# SNS COLLEGE OF PHARMACY AND HEALTH SCIENCES

## Coimbatore -641035

COURSE NAME : COMPUTER AIDED DRUG DESIGN (BP 807 T)

IV YEAR / VIII SEM

TOPIC 1 : DRUG DISCOVERY AND DEVELOPMENT

SUB TOPIC: STAGES OF DRUG DISCOVERY AND DEVELOPMENT

# INTRODUCTION

- Drug development process involves rigorous testing and optimization of selected compounds to identify the drug that is most effective.

- This testing is done in cells(in vitro) or in animals(in vivo) to study the metabolism and to produce a product that is safe and has passed all passed all regulatory requirements

# HISTORY OF DRUG DISCOVERY

- Drug discovery and development has a long history and dates back to the early days of human civilization.

- Hippocrates, the father of medicine,at about 400 BC is credited with laying down the ethics for physicians.

- Indian Medicin as- well known as Ayurveda Medcine, based on herbal formuIa.

# FOUNDATION OF CURRENT DRUG DISCOVERY AND DEVELOPMENT

- Digitalis-William Withering introduced digitalis, an extract from the plant foxglove, for treatment of cardiac problems.
- Scriivy-John Hunter (1768) noted that scurvy was caused by the lack of vitamln C.
- Rabies-Louis Pasteur (1864) discovered that micro organisms cause diseases, and he devised vaccination against rabies.

# GINNING OF MODERN PHARMACEUTICAL INDUSTRY

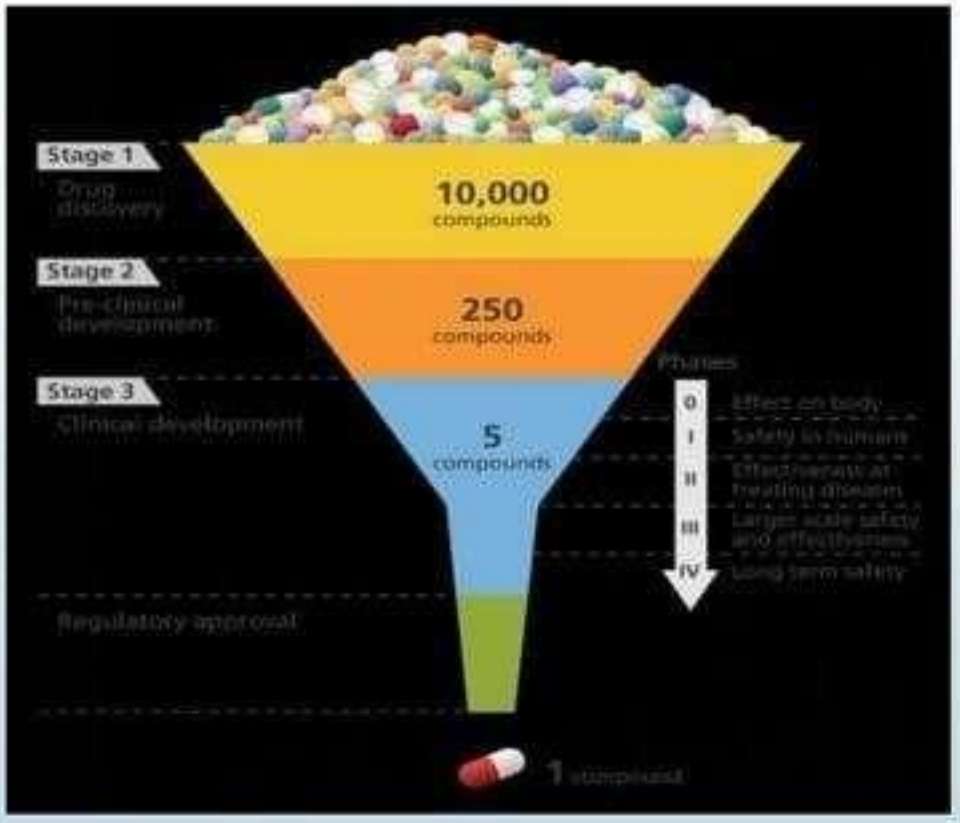
- Quinine Derived from the bark of the Cinchona tree. quinine was used to treat malaria.
- Aspirin- Extracted from the bark of willow tree. aspirin was used for the treatment of fever.
- Penicillin- in 1928. Alexander Fleming discovered that Penicil mold was active against staphylococcus bacteria. Ernst Chain rediscovered this fact some 10 years later, when he collaborated with Howard Florey.
- By 1944, large - scale production of penicillin was available through the work of Howard Florey and Ernst Chain. This work foreshadowed the commencement of biotechnology, where microorganisms were used to produce drug products.

