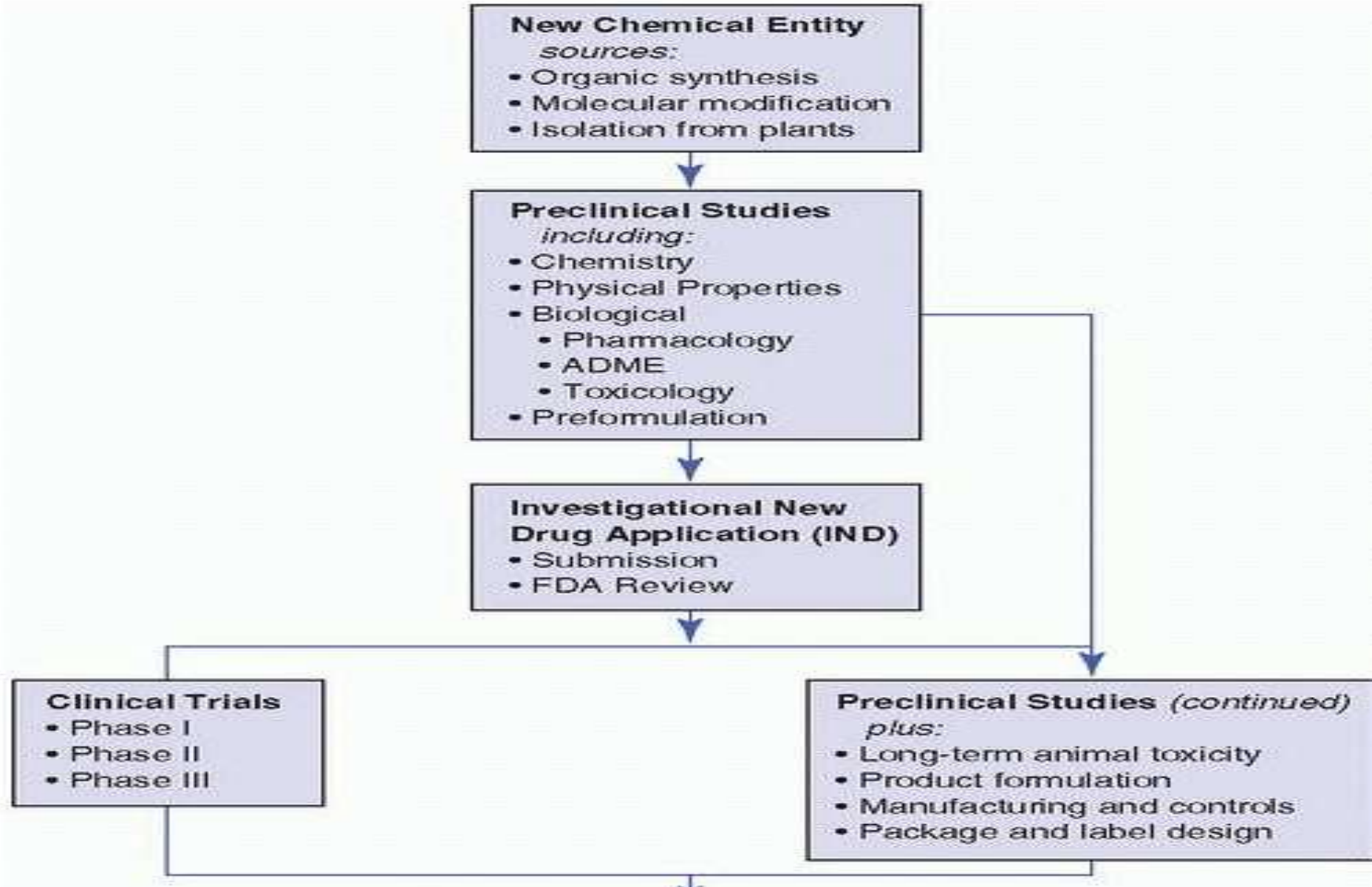
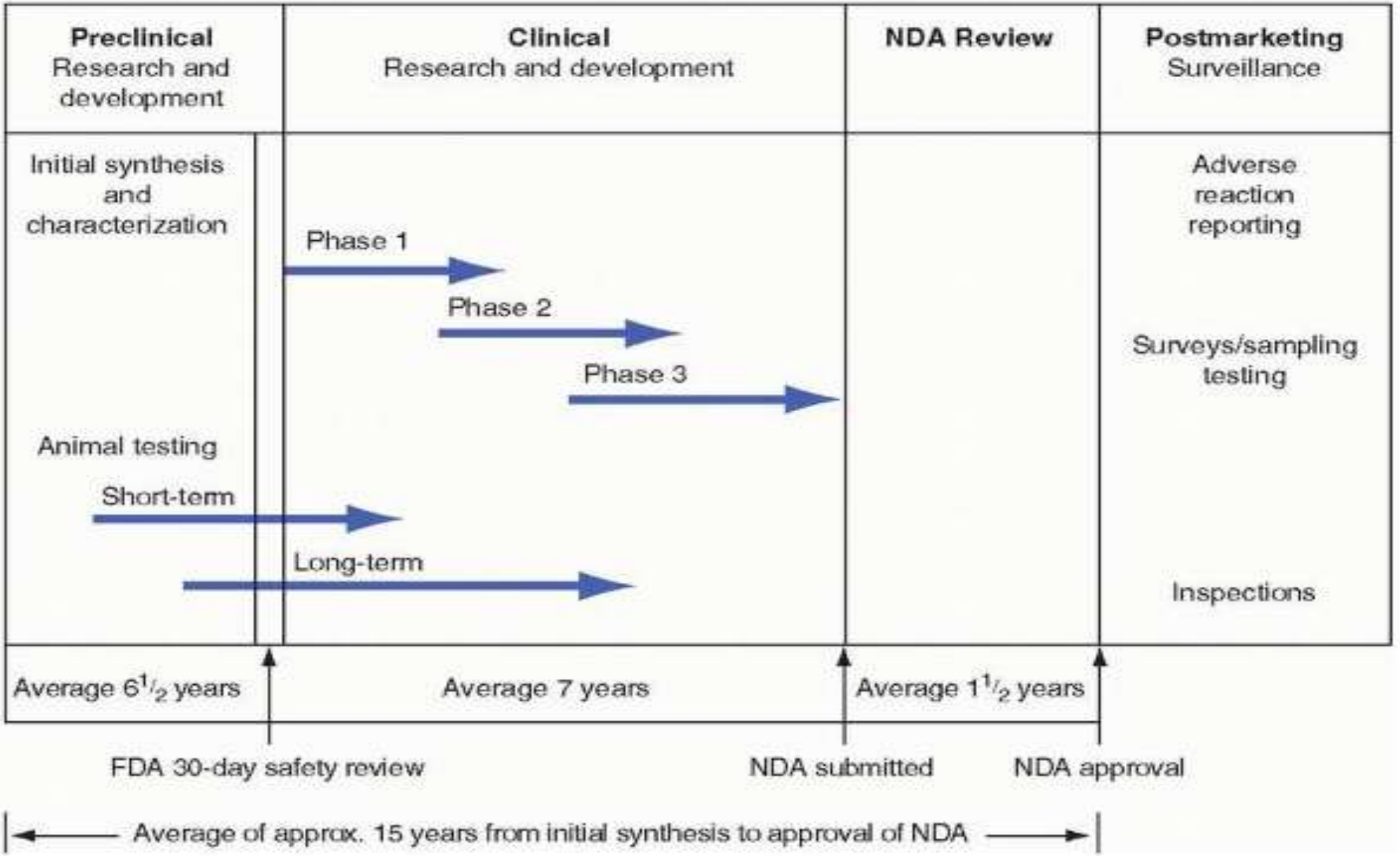
PROCESS FROM DRUG DISCOVERY TO APPROVAL FOR MARKETING




