goal to get a promotion license and begin

commercial manufacturing if clinical research shows that the medicine candidate is safe and effective for its intended use. The following papers must be included in the New Drug Application (NDA) file, in addition to any research data gathered from preclinical to Phase 3 clinical trials:

- The suggested labelling
- Safety updates;
- Information about drug misuse
- Information about patents
- The site of clinical trial research
- Compliance Preclinical research report and use instructions

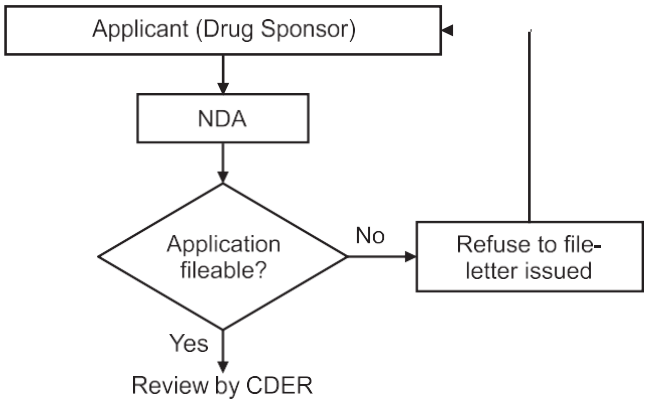
Review of NDAs

When the regulatory authority receives the NDA, it undergoes a technical examination. In order to support the submission of an NDA, this assessment makes sure that each region has received enough data and information.

When NDA review procedure has ended, the drug sponsor may receive three results:

1. Unacceptable: it lists the shortcomings and provides an explanation for the rejection.
2. Approvable: For marketing approval, a few small changes are suggested.
3. Approved by marketing.

A marketing approval letter will be sent six to twelve months after an NDA is submitted.