# DEFINITIONS

- DRUG- According to WHO- Drug is any substance or product that is used far or intended to be used or explore physiological systems or pathological states for the benefit of the recipient.
- NEW DRUG- According to Rule 122E-
- Any new substance proclaimed for therapeutic use
- An already approved drug with modified / new therapeutic
- claims, indication, dosage forms or routes of administration
- FDCs of drugs
- All vaccines and recombinant R-DNA derived products
- A New drug shall continue to be considered as new drug for four years.

# DRUG DEVELOPMENT CAN BE CLASSIFIED INTO STAGES

- Stage 1-Drug Discovery:- During which candidate molecules are chosen on the basis of their pharmacological properties.
- Stage 2-PrecIinicaI Development:- During which a wide range of non-human studies (e.g. toxicity testing, pharmacokinetic/pharmacodynamic analysis and formulation) are performed.
- Stage 3-Clinical Development:- During which the selected compound is tested for efficacy, side effects and potential dangers in volunteers and patients.
- Regulatory approval


Stage 1
Drug discovery
10,000
compounds
Stage 2
Pre-Clinical development
250
compounds
Stage 3
Clinical development
5
compounds
Phases
0
I
II
III
IV
Effect on body
Safety in humans
Effectiveness at treating disease
Larger scale safety and effectiveness
Long term safety
Regulatory approval
1 compound

# THE DRUG DISCOVERY PHASE

- Drug discovery is a process, which aims at identifying a Compound therapeutically useful in treating and curing a disease.
  - The process of drug discovery involves the identification of the candidates, Synthesis, characterisation, screening, and assays for therapeutic efficacy.

# STEPSIN DRUG DISCOVERY

- Target Identification
- Target Validation

- Lead Discovery
- Lead Optimization

## STEP1: TARGET IDENTIFICATION

Target identification is the key stage in the drug discovery.

Adrug target is the specific binding site of a drug in vivo through which the drug exerts its action.

- A specific drug target might have the following characteristics:

  The drug target is a biomolecuIe(s), normally a protein that could exist in isolated or as a complex modality.

- The biomolecules have special sites that match others.

- The biomolecular structure might change whgn the biomolecule binds to small molecules and the changes in structure normally are reversible.

- Following the change in the biomolecule s structure various physiological responses occur and induce regulation of the cell, organ, tissue, or body status.

- The physiological responses triggered by the changes in biomolecule structure play a major roIe in complex regulation and have a therapeutic effect on pathological conditions.

- The expression, activity, and structure of the biomolecule might change over the duration of the pathological process.

- Small molecules binding to the biomolecules are drugs.

# STEP2: TARGET VALIDATION

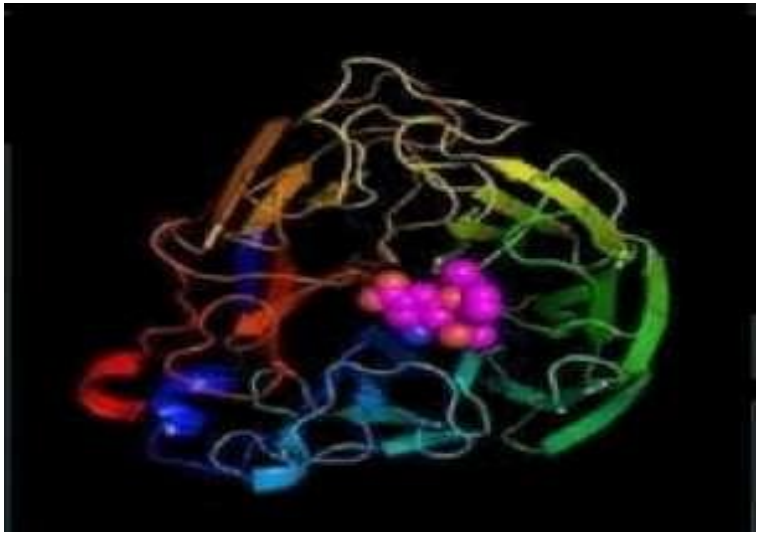
- Target validation is the process by which the predicted molecular target
- is verified.