New Drug Application (NDA)
• Submission
• FDA Review
• Preapproval plant inspection
• FDA action
Postmarketing
• Phase IV clinical studies
• Clinical pharmacology / Toxicology
• Additional indications
• Adverse reaction reporting
• Product defect reporting
• Product line extension

TIME FOR THE DEVELOPMENT OF A NEW DRUG



ABBREVIATED NEW DRUG APPLICATION (ANDA)

- 1)Used to get **approval to market**: **In comparison with product already approved** and marketed drug.(**chemistry**, **manufacturing**, **controls**, and **bioavailability** of the proposed product to demonstrate biologic equivalency to the original product).
- 2)Clinical data on drug's **safety** and **efficacy** are not required because clinical studies were provided by the pioneer sponsor.

DRUG DISCOVERY AND DRUG DESIGN

- The combined efforts of **chemists**, **biologists**, **molecular biologists**, **pharmacologists**, **toxicologists**, **statisticians**, **physicians**, **pharmacists** and **pharmaceutical scientists**, **engineers**, and many others participate in drug discovery and development.

SOURCES OF NEW DRUGS

- New drugs **discovered in lab**. by accident, or as result of many years of **work** or from **plant**.
- 270,000 known plants
- **Rauwolfia serpentina: reserpine.**

- **Natural chemical as starting material in creation.**
- **semisynthetic drugs**

- **Animals served humans in their search for drugs** in a number of ways:
- **Drug testing**
- **Biologic assay**
- **Provided drugs** that are from their tissues or through their biologic processes.
- The urine of pregnant mares is a rich source of estrogens.
- **Hormonal substances,** such as **thyroid extract, insulin, and pituitary hormone** obtained from **endocrine glands** of **cattle, sheep.**
- Today poliomyelitis vaccine prepared in cultures of **renal monkey tissue**, the **mumps and influenza vaccines in fluids of chick embryo**, the rubella (German measles) vaccine in duck embryo, and the smallpox vaccine from the skin of bovine calves inoculated with vaccinia virus.
- New vaccines for diseases such as AIDS and cancer are being developed through the use of cell and tissue cultures.

- The two basic technologies that drive the genetic field of drug development:

1. **recombinant DNA**
2. **monoclonal antibody production**

- techniques influence cells' ability to produce proteins.
- Proteins are infinite source of drugs. Made up of long chains of amino acids, their sequence and spatial configuration offer a number of possibilities.

- rDNA has the ability to produce any protein.
- Genetic material transplanted from higher species, such as humans, into a lowly **bacterium**. This so-called **gene splicing** can induce the lower organism to make proteins.

- human insulin,
- human growth hormone,
- hepatitis B vaccine,
- interferon

are being produced

monoclonal antibody production

- conducted entirely **within the cells of higher animals.**
- These antibodies have the capacity to combat the specific target.

1. Diagnostically: home pregnancy testing products.
2. stage and to localize malignant cells

Human gene therapy

- **Prevent, treat, cure, diagnose**. **(Gene therapy** is a medical intervention based on modification of genetic material of living cells).
- gene therapy entails the transfer of new genetic material to cells of patient with a genetic disease.
- The human body contains up to 100,000 genes.
- The genetic material, cloned DNA transferred into patient's cells **physically**, through **microinjection**, by chemical mediated transfer procedures, or through **disabled retroviral gene** transfer systems that integrate genetic material directly into the host cell chromosomes.

A GOAL DRUG

- In theory, goal drug produce

1. **desired effect** administered
2. **by desired route** (generally orally) at
3. **minimal dosage** and **dosing frequency**.
4. **optimal onset** and **duration**.
5. **no side effects**.
6. **eliminated from body efficiently**, **completely**, and **without residual effect**.
7. **low cost.**
8. pharmaceutically **elegant.**
9. **physically and chemically stable.**

Molecular modification

- Molecular modification is a **chemical alteration** of a known and previously characterized **organic compound** for purpose of **enhancing its usefulness as a drug.**

1. mean **enhancing its specificity for particular target site**.
2. **increasing its potency**
3. **Improving rate and extent of absorption**.
4. modifying to advantage its time course in body.
5. **reducing toxicity**.
6. **changing its physical or chemical properties** (e.g., solubility) to provide desired features .

