UNIT III – REGULATORY AFFAIRS

POINTS TO BE COVERED IN THIS TOPIC

- INTRODUCTION
- HISTORICAL OVERVIEW OF REGULATORY AFFAIRS
- REGULATORY AUTHORITIES
- ROLE OF REGULATORY AFFAIRS DEPARTMENT
- RESPONSIBILITY OF REGULATORY AFFAIRS PROFESSIONALS
- REGULATORY REQUIREMENTS FOR DRUG APPROVAL
- DRUG DEVELOPMENT TEAMS

UNIT III – REGULATORY AFFAIRS

POINTS TO BE COVERED IN THIS TOPIC

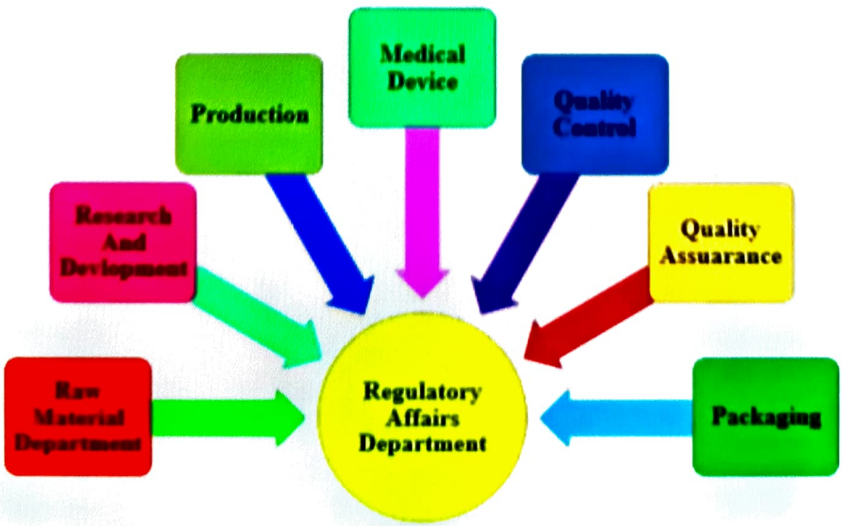
- NON – CLINICAL DRUG DEVELOPMENT
- INVESTIGATIONAL NEW DRUG APPLICATION
- INVESTIGATORS BROCHURE & NEW DRUG APPLICATIONS
- CLINICAL RESEARCH
- CLINICAL RESEARCH PROTOCOLS
- BIOEQUIVALENCE STUDIES(BE STUDIES)
- BIOSTATISTICS IN PHARMACEUTICAL PRODUCT DEVELOPMENT
- DATA PRESENTATION FOR FDA SUBMISSIONS

INTRODUCTION

- **Regulatory Affairs** (RA), also called **Government Affairs**, is a profession developed from the desire of governments to protect public health by controlling the **safety and efficacy** of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, foods, cosmetics and complementary medicines etc.
- **Pharmaceutical Drug Regulatory Affairs (DRA)** is a dynamic field that includes **scientific, legal** and **commercial aspect** of drug-development.
- **Drug development** to commercialization is **highly regulated.**
- Every drug before getting **market approval** must undergo rigorous **scrutiny and clinical trials** to ensure its **safety, efficacy and quality.**
- These standards are set by **regulatory authorities** of their respective countries such as **FDA in US and CDSCO** in India etc.

❖ REGULATION OF DRUG PRODUCTS INVOLVE FOLLOWING AREAS

- **Non-clinical** and **Clinical Drug Development Guidelines**
- **Licensing (Patent)**
- **Drug Registration**
- **Manufacturing**
- **Quality and safety Guidance**
- **Pricing and Trademark**
- **Marketing, Import** and **Distribution of Drug products**
- **Pharmacovigilance** (Adverse Drug Reactions monitoring)



HISTORICAL OVERVIEW OF REGULATORY AFFAIRS

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 process. 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