- New drug target validation might be of great help not only to new drug research and development but alsoprovide more insight into the pathogenesis of target related diseases.

- Basically, the target validation process might include five steps:
- Discovering a biomolecule of interest.
- Evaluating its potential as a target.
- Designing a bioassay to measure its biological activity.
- Constructing a high-throughput screening(hts).
- Performing screening to find k›ad compeunda

- STEP3: LEAD DISCOVERY
- A Lead compound in drug discovery is a chemical compound that has
- pharmacological or biological activity.
- Different Methods of lead discovery are-
- Random Screening :
- All compound including synthetic chemicals, natural products of
- plant, marine and microbial origin from a given series is tested.
- These are screened randomly in the hope of finding a compound with a specific biological activity.
- This approach entered a new dimension with combinatorial chemistry high through-put screening that shows considering chemistry & the screening in an automated manner.

EXAMPLE OF A LEAD (TAMÎFLU) BINDING TO THE PROTEIN TARGET (NEURAMINIDASE)



# HIGH-THROUGHPUT SCREENING TECHNIQUE (HTS)

- HTS is the process of assaying a large number of potential effectors of biological activity against targets (a biological event).

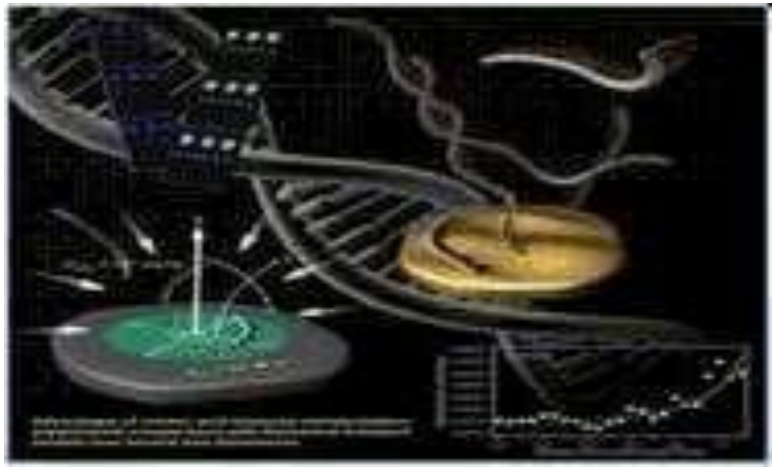
- The methods of HTS are applied to the screening of
- genomics, proteins, and peptide libraries.

- The goal of HTS is to accelerate drug discovery by screening large libraries often composed of hundreds of thousands of compounds (drug candidates) at a rate that may exceed 20,000 compounds per week.


High Throughput Screening & Combinatorial Chemistry

# GENOMICS

- Genomics is the study of entire genomes. The intention of executing the sequencing and analysis of the entire human genome was to enable more rapid and effective identification of disease-associated genes and there by provide it to drug companies with pre-validated targets.



# PROTEOMICS

- Proteomics is the systematic high-throughput separation and characterization of proteins within biological systems. it is at the protein level that disease processes become manifest and at which most drugs act.
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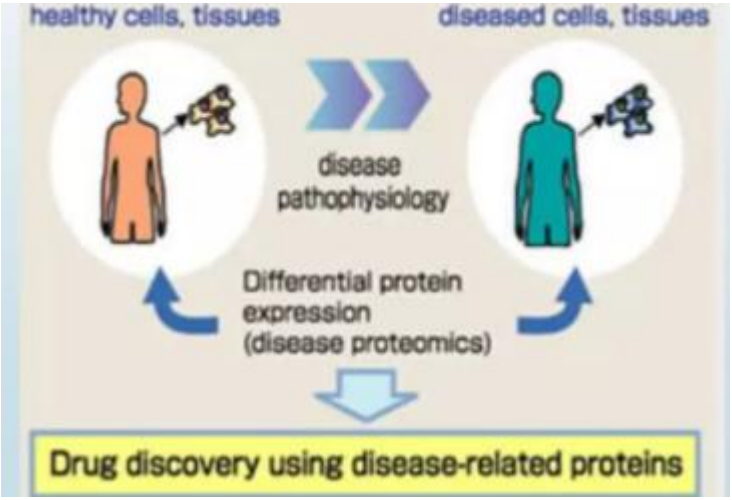


# BIOINFORMATICS

- Bioinformatics is the use Of IT in biotechnology for the data storage, data warehousing and analyzing the DNA sequences. They can now Contribute to lead discovery by exploiting high throughput methods of structure determination that provide powerful approaches to screening of fragment binding.