- Molecular modification **produces new chemical entities** and **improved therapeutic agents**.

- **interaction of drug with specific receptors**, **enzyme** systems, **or metabolic processes** of **pathogens or tumor cells**, resulting in **blocking, disruption, or reversal of the disease process.**
- For this, it is essential to understand biochemical pathway of disease process and manner in which it is regulated.

- Example on **drug design based on mechanism:** enalaprilat, the active metabolite of enalapril which inhibits angiotensin-converting enzyme (ACE) that catalyzes the conversion of angiotensin I to vasoconstrictor substance angiotensin II.

- **Inhibition of the enzyme results in decreased plasma angiotensin II**, leading to **decreased vasopressor** effects and **lower blood pressure**.

- Another example is **ranitidine** (Zantac): inhibitor of histamine at histamine H_2-receptors, including receptors on gastric cells.
- This **inhibits gastric acid secretion**, making the drug effective in the treatment of gastric ulcers.
- A third example is **sertraline** : inhibits central nervous system's neuronal uptake of serotonin, making drug useful in treatment of depression.

A LEAD COMPOUND

- A lead compound is a prototype chemical compound that has a fundamental desired biologic or pharmacologic activity.

- cephalosporin antibiotics
- benzodiazepine

PRODRUGS

- Prodrug is a compound that requires metabolic biotransformation after administration to produce the desired pharmacologically active compound.

- The conversion of inactive prodrug to active occurs through enzymatic biochemical cleavage.
- the biotransformation may occur anywhere along the course of drug transit or at the body site where the enzymes are sufficiently present.
- An example of a prodrug is enalapril maleate (Vasotec) which, after oral administration, is bioactivated by hydrolysis to enalaprilat, an ACE inhibitor used in the treatment of hypertension.
- Prodrugs may be designed for **solubility**, **absorption**, **biostability**, and **prolonged release.**

- **A prodrug may be designed to possess solubility advantages over the active** drug, enabling the use of specifically desired dosage forms and routes of administration.

- For example, if an active drug is insufficiently soluble in water to prepare a desired intravenous injection, a water-soluble prodrug, for example, **hydrocortisone sodium succinate**, could be prepared through the addition of a functional group that later would be detached by the metabolic process to yield, once again, the active drug molecule.

- **Increase Absorption**

A drug may be made more water or lipid soluble, as desired, to facilitate absorption via the intended route of administration.

- For example, for patients requiring prolonged antipsychotic therapy, the addition of the decanoate ester to the haloperidol molecule makes the molecule **less water soluble**. Subsequently, when it is administered by a deep intramuscular injection, the molecule provides a sustained effect that lasts up to 4 weeks.

Biostability

- If drug destroyed by biochemical or enzymatic processes, the design of a prodrug protect the drug during its transport in body.
- example, **valacyclovir** is a prodrug of acyclovir. bioavailability of acyclovir is 10%-20% after oral administration. Valacyclovir is converted to acyclovir by liver esterases via first pass metabolism resulting in a 55% bioavailability.
- In addition, the use of a prodrug could result in site-specific action of greater potency. For example, dopamine in treatment of Parkinson disease is unable to cross blood-brain barrier. its prodrug, levodopa, is able to cross the blood-brain barrier and then is converted to dopamine.
- Prolonged Release
- Depending on a prodrug's rate of metabolic conversion to an active drug, it may provide prolonged drug release and extended therapeutic activity.

FDA‘ DEFINITION OF A NEW DRUG:

- **new drug is any drug that not recognized as being safe and effective** in the conditions recommended for its use.
- A drug need not be a new **chemical entity** to be considered new. A **change** in a previously approved drug product's **formulation** or **method of manufacture** constitutes newness under the law since such changes can alter therapeutic efficacy and/or safety of a product.
- A **combination of two or more old drugs** or a change in the usual proportions of drugs in an established combination product is considered new **if the change introduces a question of safety or efficacy.**
- A proposed **new use** for an established drug, a **new dosage schedule or regimen, a new route of administration, or a new dosage form** makes a drug or a drug product's status new and triggers reconsideration for **safety and efficacy**.