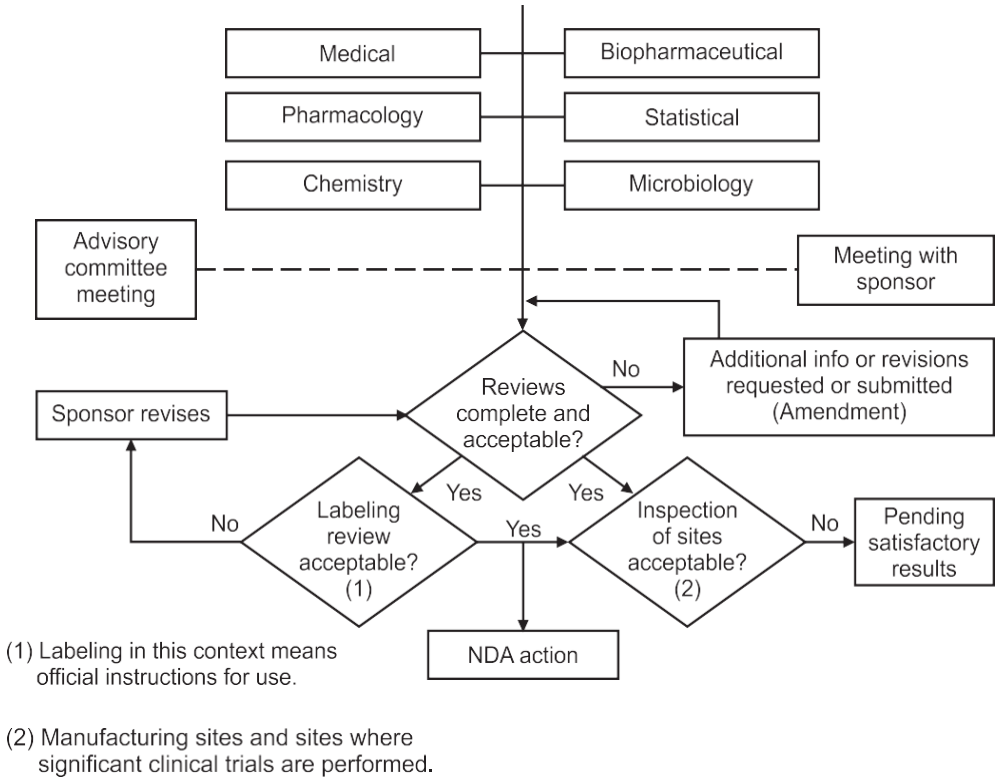


Fig. No.3.8: NDA Review Process

- **Phase IV:**

Post-approval studies known as phase IV trials monitor negative reactions to drugs (ADRs) to ensure a medication is safe after it is put on the market.. Post-marketing monitoring studies are another name for it. Following the drug's release onto the market, these studies are frequently conducted by government agencies, pharmaceutical firms, or private research teams.

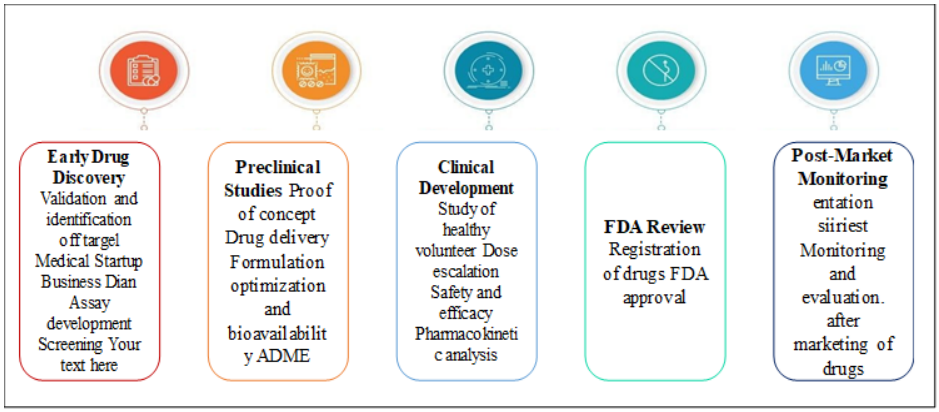


Fig. No.3.9: Various stages of the drug development process

Bioequivalence Study Bioequivalence (BE) studies are carried out to demonstrate that different medicinal product formulations or regimens are equivalent to one another in terms of their therapeutic benefit (efficacy) and non-therapeutic side effects (safety). They play a vital and important role in the development of new medications by ensuring that safety and effectiveness will be maintained when a patient switch to a new formulation available on the market. Pharmaceutical sponsors of recently developed pharmaceutical companies primarily use bioequivalence studies to prove the formulation utilised in Phase III confirmatory clinical trials is adequate for the final commercial formulation that will be provided after approval. BE studies can be seen as giving regulators the necessary and adequate assurance that the formulation to be marketed is the same as that used in the clinical confirmatory trials, without the need to repeat the development program or perform a therapeutic equivalency study in patients with clinical endpoints. It is also necessary to do bioequivalence studies following major post marketing formulation changes. When the original sponsor's formulation patent expires, the so-called "generic" pharmaceutical sector employs BE studies to get market access for formulations of proven therapeutic treatments in order to persuade authorities that the new formulation is safe, the original sponsors typically have to do a bioequivalence study if they change the formulation after approval (for example, the production site). Healthy male and female individuals are typically used in bioequivalence investigations. Each participant receives one of two formulations (T=Test or R=Reference) in one of two treatment sequences (e.g., RT and TR), where R is the "standard" formulation and T is the "new" formulation.

