Module 2: Pharmacovigilance Methods - Drug discovery onwards

What is a Drug?

- All medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes.
- Such substances (other than food) intended to affect the structure or any function of human body or intended to be used for the destruction of vermin or insects which cause disease in human beings or animals.
- components of a drug including empty gelatin capsules; and
- Such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals.

Overview

- Development of new drug involves two phases namely :Drug discovery and Drug development.
- These require coordinated collaboration of different Teams which include research, development, manufacturing, medical, regulatory, marketing and business management.
- Clinical research is an indispensable part of drug discovery process. Its scope and duration will vary widely, depending on the nature of the drug and its therapeutic application. Clinical trials on patients in the different countries are approved and monitored by different regulatory agencies

Goals of Drug Discovery

- The goals of Drug Discovery are as follows:
  - Identification of a New Chemical Entity (NCE) with a particular biological activity
  - invent medicines to address unmet medical needs
  - To develop a drug that will benefit patients, satisfy prescribers, earn profits for the company

What is Drug Discovery?

The process of drug discovery involves the

- Studying disease processes and Identification & validation of biological target
- Optimizing hit compounds to improve efficacy, safety, stability
  - Optimize to give a “proof-of-concept” molecule—one that shows efficacy in an animal disease model
- Development of assay and screening of large compound collections
  - Selection of final candidate -Optimize to give drug-like properties—pharmacokinetics, metabolism, off-target activities

Once a compound has shown its value in these tests, it will begin the process of drug development.

What is Drug Discovery?: Contd.

- **Target Identification**

Choosing a biochemical mechanism involved in a disease condition. Drugs usually act on either cellular or genetic chemicals within our body, known as targets believed to be associated with the disease.

- **Target Validation**

Up to 5000-10000 molecules for each potential drug candidate are subject to rigorous screening process. Once scientists confirm interaction with drug target, they typically validate that target by checking activity against the disease condition for which the drug is being developed.

What is Drug Discovery?: Contd.