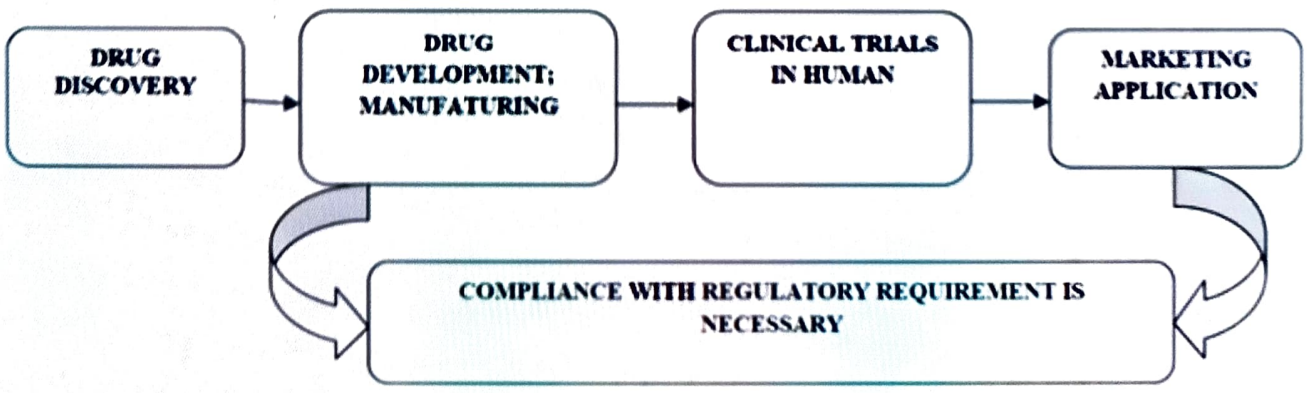
REGULATORY AUTHORITIES

- **Public health** being the prime concern, it is necessary that the drug **product available** for **human/veterinary** use and medical devices must not only be effective but also be safe for the **intended use.**
- To ensure this, various **territorial regulatory bodies** came into existence.
- Major **regulatory agencies** include **World Health Organization (WHO),** United States **Food and Drug Administration** (USFDA, United States), **European Medicines Agency** (EMA, European Union), **Medicines and Healthcare Products** Regulatory Agency (MHRA, UK), **Therapeutic Goods Administration** (TGA, Australia), Health Canada (Canada), **Pharmaceuticals and Medical Devices Agency** (PMDA, Japan) and **Central Drugs Standard Control Organization** (CDSCO, India).

ROLE OF REGULATORY AFFAIRS DEPARTMENT

✓ **In Development phase**

- **Ensuring** that the **legislative requirements** are



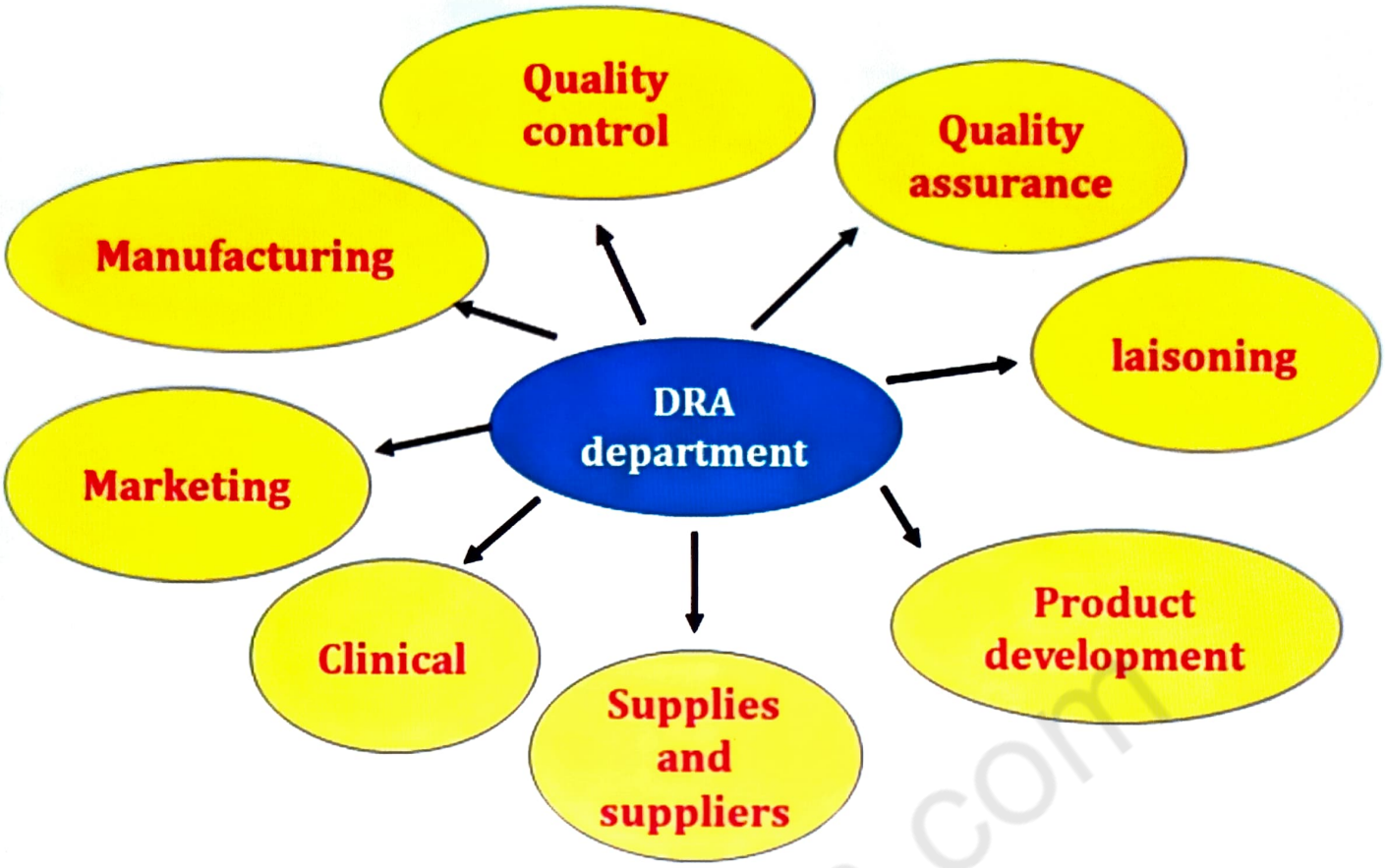
- **Recruit Scientific Advice** - authorities – Advice on development studies to **demonstrate safety,** quality and **efficacy parameters.**
- Set up **regulatory strategy.**
- Participate in **cross-functional** project teams.
- Ensure **application of guidelines** for clinical trials.
- **Submission of application** to conduct **clinical trials.**
- Managing the **regulatory submission**
  - **Minimize** time to market (every day counts!)
  - Advice on a **global development plan**
- **Optimize submission strategies** –
  - **Dossier preparation**
  - **Format, document** re-uses
  - **Electronic submissions**
  - **Review high level documents/reports**
- **Interact** with **commercial side** of business such **as pricing and reimbursement.**