The washout period, which separates each treatment and is appropriate for the medication under study, consists of five half-lives between administrations. The washout period, which separates each treatment and is appropriate for the medication

under study, consists of five half-lives between administrations. The elimination (post Cmax) component of the PK concentration versus time curve is used to determine half-life, which is basically the period of time it takes for the body to get rid of 50% of the medication that is present at any one moment. Generally speaking, very little or no medicine should remain in the circulation after five half-lives. This type of design, called a 2 × 2 cross-over, is frequently employed in bioequivalence trials [237]

Sequence Group	Period			Number of Subjects
	1	Washout	2	
1(RT)	R	—	T	$n/2$
2(TR)	T	—	R	$n/2$
R=Reference, T=Test				

Fig. No.3.10: Illustration for a 2 x 2 Cross-Over Study

The rate and degree of the drug substance's bioavailability in plasma must be similar enough to satisfy the regulatory requirement of demonstrating that the body is exposed to the drug substance in the same manner across formulations in order to show equivalence in plasma concentration profiles. Regulatory clearance requires that Cmax (rate) and AUC (extent), which are frequently used as summary metrics for the plasma concentration curves, be shown to be similar under predetermined decision rules.

1.11 Clinical Trial Protocol

A clinical experiment's goals, design, procedures, statistical considerations, and organization are all outlined in a written document called the clinical trial protocol. It also guarantees the accuracy of the data collected and the safety of trial participants. clinical studies conducted in compliance with ICH and Good Clinical Practice (GCP) principles. E6 (R2) Good Clinical Practice: ICH Integrated Addendum E6 contains the GCP-ICH rules (R1). The following subjects should typically be covered in a trial protocol:

1. General Information

a) Protocol title, protocol identification number, and date. The amendment number and date should be included with any amendment.

b) The monitor's name and address, if they are not the sponsor.
c) The name and title of the person or people who have the sponsor's permission to sign the protocol and any amendments to it.
d) The name, title, address, and phone number or numbers of the trial's sponsor's medical expert.
e) The name and title of the investigator or investigators in charge of the trial, as well as the trial site's address and phone number.

2. Background Data

a) The name and description of the product or products under examination.
b) An overview of nonclinical study results that are pertinent to the trial and may have clinical value.
c) An overview of the advantages, if any, and known and possible dangers to human beings.
d) An explanation and rationale for the dose, treatment period(s), mode of administration, and regimen.
e) A declaration that the study would be carried out in accordance with the relevant regulatory requirement(s), GCP, and protocol.
f) An explanation of the population under study.
g) Citations to data and literature that are pertinent to the experiment and give context for it.

3. Trial Goals and Purpose: A thorough explanation of the trial's goals and purposes

4. Design of the Trial: The trial design has a significant impact on the trial's scientific integrity and the reliability of its data. The following should be included in a description of the trial design:

4.1 An detailed description for trial's primary outcomes & any secondary end results that will be examined.

4.2 A schematic representation of the trial's processes, phases, and design, as well as a description of the kind of study that will be carried out (such as parallel, double-blind, or placebo-controlled).

4.3 An explanation of the steps done to reduce or eliminate bias, like (a) allocation (b) Blinding.

4.4 An explanation for experimental product's dose & regimen, as well as the trial therapy or treatments. Provide a description of the labelling, packaging, and dosage form of the experimental product or products.

4.5 The anticipated length of time that subjects will participate, as well as an explanation for order & duration of every trial stage, including any subsequent ones.

4.6 An explanation of the "discontinuation criteria" or "stopping rules" for each subject, trial segments, and the full trial.
4.7 Accountability protocols for the experimental product or products, as well as any comparison or placebo.
4.8 Upkeep of randomization codes for trial treatments and protocols for code-breaking.

5. Subject Selection and Withdrawal:

5.1 Criteria for Subject Inclusion.
5.2 Criteria for subject exclusion.
5.3 Subject withdrawal guidelines (i.e., stopping treatment with an experimental product or trial) and protocols outlining:
(a) When and how to remove participants from the experimental product therapy or study.
(b) The kind of information to be gathered and when for withdrew subjects.
(c) Whether and how to substitute subjects.
(d) The monitoring of participants removed from study or experimental product therapy.

