لجنة عمداء كليات الصيدلة
لجنة توحيد منهاج مادة Dosage Form Desgin

Dosage Form Desgin

المرحلة الخامسة

2024

Ansel's pharmaceutical dosage forms and drug delivery systems (10). Loyd V. Allen, Jr., Howard C. Ansel. —Tenth edition.

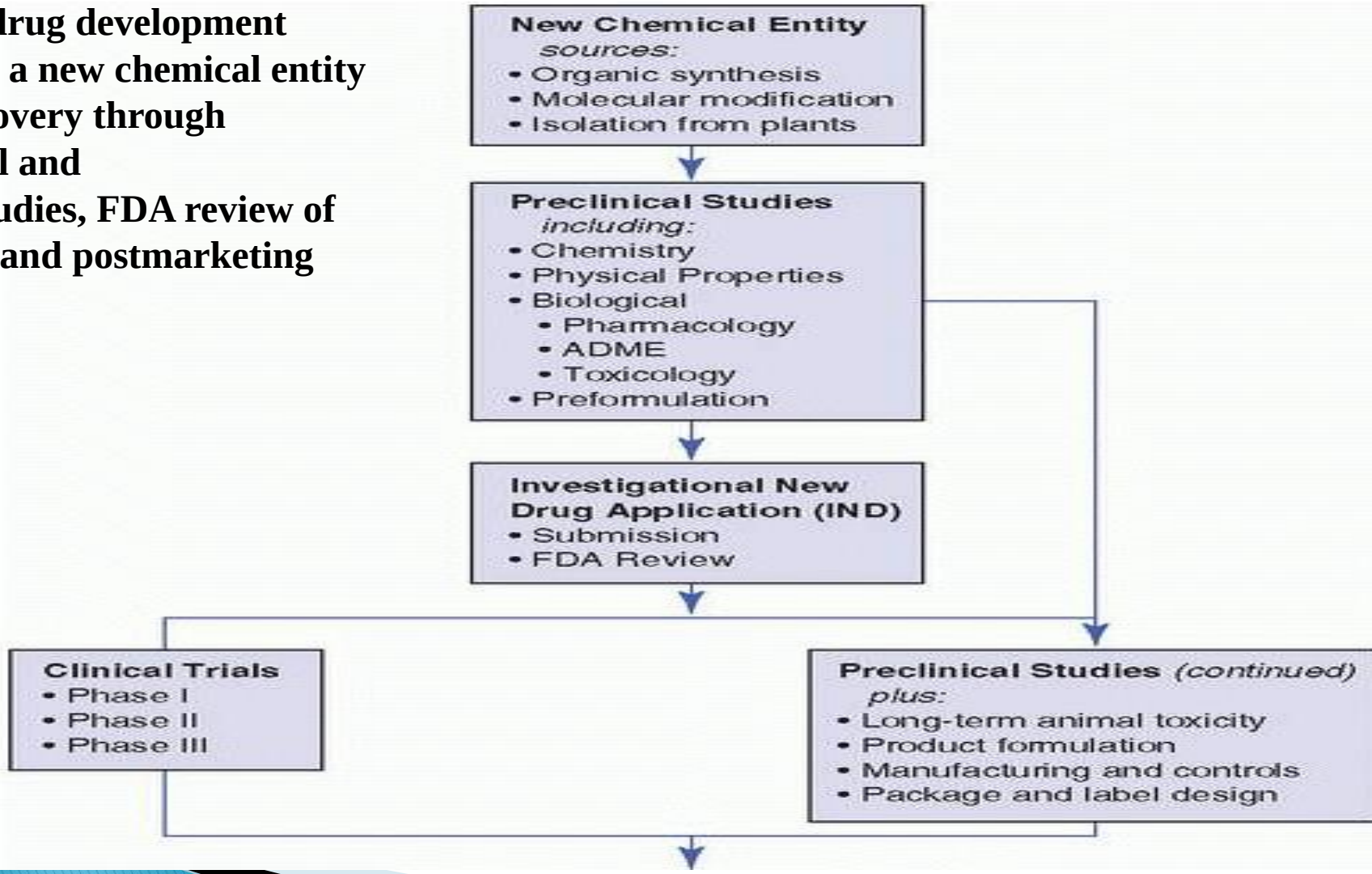
- تم اعداد ومراجعة هذا المنهج الموحد للامتحان التقويمي لكليات الصيدلة للعام الدراسي 2023-2024 من قبل اساتذة متخصصين لديهم خبرة كبيرة في التدريس والعمل الاكاديمي . لقد بذل الاساتذة قصارى جهودهم في جمع المعلومات وحرصوا على ترتيبها وتنظيمها لتكون واضحة يسيرة على طلبتنا الاعزاء . نأمل من طلبتنا الاعزاء الاستفادة منه في طريقهم الى النجاح والتفوق ، والله الموفق