✓ **In approval phase**

- **Check progress** of **evaluation** and anticipate questions.
- **Clarify raised questions**, plan response and strategies with other departments.
- **Plan and manage agency** meetings/hearings.
- **Negotiate approval** and Product Information with agencies.

✓ **In post approval phase**

- **Compliance**
- **Submission of variations/amendments**
- **Renewals**
- **Pharmacovigilance**
- **Product information review**
- **New indications** / new formulations
- **Regulatory input to development plans**/ Regulatory Intelligence.



RESPONSIBILITY OF REGULATORY AFFAIRS PROFESSIONALS

- Ensuring that their companies comply with all of the regulations and laws pertaining to their business.
- Working with federal, state and local regulatory agencies and personnel on specific issues related to their business.
- Advising companies on the regulatory aspects and climate that would affect their proposed activities.
- Keep in touch with international legislation, guidelines and customer practices.
- Keep up to the date with a company's product range.
- Collect, and evaluate the scientific data that their research and development colleagues are generating.
- Formulate regulatory strategies for all appropriate regulatory submissions such as domestic, international and/or contract projects.

- Coordinate, prepare and review all appropriate documents for example dossier and submit them to regulatory authorities within a specified time frame in conjugation with the organization.
- Prepare and review of SOPs related to RA. Review of BMR, MFR, change control and other relevant documents.
- Monitor the progress of all registration submission.
- Maintain approved applications and the record of registration fees paid against submission of DMF's and other documents.
- Respond to queries and ensure that registration/ approval are granted without delay.
- Participate in R&D training, Pilot plant Scale Up, and Post Marketing Surveillance (ADR).
- Manage and review audit reports and compliance, regulatory and customer inspections.
- Provide accurate and complete information about the quality, safety and effectiveness of the product to the physicians and other healthcare professionals.

REGULATORY REQUIREMENTS FOR DRUG APPROVAL

- Currently different nation's have to follow different requirements for the regulatory approach of drug
- Regulatory approach for the NAA, there fore, it is necessary to have knowledge about regulatory requirements for NAA of each country.
- New Drug Application [NDA] is an application submitted to the respective regulatory authority for permission to market a new drug.
- To obtain this permission a sponser submits preclinical and clinical test data for analyzing the drug information and description of manufacturing Procedures.
- This process of evaluation is made to ensure that the sufficient date and the required information - have been submitted in each justifying and filling application form.