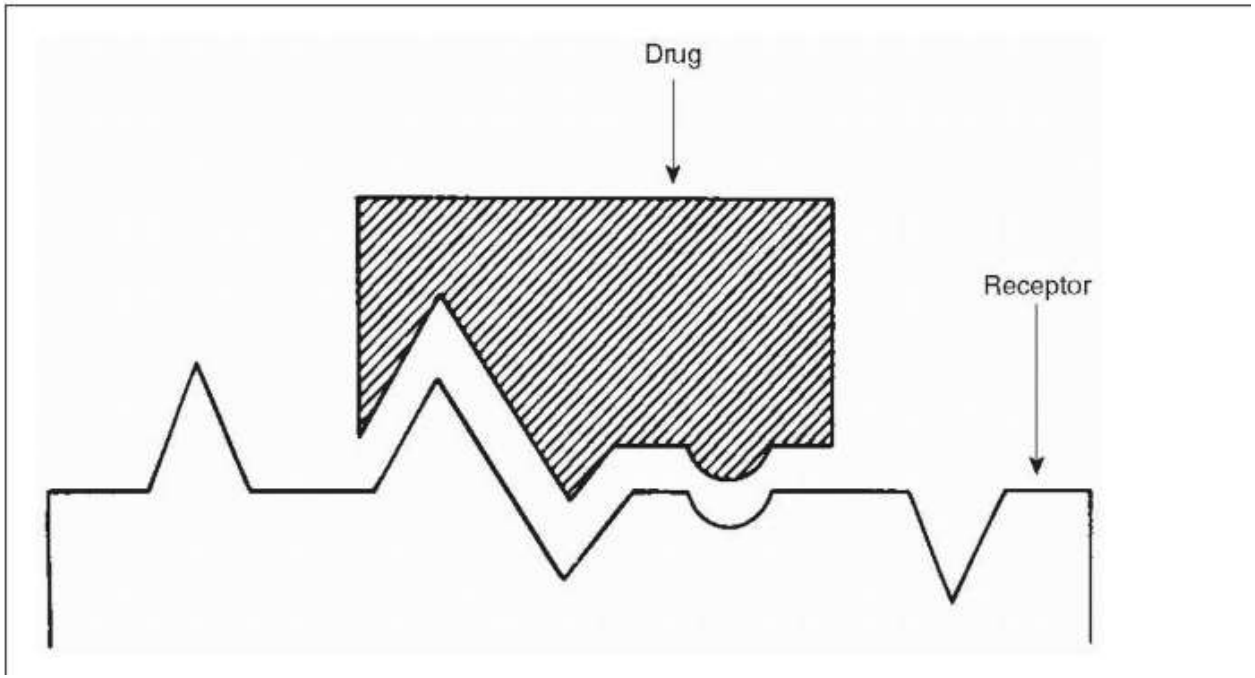
BIOLOGIC CHARACTERIZATION

- Drug undergo **preclinical testing** for biologic activity to assess their therapeutic activity.
- These studies: **pharmacology**, drug **metabolism**, and **toxicology**, involve many types of scientists, biologists, microbiologists, molecular biologists, biochemists, geneticists, pharmacologists, physiologists, pathologists, toxicologists, statisticians, and others.
- Their work leads to the determination whether chemical agent possesses safety and sufficient usefulness to pursue as a new drug.

- how it **is absorbed, distributed throughout the body, stored, metabolized, and excreted** and how it affects the action of the body's cells, tissues, and organs.
- Scientists have studies conducted outside living body by using **cell and tissue culture** and computer programs that simulate human and animal systems. Cell cultures are being used increasingly to screen for **toxicity** before progressing to whole-animal testing.

PHARMACOLOGY

- (ADME) of drugs
- identifying the cause and process of a disease and then designing molecules capable of interfering with that process.



- Receptors considered to be:
- **carboxyl,**
- **amino,**
- **sulfhydryl,**
- **phosphate**

oriented on or in the cell in a pattern **complementary** to that of drugs with which they react.