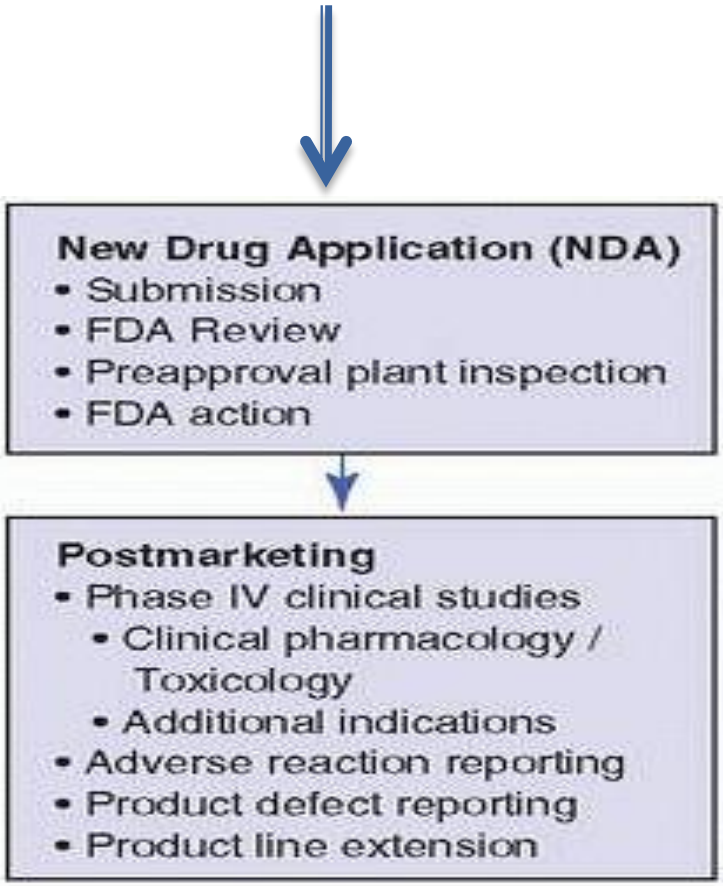
New Drug Development and Approval Process