DRUG DEVELOPMENT TEAMS

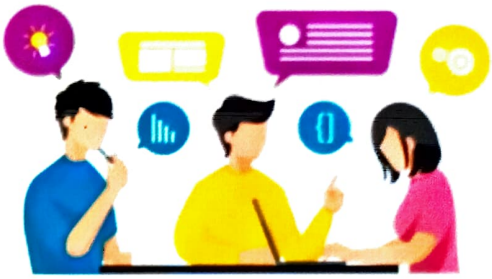
- Most **pharmaceutical and biotechnology** firms employ drug development project teams to guide the processes involved in early **drug discovery phase**, through the various **drug development stages** and finally making the **drug candidate** into a **therapeutic product.**
- The **drug development** team includes a diverse group of **individuals** with **different philosophies** and approaches to the **development process.**

❖ THE RESPONSIBILITIES OF THESE PROJECT TEAMS INCLUDE

1. **Reviewing** research results from **experiments conducted** by any of the various **scientific disciplines.**
2. **Integrating new research** results with **previously generated data.**
3. **Planning research studies** to further characterize a **drug candidate.**
4. Preparing a **detailed drug development** plan, including designation of key points or **development milestones**, generating a timeline for **completion,** and defining the **critical path.**
5. **Monitoring** the status of **research studies** to ensure that they are being conducted according to the **timeline and critical path** in the development plan and, if appropriate, modifying the plan as **new information** becomes available.
6. **Comparing research results** and development status and timelines with **drug candidates** under development by **competitors.**
7. **Conducting appropriate** market surveys to ensure that the **development of a drug candidate** is economically justified and continues to meet a **medical need.**
8. **Reporting** the status of the **drug development** program to management and **making recommendations** on the continued development of the drug candidate.

➢ DRUG DEVELOPMENT TEAMS CONSIST OF FOLLOWING GROUP OF TEAMS

1. DISCOVERY/DEVELOPMENT TEAM



- The **discovery and development** groups are **comprised** of the **basic scientists** and **chemists** who created the **new molecule.**

2. NONCLINICAL, PHARMACOLOGY AND TOXICOLOGY TEAM

- This **group studies** the **drug product** in **animal models** for **efficacy and safety** in order to identify **potential efficacy** and **safety issues** in humans.

3. CLINICAL RESEARCH TEAM

- Clinical research has the **ultimate responsibility** for testing **drug products** in humans: the monitoring of **drug safety** rests squarely on the shoulders of **clinical research.**

4. REGULATORY AFFAIRS TEAM

- The **regulatory affairs department** is the interface with the FDA. It is their **responsibility** to ensure compliance with the **rules** and **regulations** established by the **Federal Food Drug and Cosmetic Act** and its **amendments.**

5. MARKETING TEAM

- The **marketing group** has the ultimate **responsibility for marketing** and **selling** the drug.
- As a result, they **need product**, **labeling** that differentiates their drug from those **already marketed.**

6. LEGAL TEAM

- In order for a drug to be financially successful, patent protection is a key element.
- The legal group must submit patents at the appropriate time and do all in its power to avoid law suits from potential competitors.

7. MANAGEMENT TEAM

- They co-ordinate with all the respective teams and responsible for successful completion of project in a time bound manner.

NON – CLINICAL DRUG DEVELOPMENT

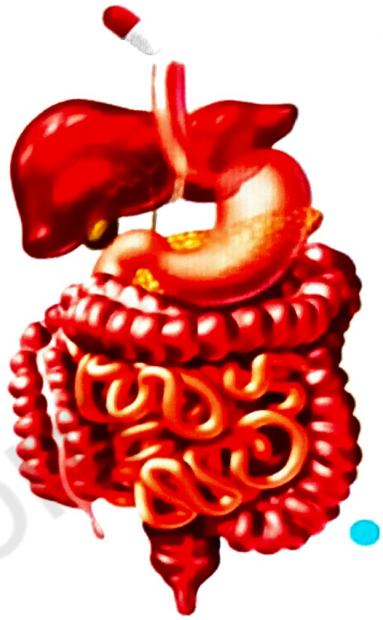
- The primary aims of the non-clinical development phase is to analyze and determine which candidate has the greatest probability of success, assess its safety, and raise firm scientific foundations before transition to the clinical development phase.