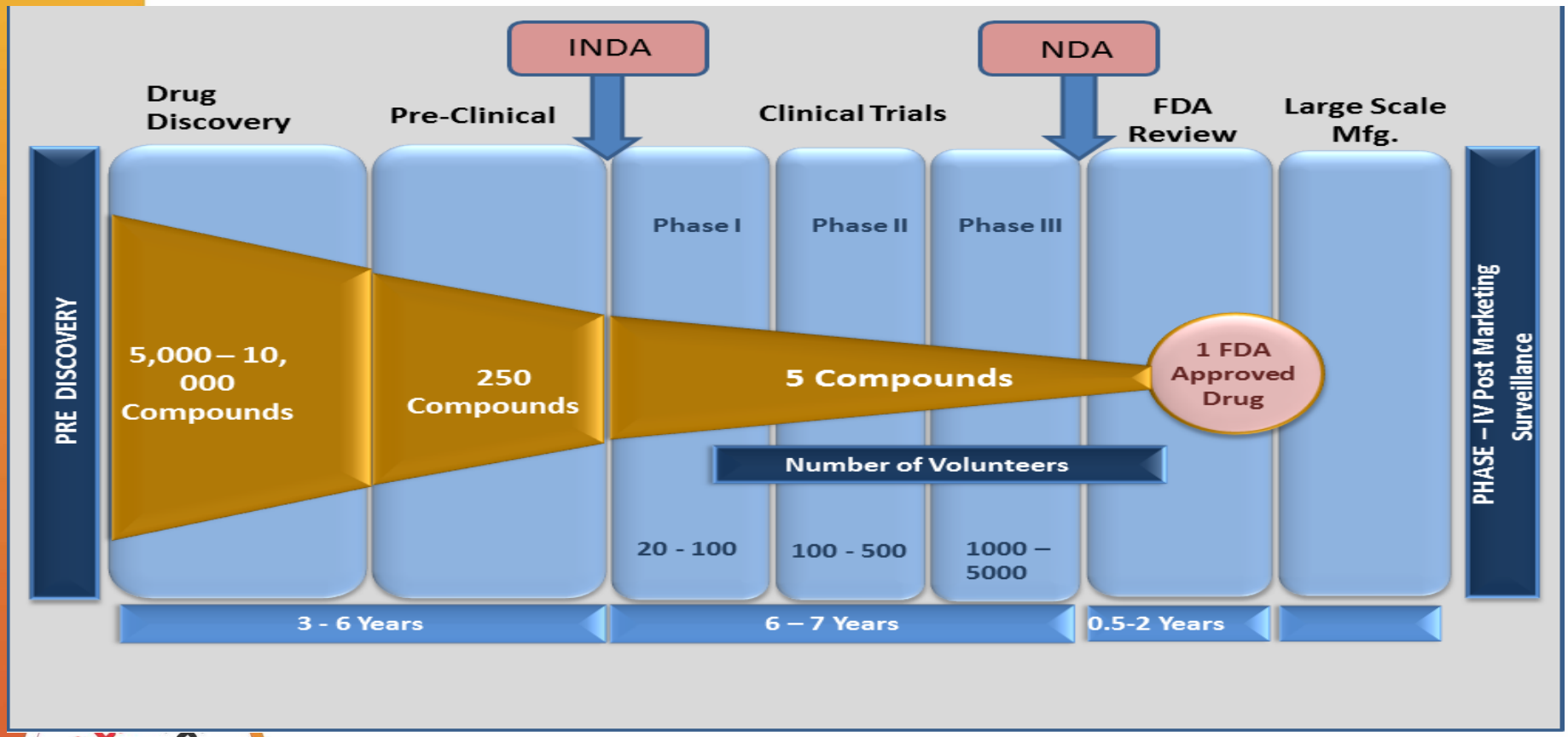
- **Lead Generation**

Scientists compare properties of various lead compounds and provide information to help pharmaceutical and biotechnology companies select compound/s with greatest potential to be developed into safe and effective medicines.

- **Lead Optimization**

Lead compounds that survive the initial screening are then "optimized," or altered to make them more effective and safer. By changing the structure of a compound, scientists can give it different properties. For example, they can make it less likely to interact with other chemical pathways in the body, thus reducing the potential for side effects

Life Cycle of the Drug



Life Cycle of the Drug: Few facts

- It takes about 10 - 15 years to develop one new medicine from the time it is discovered to when it is available for treating patients
- The average cost to research and develop each successful drug is estimated to be $ 800 million to $ 1 billion.
- Out of every 5,000 to 10,000 new compounds identified during the drug discovery process, only five are considered safe for testing in human volunteers after preclinical evaluations.
- After three to six years of further clinical testing in patients, only one of these compounds is ultimately approved as a marketed drug for treatment.

Pre-Clinical Testing

- With one or more optimized compounds in hand, researchers turn their attention to testing them extensively to determine if they should move on to testing in humans.
- Scientists carry out in vitro and in vivo tests to understand the how the drug works and what its safety profile looks like.
- Objective of Pre-clinical testing is to check following properties of investigational drug:
  - Toxicology
  - Pharmacodynamics
  - Pharmacokinetics

Investigational New Drug

- Before any clinical trial can begin, the researchers must file and Investigational New Drug (IND) application with the FDA.
- IND application contains – Preclinical testing results
  - Candidate drug's chemical information
  - Manufacturing information
  - Detailed clinical trial plan
- The FDA reviews the application to make sure people participating in the clinical trials will not be exposed to unreasonable risks.
- In addition, all clinical trials must be reviewed and approved by Institutional Review Board (IRB) at the institutions where trials will take place.

Clinical Trial (s)

A systematic study of new drug(s) in human subject(s) to verify the clinical, pharmacological (Pharmacokinetic and Pharmacodynamics), and/or adverse effects so as to determine its safety and /or efficacy

Need for Clinical Trials:

- to evaluate new drugs, medical devices, biologics or other interventions on patients in a scientifically controlled settings
- required for regulatory authority approval of new therapies.
- to assess the safety and efficacy of an experimental therapy
- to evaluate whether the new intervention is better than standard therapy
- to compare the efficacy of two standard or marketed interventions

Phases of Clinical Trial (s) & PV activities

Phase	Objective	Duration	Population	Sample Size	Pharmacovigilance activity
Phase I Human Pharmacology	Determine the metabolic and pharmacological actions and the maximally tolerated dose	Up to 1 Month	Health volunteers or individuals with target disease (such as cancer or HIV)	20 -100	Routine SAE Monitoring, co-relation with pre-clinical data and structure activity relationship
Phase II Therapeutic Exploratory	Evaluate effectiveness, determine the short-term side effects and identify common risks for a specific population and disease	Several Months	Individuals with target disease	100 -500	Routine SAE Monitoring, Data Safety Monitoring Boards, Developmental Safety Update Report
Phase III Therapeutic Confirmatory	Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall safety risk-benefit ratio in a demographically diverse sample	Several Years	Individuals with target disease	Hundreds to Thousands	Routine SAE Monitoring, Data Safety Monitoring Boards, Determine the frequency of SAEs, Characterize severity of the SAEs, Benefit Risk Assessment, RMP
Phase IV Post-marketing Trials/studies	Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved by the regulatory authority	Ongoing (Following Approval)	Individuals with target disease as well as new age groups, gender etc	Thousands	Routine SAE Monitoring, Determine the frequency of SAEs, Characterize severity of the SAEs, Periodic Benefit Risk Assessment, PASS, PMS, Registry, Epidemiological studies, REMS, RMP Update