- Chapter 2

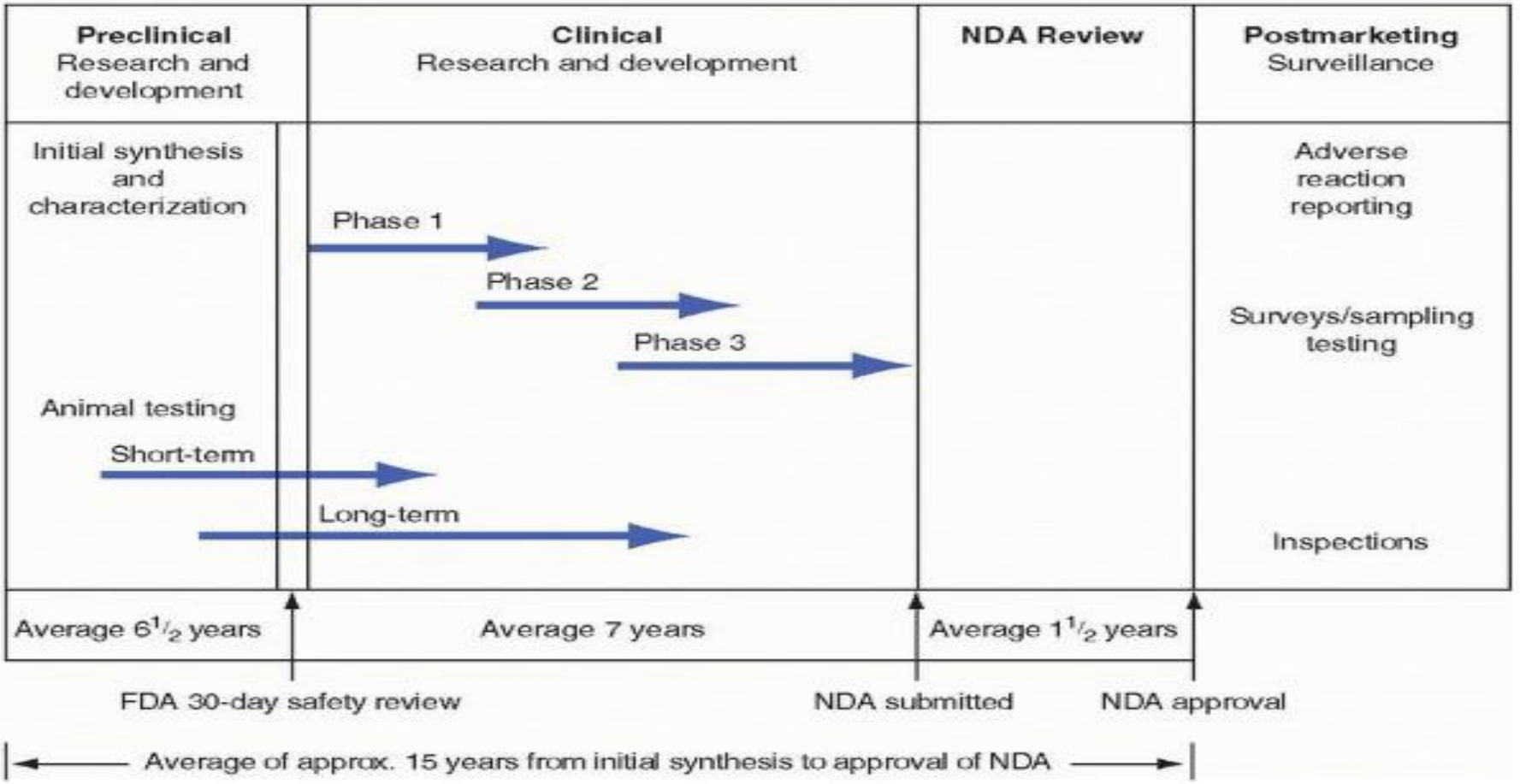
Process and time from drug discovery to approval for marketing

The new drug development process of a new chemical entity from discovery through preclinical and clinical studies, FDA review of the NDA, and postmarketing activities.




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 course for the development of a new drug.



- Only when the preclinical studies demonstrate adequate safety and the new agent shows promise as a useful drug will the drug's sponsor file an *Investigational New Drug* (*IND*) *Application* with the FDA for initial testing in humans. If the drug demonstrates adequate safety in these initial human studies, termed Phase 1, progressive human trials through Phases 2 and 3 are undertaken to assess safety and efficacy.
- As the clinical trials progress, laboratory work continues toward defining the agent's basic and clinical pharmacology and toxicology, product design and development, manufacturing scale-up and process controls, analytical methods development, proposed labeling and package design, and initial plans for marketing.