- The binding of a drug to the receptor is thought to be accomplished by:
- ionic,
- covalent,
- and other relatively weak reversible bonds. Occasionally, firm covalent bonding is involved, and the drug effect is then slowly reversible.
- When receptors saturated, the effects are maximized. Any additional drug present and not participating in interaction serve as a reservoir to replace the drug molecules released from the complex.

- Two drugs in a biologic system may **compete** for the same binding sites, with the drug having the stronger bonding attraction for the site generally prevailing.
- Already bound molecules of the more weakly bound drug may be **displaced** from the binding site and left free in the circulation.
- Certain cells within the body are capable of binding drugs without eliciting a drug effect. These cells act as **carriers** and may be important to a drug's transport to active sites or to sites of the drug's biotransformation and elimination.

- **The process of evaluating chemical compounds for biologic activity** and the determination of their mechanisms of action are the responsibilities of the **pharmacologist.**
- **In vitro cultures of cells and enzymes systems and in vivo animal models** are used to define a chemical's pharmacologic profile.
- To define a pharmacologic profile, pharmacologists progress stepwise through increasingly sophisticated levels of evaluation, based on the test compound's success in prior studies.
- Whole-animal studies are reserved for test compounds that have demonstrated reasonable potential as a drug candidate.

- Among the early studies are the determination of a compound's selectivity **for various receptors** and its **activity against select enzyme** systems.
- Studies of the compound's effects on **cell function** are then performed to detect evidence of **efficacy** and to determine whether the compound is an agonist or antagonist.
- These are followed by studies with **isolated animal tissues** to define further the compound's **activity and selectivity.**
- Then **whole-animal studies** are used to evaluate the **pharmacologic effects** of the agent on specific organ systems.
- Finally, studies are undertaken using **animal models of human disease** for which the compound is considered a drug candidate.

- Most animal testing is performed on **small animals**, usually rodents (mouse, rat) for a number of reasons including:

1. cost,
2. availability,
3. the small amount of drug required for a study,
4. the ease of administration by various routes (oral, inhalation, and intravenous), and experience with drug testing in these species.

However, in final pharmacologic and toxicologic studies, two or more animal species are used as required by the FDA, including a **rodent** and an **animal from another order.**

Drugs are studied at **various dose levels** to determine the

1. effect,
2. potency, and
3. toxicity.

- **The primary objective of the animal studies** is:
- **to obtain basic information on the drug's effects that may be used to predict safe and effective use in humans**.
- This is a difficult task because of species variation and the fact that animals are not absolute predictors of human response. However, a number of animal models have been developed to mimic certain human diseases, and these are used effectively.
- For instance, there are animal models for type I diabetes and hypertension, using genetically diabetic and hypertensive animals, respectively, and for tumor growth, using tumor transplants in various species.

- Certain animal species have been determined to be the best for certain studies of organ systems, or as human disease models, including:

1. **dogs and rats** **for hypertension**
2. **dogs and guinea pigs** **for respiratory effects**,
3. **dogs** **for diuretic activity**,
4. **mice and rats for central nervous system studies.**

- Unfortunately, useful animal models are not available for every human disease. As a drug candidate progresses in its preclinical pharmacologic evaluation, drug metabolism and toxicity tests are initiated.

DRUG METABOLISM

- A series of animal studies of a proposed drug's ADME are undertaken to determine ;
- (a) **the extent and rate of drug absorption** from various routes of administration, including the one intended for human use;
- (b) the **rate of distribution** of the drug through the body and the site or sites and duration of the drug's residence;
- (c) the rate, primary and secondary sites, the mechanism of the drug**'s metabolism** in the body, and the chemistry and pharmacology of any metabolites; and
- (d) the proportion of administered dose **eliminated from the body** and its rate and route of elimination. In these studies, a minimum of two animal species are employed (generally the same as used in the pharmacologic and **toxicologic studies), a rodent and one other, usually a dog.**

- The biochemical transformation or metabolism of drug substances is the body's means of transforming non polar drug molecules into **polar** compounds, which are more readily eliminated.