New Drug Application

- Through NDA application pharmaceutical companies formally propose that the FDA approve a new pharmaceutical for sales and marketing .
- The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:
  - Whether the drug is safe and effective in its proposed use(s), and the risk benefits evaluation.
  - Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
  - Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

PV activities: Pre-marketing

- PV activities during this stage are not as extensive as those conducted during the post marketing phase.
- This is because that the molecule is evaluated in a fairly controlled environment and is not exposed to the entire population.
- There is yet a vast amount of critical safety data generated
- Various activities performed during the drug development stage:
  - The SAE/Serious Unexpected Serious Adverse Reaction (SUSAR) Collection & Reporting
  - AE Collection
  - Authoring and Reporting of the Developmental Safety Update Reports
  - Preparation of the Developmental Safety Profile of the molecule and ongoing monitoring of the safety profile through co-relation with the non-clinical and clinical findings, structure activity relationship, mechanistic action of the drug and class effect.
  - Modification of the Clinical developmental plans, clinical study protocols, investigator's brochure, informed consent forms, Investigator notifications based on the updated safety data.

PV activities: Post-marketing

- Pharmacovigilance methods deployed during the post marketing stage are even today the main stay for decision making and action.
- The primary reason for this is that vast numbers of patients consume the drug in a relatively short period of time. Also, the post marketing set up is a real life scenario.
- Principles of epidemiology are applied when designing these methodologies. Post marketing pharmacovigilance activities are classified as Active Methods, Passive Methods and Other Methods

PV activities: Post-marketing Active Methods

- Cohort Event Monitoring (CEM)/Prescription Event Monitoring (PEM)

  This is a prospective observational cohort study of AEs associated with one or more medicines. This monitoring is deployed alongside routine clinical practice and aims at detecting early warnings and precautions typically in the early stages of marketing.

- Registry

  A registry is used to measure disease burden (disease registry), monitor safety of drug or device (drug/device registry) or monitor the outcome of pregnancy when receiving a certain drug.

- Record Linkage

  Record Linkage is a method of assembling information contained in two or more records. Health records are linked to the safety assessment of medicines and are useful for studying the long-term impact of drugs.

PV activities: Post-marketing Passive Methods

- Spontaneous Reporting

  This method relies on collection of safety data spontaneously from healthcare professionals or consumers. It is an unsolicited communication by a healthcare professional or consumer that describes one or more Adverse Drug Reaction (ADR) in a patient who was given a drug/s and is not derived from an organized data collection scheme or trial or study.

- Targeted Reporting

  These are methods used to know more about the ADR profile or to estimate the incidence of a known ADR for a specific medicine in a population

- Intensified Reporting

  An extension of the spontaneous reporting and aims to enhance the ADR reporting of specific medicines in the early post marketing phase.

PV activities: Post-marketing Other Methods (1)

- Phase IV
  - The health authority may require that certain phase IV studies be done as “commitments” immediately after marketing . This may be done to clarify some safety and efficacy issues that remained after phase III but which the health agency believed were not sufficient to prevent or delay marketing of the drug.
  - Marketing or pharmacoeconomic studies to aid in selling the product or head-on comparisons with competitor drugs.
  - Studies looking at subgroups of the approved group and indication (e.g., testing a drug approved for diabetes on diabetics who are elderly or are also in heart failure).
  - To investigate an AE or a signal that has unexpectedly occurred after marketing. Such studies may be classical clinical trials, or they may be observational or epidemiologic studies done in large databases.

PV activities: Post-marketing Other Methods (2)

- Late Phase Studies
  - These are studies done both for registration, risk, and marketing reasons.
  - They include registries (product, disease, safety/ADR), postmarketing observational studies, classic phase IV trials as discussed earlier, clinical effectiveness trials, Over The Counter (OTC) trials, community-based trials, health economic and outcomes studies (retrospective, prospective, observational), cost effectiveness, burden of illness, patient reported outcome (PRO, quality of life [QoL], chart review, survey (physicians, patients), health economic piggyback trials, risk management, expanded access, drug safety, and others.

PV activities: Post-marketing Other Methods (2)

- Investigator-Initiated Trials (IIT) or Studies
  - These studies are new ideas thought up by researchers in the academic world or occasionally suggested by the pharmaceutical company.
  - The advantages of IITs are that new ideas are found and explored, costs are usually fairly small, and the studies can be done fairly quickly. The disadvantage is that many details that should be determined before the trials are not addressed (e.g., effective dose and safety in this population). Such studies usually have to be registered with the appropriate health authority and clinical trial database (e.g., clinicaltrials.gov in the United States and EudraCT in the European Union).

Questions?