- At the completion of the carefully designed preclinical and clinical studies, the drug's sponsor may file a *New Drug Application* (*NDA*) seeking approval to market the new product. The FDA's approval of an NDA indicates that the body of scientific evidence submitted sufficiently demonstrates that the drug or the drug product is safe and effective for the proposed clinical indications, that there is adequate assurance of its proper manufacture and control, and that the final labeling accurately presents the necessary information for its proper use. Some products, however, have been approved and later removed from the market for safety reasons.

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.

- **penicillin,** antibiotic that became commercially available in **1944,**
- **15 years after its discovery in England by Sir Alexander Fleming** and 1 year before the end of the war.

SOURCES OF NEW DRUGS

- New drugs may be **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 have served humans in their search for drugs in a number of ways. They not only have yielded to drug testing and biologic assay but also have provided drugs that are mannered from their tissues or through their biologic processes.
- biologic drugs, include: monoclonal antibodies, therapeutic proteins, immunotherapies, and vaccines.
- Hormonal substances, such as thyroid extract, insulin, and pituitary hormone obtained from the endocrine glands of cattle, sheep, and swine, are lifesaving drugs used daily as replacement therapy in the human body. The urine of pregnant mares is a rich source of estrogens.
- Knowledge of the structural architecture of the individual hormonal substances has produced a variety of synthetic and semisynthetic compounds with hormone-like activity. The synthetic chemicals used as oral contraceptives are notable examples.
- tissue cultures: mumps and influenza vaccines in fluids of chick embryo. rubella (German measles) vaccine in duck embryo.
- **genetic engineering.**

- The use of animals in the production of various biologic products, including serums, antitoxins, and vaccines, has had lifesaving significance ever since the pioneering work of Edward Jenner on the smallpox vaccine in England in 1796.
- Today the poliomyelitis vaccine is 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.

- Today we are witnessing a new era in the development of pharmaceutical products as a result of the advent of genetic engineering, the submicroscopic manipulation of the double helix, the spiral DNA chain of life.
- Through this process will come more abundant and vastly purer antibiotics, vaccines, and yet unknown chemical and biologic products to combat human diseases.

rDNA

- techniques that **influence cells' ability to produce proteins.**
- **rDNA has the ability to produce any wanted protein**.
- **Genetic material transplanted from higher species, such as humans, into a lower bacterium.** called **gene splicing** can induce lower organism to make proteins.
- Such drug

products as: human insulin, human growth hormone, hepatitis B vaccine, epoetin alfa, and interferon are being produced in this manner.

Human insulin was the first recombinant biopharmaceutical approved in the United States, in 1982

Monoclonal antibody production

Whereas **recombinant DNA** techniques involve the manipulation of **proteins within the cells of lower animals**, **monoclonal antibody production** is conducted entirely **within the cells of higher animals**, including the patient. The technique exploits the ability of cells with the potential to **produce a desired antibody** and stimulates an unending stream of pure **antibody production**. These antibodies have the capacity to combat the specific target.

Monoclonal antibody production

- **monoclonal antibody production is conducted entirely within the cells of higher animals.**
- These antibodies have the capacity to combat the specific target. The development and use of monoclonal antibodies is having a profound impact in both diagnostic medicine and in the treatment of disease.

Diagnostically: home pregnancy testing products. monoclonal antibodies are used in home pregnancy testing products. In these tests, the mAb is highly sensitive to binding on one site on the human chorionic gonadotropin (HCG) molecule, a specific marker to pregnancy because in healthy women, HCG is synthesized exclusively by the placenta.

- The first FDA-approved therapeutic mAb was muromonab, a transplant rejection drug, approved in 1986.

Since then, many additional mAbs have received FDA approval for marketing with hundreds of others undergoing clinical trials.

