CHAPTER 3

[Regulatory Affairs]

1. Introduction:

- Regulatory Affairs is the bridge/ interface between Pharmaceutical company & Govt. agencies/ regulatory agencies.

2. Regulatory authorities:

- Drug Regulatory Authorities across the world are:

✓ CDSCO- India
✓ USFDA- United States
✓ EMEA- European countries
✓ MHRA- United kingdom
✓ TGA- Australia
✓ MCC- South Africa

3. Role and Responsibility of Regulatory Affairs department:

- Regulatory Affairs is a comparatively new profession that developed from the desire of the government to protect public health by controlling the safety & efficacy of medicinal products, medical devices and cosmetics.
- To keep track of the ever changing legislation.
- Sending registration documents to regulatory agencies.
- To give strategic & technical advice to R&D, Production, QC department etc.

4. Drug Development Team:

- Drug development team is a team of non clinical experts offering "Concept to commercialization" consultation services for innovators and drug discoverers seeking to maximize the potential value of their innovative ideas into clinical stage assets.
- The team has been assembled to bring together years of drug discovery and development experience in pharmacology, toxicology and all types of regulatory interaction and documentation.

5. Non-Clinical Drug Development:

- The non-clinical or pre-clinical development phase aims to identify which candidate therapy has the greatest probability of success, assess its safety, and build solid scientific foundations before transition to the clinical development phase.
- During the non-clinical development phase, the candidate compound must meet non- medical objectives, including defining the intellectual property rights and making enough medicinal product available for clinical trials.
- The non-clinical development of a medicine is complex and regulatory driven.

6. General considerations of Investigational New Drug (IND):

- After pre-clinical investigations when the new molecule screened for pharmacological activity and acute toxicity potential in animals the sponsor requires permission from FDA for clinical trials in humans.
- The sponsor submits the application for conduct of human clinical trials called Investigational New Drug (IND) to FDA or DCGI.
- Once IND application is submitted, the sponsor must wait for 30 days before initiating any clinical trial.
- Clinical trials in humans can begin only after IND is reviewed by the FDA and a local institutional review board (IRB).

- IRBs approve clinical trial protocol, informed consent of all participants and appropriate steps to prevent subjects from harm.
- If the FDA accepts the IND request within 30 days of submission, clinical testing of the new drug molecule on human may begin by the investigator.

7. General considerations of New Drug Application (NDA):

- The New Drug Application is the vehicle through which the drug sponsors formally propose FDA or DCGI to approve a new investigational drug for sale & marketing after successful completion clinical trials.
- NDA requires submission of :

✓ Well –controlled clinical studies to demonstrate effectiveness.

✓ Preclinical and clinical data to show safety.

✓ Details of manufacturing & Packaging.

✓ Proposed annotated labeling.

8. General considerations of Abbreviated New Drug Application (ANDA):

- Generic drug applications are referred to Abbreviated New Drug Application.
- Pharmaceutical companies must admit ANDAs and receive FDA's approval before marketing new generic drugs.
- Once ANDA is approved, an applicant can manufacture and market generic drug to provide safe, effective and low cost alternative of innovator drug product to the public.
- Generic drugs are termed "abbreviated" as they are not required to include preclinical and clinical data to establish safety and efficacy.

  They must scientifically demonstrate
- Bioequivalence to Innovator (brand drug).

9. Investigator's Brochure (IB):

- Investigator brochure is a collection of the clinical and non-clinical data on the investigational product that are relevant to the study of the product in human subject.
- IB is a comprehensive document summarizing the information about the investigational product obtained during clinical trials.
- The information should be presented in a short, simple, objective and non-promotional form that enables a clinical or potential investigator to understand it.
- IB is prepared by the sponsor who also controls the distribution of the document.
- The sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator and investigators are responsible for providing the up-to-date IB to the Responsible IRB/IEC.
- IB provides the investigator and other staff with background information about the investigational medicinal product.