- STEP4**:** LEAD OPTIMIZATION
- Lead optimization is a process that begins with a compound that displays an interesting biological action and ends with the identification of the best analog.

- Molecules are chemically modified and subsequently characterized in order to obtain compounds with suitable properties to become a drug.

- Leads are characterized with respect to pharmacodynamic properties such as efficacy and potency in vitro and in vivo, Physiochemical properties, pharmacokinetic properties, and toxicological aspects.

- Potency - refers to the amount of drug required for its
- specific effect to occur.
- Efficacy - measures the maximum strength of the effect itself, at saturating drug concentrate ions.
- Pharmacokinetics – It explains about ”What the body does to the drug”,It often divided into areas examining the extent and rate of absorption, distribution,metabolism, and excretion (ADME).
- Pharmacodynamics- It determines the biochemical and physiological effects of drugs, the mechanism of drug action and the relationship between drug concentration and effect. It explains about What the drug does to the body’.

- STEP 5: PRE-CLINICAL DEVELOPMENT

- The aim of preclinical development is to satisfy all the requirements that have to be met before a new compound is deemed ready to be tested for the first time in humans.
- Mainly done on Mice, Rabbit, Rat, Monkeys.
- It is divided into four main categories:
- 1. Safety Pharmacology -Pharmacological testing to check that the drug does not produce any obviously hazardous acute effects, such as bronchoconstriction, cardiac dysrhythmias, blood pressure changes and ataxia.

Preliminary toxicological testing to eliminate genotoxicity and to determine the maximum non toxic dose of the drug {usually when given daily for 28 days, and tested in two species)

- As well as being checked regularly for weight loss and other gross changes, the animals so treated are examined minutely .post mortem at the end of the experiment to search for histological and biochemical evidence of tissue damage.

Pharmacokinetic ance pharmacodynamic (PK/PD) testing.

Chemical and pharmaceutical development to assess the feasibility of large-scale synthesis and purification, to assess the stability of the compound under various conditions and to develop a formulation suitable for clinical studies.

GOOD LABORATORY PRACTICE:

Much of the work of preclinical development, especially that relating to safety issues, done under a formal operating code, known as Good Laboratory practice {Glp}, which covers such aspects as record-keeping procedures, data analysis, instrument calibration and staff training.

The aim of GLP is to eliminate human error as far as possible and to ensure the reliability of the data submitted to the regulatory authority, and laboratories are regularly monitored for compliance to GLP standards.

STEP 6 CLINICAL DEVELOPMENT:

Clinical development proceeds through five distinct phases of

- clinical trials:-
- 1. Early Phase I (Formerly K/A Phase 0)
- A phase of research used to describe trials conducted before traditional phase 1 trials to investigate how a drug affects the body.

- They involve very limited human exposure to the drug and have no therapeutic or diagnostic goals (for example, screening studies, micro dose studies).

PHASE I:

- A phase of research to describe clinical trials that focus on the safety of a drug. They are usually conducted with healthy volunteers.

- The goal is to determine the drug's most frequent.

- and serious adverse events and how the drug is broken
- down and excreted by the body(Dosage).

- It is performed on a small group normally (20-80) of volunteers - often healthy young men but sometimes patients.

- Approximately 70% of drugs move to the next phase.

Their aim is to check for:—

- signs of any potentially dangerous *effects*, for eg: QT prolongation, a sign of potentially dangerous cardiac arrhythmias, is a common cause of failure in early development.
- Tolerability
- Pharmacokinetic properties
- Pharmacodynamic properties
- clinical trials need to be performed under equally strict good clinical practice (GCP) conditions.