Human gene therapy

- Used to prevent, treat, cure, diagnose human diseases caused by genetic disorders. **(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. Genes that are aligned on a double strand of DNA in the nucleus of every cell control all of the body's functions.
- Base pairs of **adenine and thymine** (A and T, respectively) and **cytosine and guanine** (C and G, respectively) **constitute the instructions on a gene**. Only genes necessary for a specific cell's function are **active or expressed.**

- When a gene is expressed, a specific type of protein is produced. In genetic diseases, gene expression may be altered and/or gene sequences may be mismatched, partly missing, or repeated too many times, causing cellular malfunction and disease.
- Gene therapy is a medical intervention based on the modification of the genetic material of living cells. Cells may be modified outside the body (ex vivo) for subsequent administration, or they may be modified within the body (in vivo) by gene therapy products given directly to the patient. In either case, gene therapy entails the transfer of new genetic material to the cells of a patient with a genetic disease. The genetic material, usually **cloned DNA**, may be transferred into the patient's cells **physically**, as through **microinjection**, through chemically mediated transfer procedures, or through disabled retroviral gene transfer systems that integrate genetic material directly into the host cell chromosomes

- The first human gene therapy used was to treat adenosine deaminase (ADA) deficiency, a condition that results in abnormal functioning of the immune system. Therapy consisted of the administration of genetically modified cells capable of producing ADA
- Many emerging biopharmaceutical companies are exploring the application of gene therapy to treat sickle cell anemia, malignant melanoma, renal cell cancer, heart disease, familial hypercholesterolemia, cystic fibrosis, lung and colorectal cancer, and AIDS
- The FDA has established guidelines for cellular and gene therapy

A GOAL DRUG

In theory, goal drug may 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.**

Combinatorial chemistry

- Techniques capable of examining **15,000 chemical** compounds a **week** **using 10 to 20 biologic** assays.

Molecular modification

- **Is a <u>chemical alteration</u> of known organic compound for enhancing its usefulness as a drug.**

This could mean:

- **enhancing specificity** for a particular body target site.
- **Increasing potency**.
- **Improving rate and extent of absorption.**
- **Modifying** time course in the body.
- **Reducing toxicity**.
- **Changing physical or chemical** properties (e.g., solubility) to provide desired features.

- The molecular modifications may be:
- slight or substantial, involving **changes in functional groups**, **ring structures**, or **configuration**. Knowledge of **chemical structure-pharmacologic activity relationships** plays important role in designing new drug molecules.
- **Molecular modification produces new chemical entities and improved therapeutic agents.**

- Drug design is **molecular modification to design a drug that interferes specifically with the known or suspected biochemical pathway or mechanism** of a disease.
- result in blocking, disruption, or reversal of disease process.

- Example of **mechanism-based drug design** is compound 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**.
- This **inhibits gastric acid secretion**, making the drug effective in the treatment of gastric ulcers.
- A third example is **sertraline** which inhibits the central nervous system's neuronal uptake of serotonin, making drug useful in treatment of depression.

- The **initial bioassays** : **in vitro using cell cultures**
- to test new agent's effect against enzyme or tumor cells.
- **subsequent bioassays** performed **in vivo** use **disease-specific animal** models.

Molecular graphics

- **the use of computer graphics** to represent the **structure of drug** molecule to fit the simulated molecular structure of the receptor site, is a useful complementary tool in drug molecule design.

A LEAD COMPOUND

- **A lead compound is a prototype chemical compound that has desired biologic or pharmacologic activity**.
- Although active, the lead compound may not possess all of the features desired, such as potency, absorbability, solubility, low toxicity, and so forth. Thus, the medicinal chemist may seek to modify the lead compound's chemical structure to achieve the desired features while reducing the undesired ones. The chemical modifications produce analogs with additional or different functional chemical groups, altered ring structures, or different chemical configurations. The results are modified chemical compounds capable of having different interactions with the body's receptors, thereby eliciting different actions and intensities of action.

- The synthesis of derivatives of the prototype chemical may ultimately lead to successive generations of new compounds of the same pharmacologic type.

Exemple:

- the development of new generations of cephalosporin antibiotics,
- additional H2-antagonists from the pioneer drug cimetidine, and the large series of antianxiety drugs derived from the benzodiazepine structure and the innovator drug chlordiazepoxide (Librium).