➢ PHARMACOLOGY

- Study of effects of chemical substances on living systems
- This includes the scientific evaluation and study of Potentially effects of a life threatning Pharmacological effect of a potential drug which is unrelated to the desired therapeutic effect and therefore may present a hazard.
- Safety pharmacology seeks to identify unanticipated effects of new drugs on major organ function.
- It is aimed to detecting possible undesirable or dangerous effects of exposure of the drug in therapeutic dose.
- The emphasis is on acute , effects produced by single – dose administration rather than effects on chronic exposure as in toxicological studies.
- The pharmacology assessments help in choosing the dose levels and route and frequency of administration for preliminary and final toxicology studies.

- These **developability** pharmacology studies should be performed with dosing to **steady state**, unless the **dosing rate** to be used in **clinical trials** is a **single dose therapeutic .**

➢ DRUG METABOLISM



- Estimation of **drug metabolism** , **ADME** gives information about the rate of a compound in the, **body, drug metabolism** studies in animal species already used or to be used in **toxicology studies.**
- The amount of **total metabolites** present is estimated **substracting** the parent compound **concentration** in a sample of **plasma, serum, urine, bile.**
- The extent of **metabolism** is low if the **difference minimum** and does not vary with time.
- One of the first metabolism studies performed should be **protein binding** in physiological fluid of animals and humans.
- The unbound **drug passes** through the **cell walls** of blood vessels and spreads to **different organs**, like **pharmacological and toxicological** action sites.
- The **preclinical drug** metabolism studies also involve metabolite Profiling in **plasma specific tissues**, **urine and bile** to evaluate the distribution and disposition of potential metabolites.
- **Metabolite profiling** requires a technique for separating the parent compound from **metabolites** and other **endogenous compounds** using HPLC.

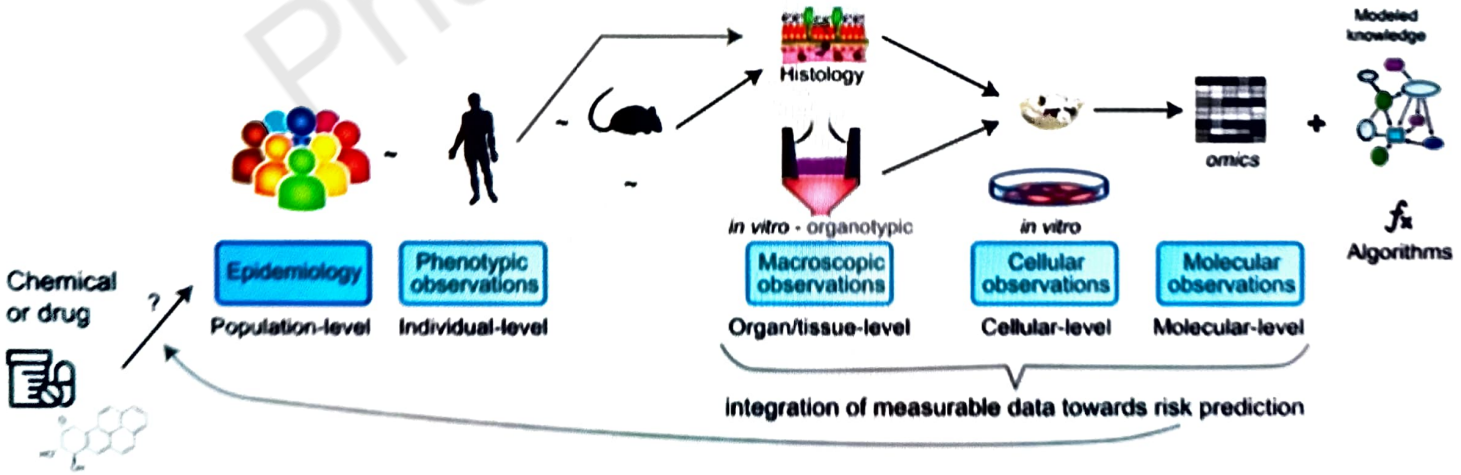
➢ TOXICOLOGY

❖ ACUTE TOXICITY

- Acute toxicity studies should be carried out in at least 2 species, usually mice and rats using the same routes as intended for humans
- The Symptoms, signs and made of death should be reported, with appropriate macroscopic and microscopic findings where necessary.

❖ LONG TOXICITY

- These Studies should be carried out in at least two mammallian species.
- The duration of study will depend on the factor that wheather the application is for marketing permission for clinical trials.
- The toxicokinetic assays are usually performed during toxicology studies and should be conducted in accordance with GLP rules
- The toxicokinetic assays measure the systemic exposure of a substance is in animal and establish the relationship between the dose administered and time course of the substance in the toxicity studies.



INVESTIGATIONAL NEW DRUG APPLICATION

- Investigational New Drug is a program by which any pharmaceutical Company can **approach to obtain permission for the initiation of human clinical trials** and to ship an **experimental drug across state line** before a marketing application for the drug has been approved.