6. Subject Treatment:

6.1 The treatment or treatments to be administered, including the name or names of all products, the dose or doses, the dosing schedule or schedules, the route or mode of administration, and the treatment period or periods, including the follow-up period or periods for subjects for each trial treatment group, investigational product treatment, or trial arm.
6.2 Before and/or during the experiment, some medications and treatments—including rescue medication—are allowed and others are not.
6.3 Methods for keeping an eye on subject compliance.

7. Efficacy Assessment:

7.1 Defining the criterion for efficacy.
7.2 Timelines and procedures for evaluating, documenting, and analyzing effectiveness metrics.

8. Safety Assessment:

8.1 Safety parameter specification.
8.2 The procedures and schedule for determining, documenting, and evaluating safety criteria.
8.3 Methods for gathering information on adverse events and coexisting diseases, as well as for documenting and reporting them.
8.4 The kind and length of the subjects' post-adverse incident follow-up.

9. Data:

9.1 An explanation of the statistical techniques that will be used, together with the schedule for any interim analysis that is planned.

9.2 What is the expected number of enrolled subjects? In multicenter trials, the expected number of participants for each research site should be specified. Clinical reason and the rationale for the sample size selection.

9.3 The appropriate degree of significance.

9.4 Requirements for ending the trial.

9.5 How to account for false, underused, and missing data.

Protocol and/or final report, as applicable, should explain and justify any deviations from the original statistical design. Procedures for reporting such deviations should be outlined.

10. Instant Access to Source Data and Documents: For the purposes of monitoring, audits, IRB/IEC review, and regulatory inspections, the sponsor should ensure that the protocol or other written agreement expressly specifies that the investigator or institutions will permit direct access to source data and documents.

11. Quality Assurance & Control

12. Ethics: A justification of the trial's moral dilemmas.

13. Managing Data and Maintaining Records

14. Finance and Insurance: If not covered in a different contract, finance and insurance.

15. Publication Policy: If not covered in a different agreement, publication policy.

16. Supplements

1.12 Biostatistics In Pharmaceutical Product Development

The development of novel medicinal drugs depends heavily on statistics. The appropriate use of statistics, which is necessary for trial planning and analysis, is critical to the efficacy of drug development programs. The following are some ways that biostatistics is used in the development of pharmaceutical products:

- Apply a scientific perspective to the process of identifying targets.
- Determine if an animal model can be applied to humans by evaluating the capacity to quantify the effect on the target of interest.
- How is an effective dose going to be determined?
- Contribute significantly to risk quantification (risk assessment) and establish standards for halting dosage increase.

- Assist in selecting the optimal study design and primary outcomes; evaluate safety margins using animal data; and support the development of go/no-go decision criteria (p value for significance testing).
- Examine safety margins derived from animal evidence. Help choose the best research design and primary outcomes.
- Randomization system design and implementation in research design.
- Assist with sample collection, data analysis and refining, bias & error detection, formulation design and optimisation, and process parameter optimisation in pilot plant scale up. Utilized as a technique for validating analytical methodologies.

Below is a summary of the main statistical supports for the various stages of drug development.