PRODRUGS

- **compound that requires metabolic biotransformation after administration to produce desired pharmacologically active compound.**
- The conversion of inactive to active occurs through enzymatic cleavage.
- Biotransformation occur at body where enzymes are present.

- Example of prodrug **enalapril maleate** which, after oral administration, is bioactivated by hydrolysis **to enalaprilat**, an ACE inhibitor used in treatment of hypertension.
  Prodrugs: 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.

- **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'S DEFINITION OF NEW DRUG

- **New drug is any drug that is not recognized as being safe and effective in conditions recommended for its use in the labeling among experts.**

- A drug not need to be a **new chemical entity** to be considered new. A change in **formulation** or **method of manufacture** constitutes newness under 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 substances undergo **preclinical testing** for biologic activity to assess their potential as useful therapeutic agents. These studies, which fall into the general areas of pharmacology, drug metabolism, and toxicology, involve many types
- of scientists, including **general biologists**, **microbiologists**, **molecular biologists**, **biochemists**, **geneticists**, pharmacologists, physiologists, pharmacokineticists, pathologists, toxicologists, statisticians, and others.

Their work leads to determination safety and usefulness of new drug.

To judge whether drug safe and effective:

- Study how drug **absorbed, distributed, stored, metabolize, excreted** and how it affects action of body's cells, tissues, and organs.
- Scientists developed studies conducted outside living body using **cell and tissue culture** and **computer programs** that simulate human and animal systems.
- Cell cultures used increasingly to see toxicity before animal testing.
- Computer models help to predict the properties of substances and their probable actions in living systems.

PHARMACOLOGY

- the science concerned with drugs, their sources, appearance, chemistry, actions, and uses.
- can be expanded to include:

1. **properties,**
2. **biochemical and physiologic effects**
3. **mechanisms of action,**
4. **absorption, distribution, biotransformation, and excretion.**

pharmacodynamics

- the study of biochemical and physiologic effects of drugs and their mechanisms of action.

- pharmacokinetics, study (ADME).

- clinical pharmacology, applies pharmacologic principles to the study of effects and actions of drugs in humans.

Receptors

- Different drug substances produce different effects on the biologic system because of the specific interactions between a drug's chemical structure and specific cells called receptors.
- Receptors like active centers of enzymes, are: **carboxyl, amino, sulfhydryl, phosphate**, and similar reactive groups oriented on or in the cell in a pattern **complementary** to that of drugs with which they react.
- The binding of a drug to: **ionic, covalent, and other relatively weak reversible bonds.** Occasionally, firm covalent bonding is involved, and the drug effect is then slowly reversible.

- There is relationship between the **quantity of drug** molecules available for interaction and the **capacity of the specific receptor site**.
- When the receptors are saturated, the effects of the specific interaction are **maximized.**
- Any additional drug present (as in circulation) and not participating in the interaction may serve as a **reservoir** to replace the drug molecules released from the complex.

Two drugs

- 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 body capable of **binding drugs without** 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.

To define a pharmacologic profile,

- **In-vitro cell culture and enzymes systems and in vivo animal models are used to define a chemical's pharmacologic profile.**
- **Whole animal**: pharmacologic effects of agent on specific organ systems.
- followed by studies with **isolated animal tissues**.
- 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
5. 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(such as headache),.
- 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.

final pharmacologic and toxicologic studies, two or more animal species are used as required by the FDA.

- **Dogs and rats** for hypertension.
- **Dogs and guinea pigs** for respiratory effects.
- **Dogs** for diuretic activity.
- **Rabbits** for blood coagulation.
- **Mice and rats** for central nervous system studies.

DRUG METABOLISM

- A series of animal studies of a proposed drug's ADME are undertaken to determine:

(a) Extent and rate of absorption from various routes.

(b) Rate of distribution of drug through body and duration of drug's residence.

(c) Mechanism of drug's metabolism in body, and chemistry and pharmacology of any metabolites.