- The IND application is to provide the data showing that it is reasonable to begin tests of a **new drug on humans.**
- The IND application is also the vehicle through which of sponsor advances to the **next stage of drug development known as clinical trials.**

CLASSIFICATION OF IND

Commercial

Permits sponser to collect data on clinical safety and effectiveness needed for application for marketing in the form of NDA

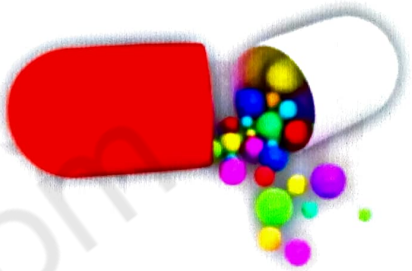
Research

Permits the sponser to use drug in research to obtain advanced scientific knowledge of new drug , no plan to market the product

❖ APPLICATION

✓ Investigator

- In this an application is submitted by a **physician** who both initiates and conducts an **investigation** and under whose immediate direction the investigation of drug is **administered or dispensed.**
- A physician might submit a **research IND application** to propose Studying of drug an unapproved drug.
- An approved product for a **new indication** or an approved product in a new patient population.

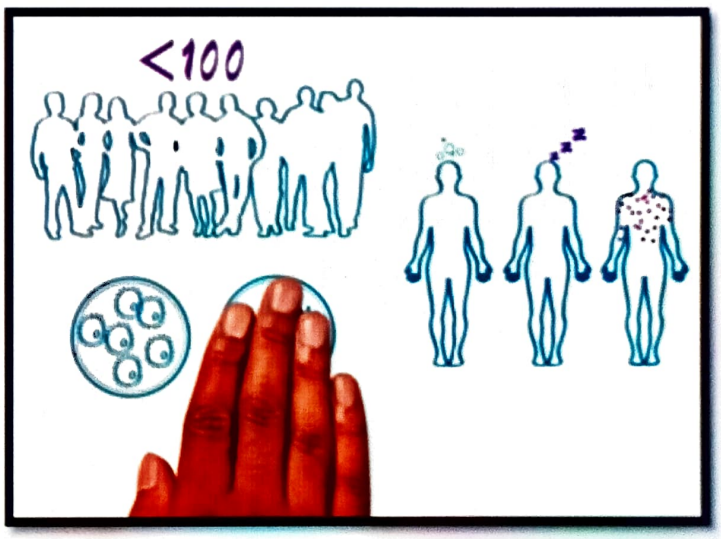


✓ Emergency Use

- This application allows the FDA to authorize use of on **experimental drug** in an emergency situation that does not allow time for submission of an **IND application.**

✓ Treatment

- This application is submitted for experimental drugs Showing Promise in clinical testing for **serious** or **immediately life-threatening conditions** while the final clinical work is conducted.
- A ding that is not approved for marketing may be under clinical investigation for a serious or life threatening disease Condition in patients.
- In the case of a serious disease a drug ordinarily may be made available for treatment use during **phase III investigations** after all clinical trials have been completed.



✓ **Screening**

- It is filed for multiple closely related compounds in order to Screen for the **preferred Compounds** or **formulations**.
- The preferred compound can be developed under a **separate IND.**
- It can also be used for Screening different salts, esters and other drug derivatives that are chemically different but Pharmacodynamically Similar.

INVESTIGATORS BROCHURE & NEW DRUG APPLICATIONS

- The investigator Brochure is a compilation of the **clinical** and **non-clinical data** on the **investigational products** that are relevant to the Study of the **products human subject.**

❖ PURPOSE OF INVESTIGATORS BROCHURE

- Its purpose is to provide information to the **investigators** and **others** involved in the trial such as the **dose, dose frequency, method of administration and safety monitoring procedures.**
- The IB also provides insight support the **clinical management** of the Study Subjects during the Course of clinical trial.