## PHASE II

- A phase of research to describe clinical trials that gather preliminary data on whether a drug works in *people* who have a certain condition/disease (that is, the drug's effectiveness. For example, participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance {called a placebo) or a different drug. Safety continues to be evaluated, and short- term adverse events are studied.
- Phase II studies are performed on groups of patients (normally 100-300) for several months to 2 years.
- Approximately 33% of drugs move to the next phase.

# PHASE III

- A phase of research to describe clinical trials that gather more information about a drug's safety and effectiveness by studying different populations with disease and different dosages and by using the drug in combination with other drugs.
- It is aimed at comparing the new drug with common|y used alternatives. These are extremely costly, difficult to organize and often take years to complete.
- It is performed as double-blind, Randomised trials, commonly
- as multicenter trials on thousands of patients(300-3000).
- Approximately 25-30% of drugs moves to the next phase.

PHASE IV

- A phase of research to describe clinical trials occurring after regulatory body of the country has approved a drug for marketing.
- They include post market requirement and commitment studies that are required of or agreed to by the study sponsor.
- These trials gather additional information about a drug's

  safety, efficacy, or optimal use.
- Eg:- withdrawal of Rofecoxib (a cycIo-oxygenase-2 inhibitor) when it was found (in a phase 0I trial for a new indication) it increase the frequency of heart attacks.

# CENTRAL DRUGS STANDARDCONTROL ORGANIZATION

- The Central Drugs Standard Control Organization (CDSCO) is the Central Drug Authority for discharging functions assigned to the Central Government under the Drugs and Cosmetics Act.
- MAJOR FUNCTIONS OF CDSCO
  - Regulatory control over the import of drugs, approval of new drugs and clinical trials
  - Meetings of Drugs Consultative Committee (DCC) and Drugs Technical Advisory Board (DTAB),
  - Approval of certain licenses as Central License Approving Authority

DRUG CONTROLLER GENERAL OFINDIA

Clinical Research is regulated in India by Drug Controller

- General of India (DCGI).
- The office of DCGI runs under CDSCO
- Main responsibilities of DCGI are-
- All Matters related to drug/product approval and standards
- Clinical trials
- Introduction of new drug
- Provide licenses to the new drugs.

# LEGAL PROVISIONS FOR REGULATION OF CLINICAL TRIAL

- Drugs and Cosmetic Act, 1940 and Rules 1945
- Schedule Y- Requirements and Guidelines for Permission to manufacture/import of New Drugs to undertake clinical trials
- Rule 122 DA- Permission to conduct clinical trial.
- Rule 122 DAA- Definition of Clinical Trials
- Rufe 122 DAB- Compensation in case of trial related injury or death
- Rule 122 DAC - Condition of dintcal trial permission and inspection
- Rule 122 DD - Registration of Ethics Commhtee
- Rule 122 E- Definition of New Drugs
- GCP Guidelines,2001

## DRUG APPROVAL PROCESS

- A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process.

A drug approval process comprises of various stages:

Stage 1-Application to conduct clinical trials far evaluating safety and efficacy

Stage 2-Conducting clinical trials,

Stage 3-Application for marketin9 authorization of New drug,

Stage 4-Post-marketing studies.

# STAGE 1—APPLICATION FOR CLINICAL TRIAL OF A INVESTIGATION NEW DRUG(IND)

- When a company in India wants to manufacture/ import a new drug it has to apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 194S.
- Form 44- Application for Permission to undertake clinical trial/Manufacture/lmport of New Drugs with details Df documents to be submitted along with prescribed fees.