10. Clinical Research:

Introduction:

- Branch of medical science.
- Systematic, observational & experimental biomedical studies.
- Ultimate goal is to improve the quality of life.
- Clinical trial is the one form of clinical research.
- Clinical trial is used to evaluate the safety & effectiveness of medications or medical devices or biologics etc.

Importance of Clinical Research:

- To develop new techniques for screening and diagnosing of a disease.
- To launch new drugs to the market.
- To develop new methods of surgery.

- To develop new combinations of standard treatments.
- To develop new techniques such as Gene therapy.

11. Types of Clinical Trials:

- Phase 0
- Phase I
- Phase II
- Phase III
- Phase IV

Phase 0:

- Also called Human Micro-dosing studies.
- Gathers preliminary data Pharmacodynamics and Pharmacokinetics.
- Gives no data on safety or efficacy.
- Small number of subjects (10-15).

Phase I:

- First stage of testing in human subjects (20-100).
- Designed to assess the safety, tolerability, PK and PD of the drug.
- Dose ranging – Dose escalation.

Phase II:

- Therapeutic Exploratory Trial (20-300 Subjects).
- Efficacy in patients (Primary objective).
- Safety issues (Secondary objective).
- Optimum dose finding.

- Phase II

✓ Phase II A: Designed to assess dosing requirements.

✓ Phase II B: Designed to study efficacy.

Phase III:

- Therapeutic confirmatory trials (300-3000 subjects).
- To establish efficacy of the drug against existing therapy in large number of patients, method of usage etc.
- Sub types:

✓ Phase- III A: to get sufficient & significant data.

✓ Phase- III B: allows patients to continue the treatment, label expansion, additionalsafety data.

Phase IV:

- Post Marketing Studies (PMS).
- Involves safety surveillance
- Determine behavior of drug in real life situations.
- Evaluate action of drug in a situation of missed dosage or over dosage.

12. Clinical Research Protocols:

- A complete written description of, and scientific rationale for, a research activity involving human subjects.
- Roadmap for investigative team
- Required for scientific & ethical review.
- Basis for preparing study reports.
- Parts of the protocol are:

✓ Introduction

✓ Abstract

- ✓ Objectives
- ✓ Background
- ✓ Rationale
- ✓ Eligibility criteria
- ✓ Study design/ methods
- ✓ Criteria for Evaluations
- ✓ Study treatments
- ✓ Clinical assessment

13. Bioequivalence studies:

Definition:

Bioequivalence denotes that the drug substance in two or more identical dosage forms, reaches the systemic circulation at the same relative rate and to the same relative extent (their plasma concentration –time profiles will be identical) without significant statistical differences.

Requirements/objectives for Bioequivalence studies:

- New product is intended to be a substitute for an approved medicinal product as a pharmaceutical equivalent or alternative.
- In order to ensure clinical performance of such drug products, bioequivalence studies should be performed.
- Bioequivalence can be demonstrated either *In vivo*, or *In vitro*.

14. Management of Clinical studies:

- A clear objective aimed to bring about change.
- Requiring a team.
- A set time table.

- Defined resources to achieve its objective.
- Tasks which need to be completed (to a pre -specified standard).
- All projects consist of a series of processes, a set of actions needed to bring about results.

Learning Outcome:

1. To know about different Laws and Acts that regulate pharmaceutical industry.
2. To understand the Approval process and Regulatory requirements for drug products suchas IND,NDA and ANDA.
3. To understand the approval process of New drugs in India.

Important questions:

[Two marks Questions]

1. Define Regulatory Affairs.
2. What is Clinical Research?
3. What is NDA?
4. What is IND?
5. What is ANDA?

[Five marks Questions]

1. What are the objectives of Pre- clinical Research?
2. What is the role of Regulatory affairs department ?
3. Discuss the Responsibilities of Regulatory affairs department in detail.
4. Discuss the different phases of clinical trials.
5. Add a note on NDA and ANDA
6. Explain bioequivalence studies in detai

[Ten marks Questions]

1. Explain the IND, NDA and ANDA in detail.
2. Define clinical research. Explain clinical research protocol and information brochure in detail.