❖ CONTENTS OF INVESTIGATORS BROCHURE

- ✓ **Summary**
- ✓ **Introduction**
- ✓ **Description of IP**
- ✓ **Non-clinical studies**
- ✓ **Effect in humans**
- ✓ **Summary of data guidance for the investigators**

❖ NEW DRUG APPLICATION (NDA)

- After the successful completion of clinical research, if the drug candidate proven satisfactory to be **safe** and **effective** for its intended use, then **drug sponsor** can submit New Drug Application (NDA) to respective regulatory authority in order to get **marketing license** and **start commercial production.**
- To submit New Drug Application (NDA) filing, drug sponsor must provide all the research data which are obtained from **preclinical** to **Phase 3 clinical trial** along with following documents-
  - ✓ Proposed labeling
  - ✓ Safety updates
  - ✓ Drug abuse information
  - ✓ Patent information
  - ✓ Location where the clinical trial studies have been conducted compliance Report of preclinical study
  - ✓ Directions for use

CLINICAL RESEARCH

➢ CLINICAL RESEARCH

- The preclinical research provides **answers** to **basic questions** regarding a **dung's safety.**
- Clinical research involves the **studies of trials** Conducted in **human subjects.**
- While designing the clinical study, the developers will Consider what they want to accomplish for each Clinical research phase.

➢ CLINICAL RESEARCH PHASE

❖ Phase – 0

- The trials of this phase are the **first clinical trials** conducted in human subjects.
- Their objective is to learn the **processes a drug undergo within the body and the effect is produces in the body.**

❖ Phase – I

- **The trials of this phase are conducted to determine that goes of a new drug which will produce the least side effects.**
- In these trials the drug is tested in **15-10 patients.**
- The physicians administer the drug to a few patients in very either low dose and other patients the drug given in high dose till the time either severe side effects is observed.

❖ Phase – II

- **The trials of this phase evaluate the safety and effectiveness of the drug.**
- The drug is tested in patients having a **specific type of concern.**
- These trials are conducted in around large number of patients using new drug combinations.
- Patients are monitored to check the drug effect and if it is found to be effective is proceed to phase III.

❖ Phase III

- The trials of this phase compare a new drug to the standard of care drug being used these trials are conducted in around 100 or more patients to evaluate the side effects each drug and determine the drug showing better efficacy.
- **Phase III trials can improve more than 2 treatment and the other groups get new treatment.**
- If the new drug produces severe side effects or if one group shows much better results, the phase III trial stopped early.

❖ Phase IV

- **The trials of these phase are conducted to test the FDA approved new drugs in several 100 or 1000 of patients.**
- This allows for better research on short live and long lasting side effects and safety.
- In some cases, some rare side effects are only found in large groups of people.

CLINICAL RESEARCH PROTOCOLS

- Clinical investigations are of clinical Started with the development of **clinical protocol**, which is a document that describes the **objectives, design, methods, statistical consideration** and **organization** of a **clinical trial** and ensure the **safety** of trial subjects and **reliability** of the obtained data.
- **A research protocol is a document that describe the objectives, design method statistical consideration and organization of a clinical research project according to ICH guidelines.**
- The contents of a trial protocol should generally include the following topics:

1. GENERAL CONSIDERATION

- **Protocol title, protocol identifying number**, and **date**.
- **Name** and **address** of the sponsor and monitor
- **Name** and **title** of the person authorized to sign the protocol and the protocol amendment for the sponsor.
- Name, title, address, and telephone number of the sponsor's medical expert for the trial.

2. BACKGROUND INFORMATION

- **Name** and **description** of the investigational product
- A **summary of findings** from nonclinical studies that potentially have clinical significance and are relevant to the trial.
- **Summary** of the known and potential risks and benefits, if any, to human subjects.
- **Description** of and **justification** for the route of administration, dosage, dosage regimen, and treatment period.
- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement.
- **Description** of the population to be studied.
- References to **literature** and **data** that are relevant to the trial, and that provide background for the trial.

3. STUDY OBJECTIVES AND PURPOSES

- A detailed description of the **primary** and **secondary** objectives and the purpose of the trial.

4. STUDY DESIGN

- It influences the **scientific reliability** of the study and the integrity of the data attained.
- This section of the protocol describes-
  - ✓ **Primary** and **secondary** end points to be measured.
  - ✓ Study type along with the **Systemic diagram** of the study design.
  - ✓ Dose, dosage form regimen, packaging and labeling of investigational product.
  - ✓ Maintenance of study treatment randomization codes and procedures for breaking codes.
  - ✓ **Identification** of the any data to be recorded directly on the case report forms and considered to be source data.

5. ASSESSMENT OF EFFICACY

- Description of the methods to be used for **determining the treatment, effectiveness.**

6. ASSESSMENT OF SAFETY

- Description of the methods to be used for **monitoring the study and dealing with adverse events.**
- **Specification of Safety criteria methods** and **timing-** for evaluating, recording and analyzing the effectiveness criteria.