Table No.3.4 : Development of Drug Products and Statistical Assistance

Milestones	Activities	Statistical support
Nominate an API for clinical development	Discover the API and perform various preclinical studies	Multiple comparison techniques for combinatorial chemists; analysis of genomic data; design and analysis of animal safety studies, etc.
Perform Phase I clinical studies	Determine Phase I dosage type (e.g., liquid, capsule, tablet [or new technology])	Analysis of historical data; statistical thinking (design and analyze experiments)
	Excipient compatibility studies	Design and analyze experiments
	Accelerated stability studies	Regression analysis
Perform Phase IIA (dose ranging) and IIB (proof of concept) clinical studies	Determine Phase II dosage type (new technology)	Analysis of historical data; statistical thinking (design and analyze experiments)
	Evaluate excipient compatibility (if not performed previously)	Design and analyze experiments
	Develop Phase II dosage formulation	Design and analyze factorial and/or mixture experiments
	Develop Phase II manufacturing process	Design and analyze factorial and/or response surface experiments
	Stability studies	Regression analysis
Perform Phase III clinical studies	(If necessary, determine Phase III dosage type)	(Design and analyze experiments to investigate scalability and/or economic concerns with Phase II dosage type)
	Develop and/or scale Phase III dosage formulation	Design and analyze factorial and/or mixture experiments
	Develop and/or scale Phase III manufacturing process	Design and analyze factorial, mechanistic, and/or response surface experiments
	Develop PAT applications	Multivariate analysis
	Transfer technology to commercial manufacturing division	Write reports and consult
Submit new-drug application	Develop and/or scale commercial formulation and process	Design and analyze factorial, mechanistic, mixture, and/or response surface experiments
	Define design and knowledge spaces for DP formulation and process	Design and analyze product- and process-understanding experiments
	Conduct ICH campaign	Analyze ICH stability studies (set expiry)

Data Display intended for Submission to the FDA: When filing an NDA or other regulatory application, the following considerations should be made.

1. Text Exposure:

A. Content:

The majority all NDA filings include a great deal of material that is not fully revealed in the document's body. When determining which facts are most crucial to present and explain in a given document, critical judgement must be used, even when all of the data gathered for a single subject or patient (or groups of subjects or patients) may be significant. Instead of being in a separate appendix, which would complicate the review process, information needed to support a certain thesis should be incorporated in the body of the paper. Less important material can be included in appendices, condensed, and explicitly mentioned in the text. Since all given data must be reviewed, adding extraneous information will slow down the application screening process. Such information should be disclosed in the application and made available upon FDA request.

B. Tone: The text should have a formal yet relaxed tone. Avoid using legal jargon as well as informal or colloquial language.

C. Conciseness: How to make NDA documents shorter is covered in the paragraphs that follow.

Make sure your wording is clear and basic.

1. If initialisms and acronyms were widely used and have been introduced at the outset, use them to expedite the text's flow. It's important to identify those that can be used in place of another that appears in the same text.
2. Eliminate unnecessary information. If the content is properly reviewed, many words, phrases, and even sentences can be removed. Sentences may often be made more fluid by eliminating repetitive phrases.

D. Correctness:

Both the textual presentation and the data source (the case report and other clinical papers) should be reflected in the tabular data in the document. The scientific significance of the submission depends on this. If there is a discrepancy within the in-text data and the source documents, the reviewer may doubt the submission as a whole and be more inclined to look at the raw data to ensure the conclusions are accurate.

E. Consistency:

All writings with sound judgment should use consistent punctuation, capitalization, abbreviations, and other stylistic rules.

F. Clarity:

Instead of pausing to try to comprehend a written presentation, an FDA reviewer must be capable to swiftly read an application. Clarity may be fostered by closely observing the following:

1. Timeliness.
2. The length and form of sentences.
3. Incorrect modifier placement.
4. Parallelism. Parallel organization is crucial for presenting data in an NDA since a large portion of the data includes comparisons across groups.

G. Section and Subsection Outline:

The evaluation of a document is based on how well one section connects to the others. A common outlining method that is simple to use and can be automatically configured in any modern word processing program is the decimal system. The alphanumeric style, in which section headers alternate between letters and numbers, is another well-liked outlining technique.

H. Indenting:

Long text paragraphs should not be indented. With the proper headers to indicate the section, the majority of the content ought to be flush to the left margin. It takes up space and is confusing to use multiple and sequential indenting. Conventions like utilising bullets to divide lengthy text passages are helpful, and short lists are properly indented.

I. Global to Specific:

Before getting into the minutiae of each subject, start with broad observations or statistics. For example, while describing unpleasant events, the events should be presented as a whole before being broken down by subgroup, severity, relationship, etc. When discussing the populations that are assessed in a certain paper, it is very crucial. Define the subpopulations after starting with the inclusive population.