## STAGE 2—CONDUCTING CLINICAL TRIAL

Phases of clinical trial done are-

- Early Phase 1
- Phase 1
- Phase 2
- Phase 3

# STAGE 3 - APPLICATION FOR MARKETING AUTHORIZATION OF THE NEW DRUG

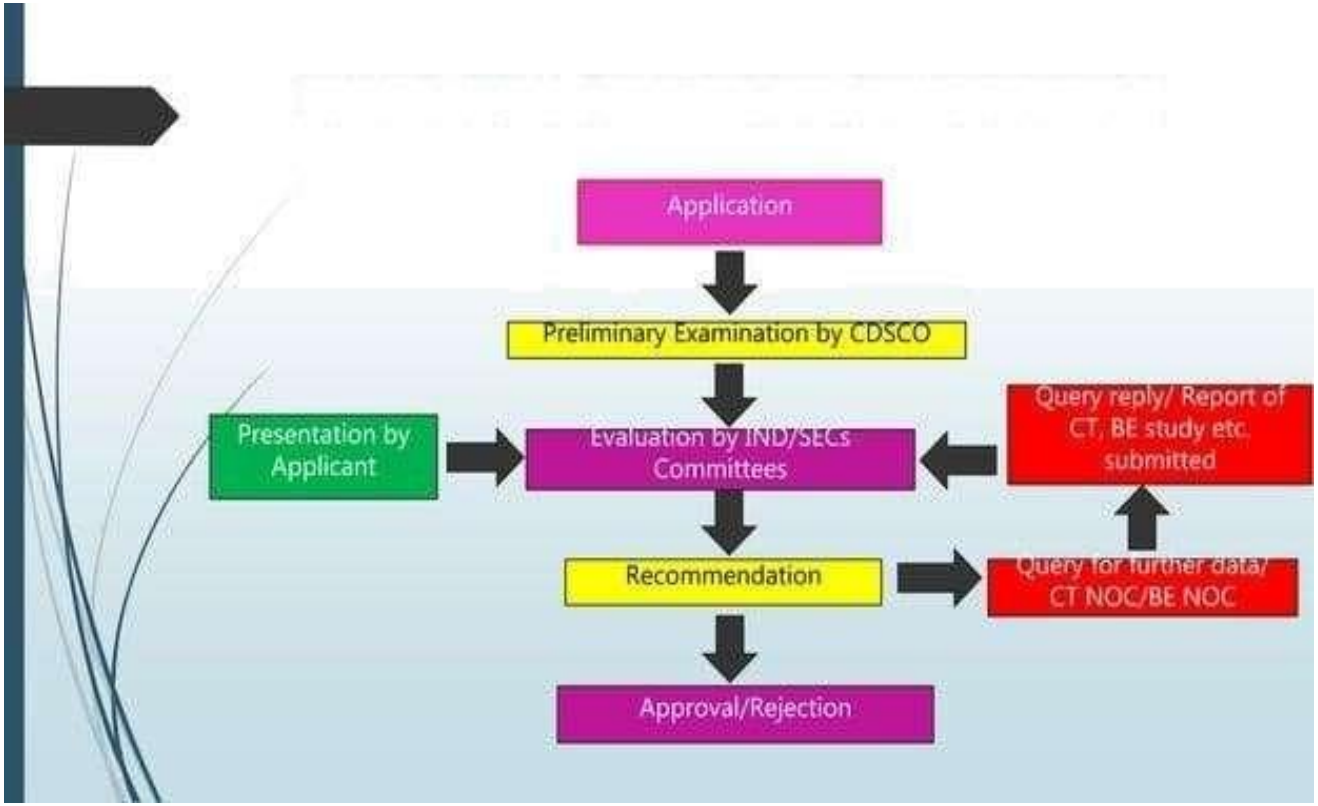
New Drug Application(Data Required)-

- Chemical and Pharmaceutical information
- Animal Pharmacology
- Animal Toxicology
- Phase I,II,III Clinical Trials
- Label
- Prescribing informatiDn.

- COMMITTEES FOR EVALUATION OF APPLICATIONS

- IND Committee Evaluation of Investigational New Drugs (new molecules discovered in India›. Chaired by DG, ICMR & Secretary, Department of Health Research.
- Subjects Expert Committee(SEC) 25 panels of about 350 various medical experts for evaluation of applications of clinical trial and new drug approvals except IND.
- Technical Comittee(TC) - Separate committee of experts chaired by Director General Health Services to review proposals Clinical trials.
- Apex Committee- Reviews recommendations of
- Technical Committee in cases of Clinical trial.

# EVALUATION OF APPLICATION BYIND/SEC



## STAGE 4- POST-MARKETING STUDIES

Post Marketing Survei1lance of a Pharmaceutical Product entails:

- Submission of Periodic Safery Update Reports
- Active/Passive Surveillance
- Structured Phase IV trial
- Observational Study.
- Pharmacovigilance Program of India through 210 ADR
- monitoring Centers located in medical colleges and hospitals
- Quality Monitoring of the marketed product the Regulatory system

THANK YOU