7. DIRECT ACCESS TO SOURCE DATA OF DOCUMENTS

- The sponsor should **safeguard** that the protocol to other hand written agreement states that Study investigators or institutions will provide **direct access** to **data documents.**

8. QUALITY CONTROL AND QUALITY ASSURANCE

- A detailed quality assurance plan describing the Set standards and controls to ensure that each step follows the accepted plan.
- The protocol should describe the quality assurance methods

9. DATA MANAGEMENT

- A detailed data managements plan describing the methods of **Collecting**, **documenting**, **submitting** and **achieving** Study data should be submitted as separate document.
- The protocol Should describe for **data management activities** related to the protocol.
- The data management plan describes the procedure to ensure the data reliability during the study and study sites.

10. FINANCING AND INSURANCE

- Description of how the study will be **financed** and **insured** should be submitted.
- In some research networks these issues are discussed in a separate agreement and are **not included in the protocol.**

BIOEQUIVALENCE STUDIES(BE STUDIES)

- Bioequivalence is a **comparison of Bioavailability two or more drug.**
- The same active ingredient are said to be bio-equivalent if their **rate** and **extent of absorption is same.**
- It refers to the drug substance in two or more identical dosage forms, reaches. systemic circulation at the same rate and to the same relative extent.

❖ TYPES OF BIOEQUIVALENCE STUDIES

- Bioequivalence can be demonstrated studies
  - ✓ **In – vivo**
  - ✓ **In – vitro**

BIOSTATISTICS IN PHARMACEUTICAL PRODUCT DEVELOPMENT

- Biostatics involve the use of **scientific** and **quantitative procedures** in **descriptive** and **interfacial statics** to evaluate the quality of evidence in biological science.
- It involves the **statistical processes** and **methods** used for analyzing the **biological phenomena.**
- Biostatics is a science that includes **designing of biological** and **experimental analysis study** designs as well as synthesis, analysis and interpretation of data obtained from such studies.
- Biostatical analysis is an important step in **Human clinical trials** that are Conducted in the last stages of **pharmaceutical development.**
- Biostatics is wide branch of biological sciences in which the theories in statics are applied to the living world problems in health and diseases.
- It involves Various and statistical operations such as designing and conducting biomedical experiments, clinical trial and development of related algorithms.
- Biostatics forms an important part in **epidemiological research, development** of health policies, health economics, public health administration, Practice in clinical medicine, genomics, and development

of various pharmaceutical products.

DATA PRESENTATION FOR FDA SUBMISSIONS

- Study data Standards describe a **standard way to exchange clinical and Non-clinical study data.**
- These standards provide a consistent general framework for organizing study data, including templates fat data sets.
- Data Standards also help FDA receive process, review and achieve submissions more efficiently and effectively. Steps are :
  - ✓ **FDA has been working towards a standardized approach to capture, receive and analyze study data.**
  - ✓ **Standardization of study data to improve public health and patient safety.**
  - ✓ **Central to this vision is the creation of an enter price data infrastructure.**

➢ DATA STANDARDS

- Data standards can be divided into 2 categories

Exchange standards

- It provides a consistent way to exchange information which help to ensure that sending and the receiving system both understands

Terminology standards

- It provides a consistent way to describe concepts, FDA provides consistent way to describe substance in foods and drugs.

MANAGEMENT OF CLINICAL STUDIES

- Clinical Data Management is involved in all aspects of **processing the clinical data, working with a range of computer applications, database systems to support collection, cleaning and management of subject or trial data**

- Clinical Data Management is the **collection, integration and validation of clinical trial data**
- During the clinical trial, the investigators collect data on the **patients health** for a **defined time period.** This data is sent to the trial sponsor, who then analyzes the pooled data using statistical analysis.

DATA DESIGN
↓
DATA COLLECTION
↓
DATA ENTRY
↓
DATA VALIDATION
↓
DATA CLEANUP
↓
DATA ANALYSIS
↓
DATA REPORTING
↓
DATA PRESENTATION

➢ IMPORTANCE OF CDM

- **Review** & **approval** of new drugs by Regulatory Agencies is dependent upon a trust that clinical trials data presented are of sufficient integrity to ensure confidence in results & conclusions presented by **pharma company.**
- Important to obtaining that trust is adherence to **quality standards** & **practices**.
- Hence, Companies must assure that all **staff** involved in the clinical research are **trained** & **qualified** to **perform** data management tasks.

➢ KEY MEMBERS

- The Key members involved in Data Management:
  - ✓ **Project Manager /Data Manager**
  - ✓ **Database Administrator**
  - ✓ **Database Programmer / Developer**
  - ✓ **Clinical Data Associate**