1. **TABULAR PRESENTATION:** If tables streamline the demonstration then allow for a substantial text reduction, they should be used in-text. Extensive multipage tables that divide material should be avoided unless absolutely required. However, if the tables are truly important, they could be included as an appendix in the same volume. Data may frequently be shortened to fit in the in-text table while still referring to the entire table in a readily accessible appendix. Note that any tables, figures, and graphs in the appendices must have in-text references. Information from the tables should not be repeated in the text unless it is a final remark about the tabular data or a pattern seen in the data. The table

containing the commentary on the data from the tables should be preceded by an introduction to the table by number and a statement outlining the type of data it contains.

The table may be followed by additional commentary that is relevant to the table but not based on the tabular data.

A. Title: All tables must have succinct yet informative titles.

B. Data Source:

The source of the data in each table must be indicated; The number of volumes and page numbers will be added at the end of the project, and this is often done in a footnote to the table.

C. Footnotes:

To avoid confusion with the data, footnotes should be assigned letters (superscripted) rather than symbols or numbers. The sequence in which footnote letters appear on a given table page should be followed when creating multipage tables. To prevent the footnotes from altering when the tables change due to the insertion of older information, always start such tables on a new page.

D. Orientation:

In general, portrait tables are better than landscape ones. Try shifting the table's axes so that the axis with more individual descriptions is vertical and the axis with fewer items (column headers) is horizontal if the data doesn't seem to fit in portrait mode. Additionally, think about creating distinct portions of the table with relevant titles that cover the whole width of the table, all under the same column headers.

E. Data Presentation Order:

When displaying data in tables with similar information, try to keep the order consistent. If the active drug is constantly listed in the first column and the placebo or comparative agent is listed in the second, keep this order consistent across all tables. It is useful to retain the subgroup of interest (such as women, the elderly, racial groups, or poor renal function) in the same column of each table when looking at data by demographic or illness subgroup.

F. Present Meaningful Data Together:

Instead of dispersing the data that will be studied and compared over the table, try to present them as near together as you can.

Controlling Clinical Trials: The fundamental elements of clinical program management are as follows.

Selection of investigators: Only investigators who possess the necessary training and expertise to evaluate an investigational product may be selected by a sponsor, in accordance with the US GCP Federal Regulations & the ICH GCP Guidelines (21 CFR 312.53). The ICH GCP Guidelines make reference to this as well.

Pre investigational site visits (PISV): After pre-screening for possible investigators has been established, a PISV at the investigational site with the investigator and their team is necessary to further evaluate their eligibility to conduct the trial. The monitor or another approved person selected by the sponsor company often conducts the PISV.

Study initiation visits (SIV): A SIV is carried out once the PISV is finished. The initial visit is a training program. Before they start recruiting study volunteers, the investigators and their team will get this final protocol training. During this conference, the monitor will go over the following topics in detail: completing Case Report Forms (CRFs), analysing source and regulatory documentation, product distribution and responsibilities, adverse experience and serious adverse experience paperwork and reports, and the research protocol.

Trial conduct and execution: Subject recruitment, informed consent, product responsibility for IRBs and IECs, reporting of bad experiences and adverse reactions, financial transparency, and record keeping are some of the other critical aspects of trial execution that will require particular attention. The overall success of a clinical study depends on each.

Periodic monitoring visits: The sponsor is required under the CFR and ICH GCP standards to keep an eye on the clinical study's development at the trial site. In order to protect the rights of clinical trial participants and guarantee that the data reported is accurate, complete, and verifiable, the sponsor's monitor conducts these recurring monitoring visits to ensure that the investigators and their staff follow the protocol and comply with GCP regulations and guidelines.

Subject Recruitment: Finding trial participants as soon as possible is one of the best strategies to reduce the total amount of time needed to finish a clinical study. Planning where and how to attract a topic group is the key to successful subject recruiting. Understanding and identifying the subject group that will satisfy the protocol requirements is essential when organizing a recruiting effort. Why did these people choose to take part in the clinical study? Who are they seeing to get this therapy, and what type of medical care are they currently receiving? How is their health right now?

Product accountability: Clinical trials evaluate new experimental drugs and devices that have not yet received the appropriate regulatory body's approval for commercialisation. Therefore, any experimental product has to be closely monitored. The test product is the investigator's duty. Only the investigator or permitted sub-

investigators should prescribe investigative goods. Retrieving and confirming the proper disposal of any unwanted or abandoned goods is the sponsor's responsibility. Throughout a trial, thorough records of product accountability must be kept. This comprises the subject identity (subject number), the quantity dispensed, the date of dispensing, and the batch number of the prescribed product.

AE and ADR reporting: Adverse events and medication safety are strongly inversely correlated. In the US, the FDA exerts strict legislative monitoring over the safety of medications. Federal regulations mandate that during the exploratory and post-marketing stages of an experimental product, a sponsor must document unfavourable events and reactions.

Financial disclosure: One of the newest elements of a clinical trial is financial disclosure. Any ongoing or ongoing clinical research that are presented in an IND are subject to this regulation, which became operative in the US on February 2, 1999.A substantial stock investment in the study's sponsor, income related to the study's outcome, intellectual interest in the product (like a patent), and other significant payments to the researcher or organisation (like honoraria or equipment) are all considered financial disclosures, according to the FDA. This rule was put in place to guarantee the FDA that, even in cases where an investigator had a financial stake in a new product, the proper steps were taken to avoid bias in the planning, execution, reporting, and analysis of the trials.

Study close-out visits (SCV): The research must be suitably ended when a trial at an investigating location is finished. This cannot happen until all participants have finished the study, been dropped, or had their participation removed, and until all data questions and issues have been addressed and resolved in the final assessments. The monitor can only move forward with a close-out visit once this is finished. The monitor can complete the SCV with the help of the following checklist: Every participant in the experiment has been identified and validated. Every CRF page has been finished and obtained. Every data question has been answered. Every adverse medication response and adverse occurrence has been documented and reviewed. Every experimental product has been found and either disposed of or returned to the sponsor. Every CRF and related material is returned or disposed of appropriately. The Trial Binder includes thorough and organized regulatory documents. Every unresolved matter has been resolved.

Inspections and record retention: The continued validity of the study data depends on record retention. At some point after the New Drug Application (NDA) is filed, the FDA or other health care authorities may visit the site to confirm the information from a particular site. The website must have easy access to this information. Records

must be kept for two years following the approval of a marketing application, under both the CFR and the ICH.

Review Questions

Short Answer 02 marks

1. Describe the procedure for medication approval.
2. List the requirements for drug regulatory affairs.
3. Describe RA and its goals.
4. Describe the NDA
5. Define the following: field copy, review copy, archival copy, and CTD.

Short Essay 05 marks

1. List the different regulatory bodies.
2. Discuss about or bring up the responsibilities and role of RA professionals.
3. Discuss about the legal specifications and approval processes for novel medications.
4. What is a brochure for investigators? Discuss its substance.
5. Discuss about the parameters examined in the investigation of reproductive toxicity.
6. Describe the mutagenicity research in brief.
7. Compose the Investigators Brochure's information and contents.
8. Describe the stages of drug development that are clinical.
9. Describe the significance of bioequivalence studies in the process of developing new drugs.
10. Bring up the use of biostatistics in the creation of pharmaceutical products.

Long Essay 10 marks

1. Describe in depth RA's historical overview.
2. Provide a thorough explanation of the legal criteria for new medicine approval.
3. Give a thorough explanation of the New Drug Application, the Investigational NDA, the Clinical Trail Protocol, and the function of biostatistics in the creation of pharmaceutical products. How it will support the process of developing and producing drugs.

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Introduction

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