(d) **Dose eliminated** from body and its rate and route of elimination.

In these studies, a minimum of **two animal species** are used (same as used in pharmacologic and toxicologic studies), a rodent and one other, usually a dog.

- Metabolism of drug**: Non polar drug molecules into polar .**
- Enzymes: **Liver, kidneys, lungs, and GIT**.
- determine whether a drug's metabolic products are toxic or nontoxic to the animal and later to the human.

TOXICOLOGY

- deals with adverse effects.
- Drug toxicity studies undertaken to determine;
- (a) **The substance'toxicity with short-term (**acute effects) or **long-term use** (chronic effects);
- (b) specific **organ toxicity**;
- (c) The mode, site, and **degree of toxicity**;
- (d) **dose-response relationships** for low, high, and intermediate doses over specified time;
- (e) **Gender**, **reproductive**, or **teratogenic** toxicities;
- (f) **carcinogenic** and **genotoxic** potential.

- Initial toxicology studies are conducted on **rodents.**
- Another animal, usually a **dog**.
- acute or short-term toxicity,
- subacute or subchronic toxicity,
- chronic toxicity,
- carcinogenicity testing,
- reproduction studies, and
- mutagenicity screening.

Acute or Short-Term Toxicity Studies

- Determine toxic effects of test compound administered in **single dose** and/or **multiple doses over short period**, usually **single day**.

- Test compound administered at **various dose levels**, with toxic signs observed for:

1. **Onset.**
2. **Progression or reversal.**
3. **Severity,**
4. **Mortality.**
5. **Rates of incidence.**

- **Doses are ranged to find;**

1. **Largest single dose** of test compound that will not produce toxic effect.
2. **Dose** level at which **severe toxicity occurs**.
3. **Intermediate toxicity** levels.

The animals observed and compared with controls for:

1. Eating and drinking habits.
2. Weight change.
3. Toxic effects,
4. Psychomotor changes, and
5. Any other signs of untoward effects, usually for **30-day post dose period**.

- **Feces and urine specimens are collected**
- **clinical laboratory tests performed** to detect changes in clinical chemistry and other changes that could indicate toxicity.
- When they occur, **animal deaths** are recorded, studied by **histology and pathology**, and statistically evaluated on the basis of **dose-response, gender, age, intra species and interspecies findings**, and against laboratory controls.

Sub acute or Sub chronic Studies

- Animal toxicity studies **2 weeks** of daily drug administration at **three or more** dosage levels to two animal species are required to support the initial administration of a single dose in human clinical testing.

TOXICOLOGY

- **Deal with adverse or undesired effects of drugs.**
- **Initial toxicology studies are conducted on rodents.**
- **Another animal: Dog is added.**

The toxicology profile

- **Acute** or short-term toxicity.
- **subacute.**
- **subchronic** toxicity.
- **chronic** toxicity.
- **carcinogenicity** testing.
- **reproduction** studies.
- mutagenicity screening.

Acute or Short-Term Toxicity Studies

- Designed to determine the toxic effects of a test compound when administered in a single dose and/**or in multiple doses over a short period**, usually a **single** day.

- Animals compared with **controls** for **eating** and **drinking** habits, **weight change**, **toxic effects**, **psychomotor** changes, and any other signs over **30** day post dose period.
- **Feces and urine specimens** are collected and clinical laboratory **tests** performed to detect changes in clinical chemistry and other changes that could indicate toxicity.
- unwanted effects, for 30-day post dose period. Feces and urine specimens collected and laboratory tests performed to detect changes

- Animal deaths are recorded

Subacute or Subchronic Studies

- Animal toxicity studies of **3 doses daily for 2 weeks to 2 animal species** are required.
- The initial human dose is 1/10 of highest nontoxic dose (in mg/ kg of subject's weight) shown during animal studies.

Chronic testing

- Drugs given to **humans** for **week** or more, animal studies of **90 to 180** days.
- animal studies for **1 year**. Some animal toxicity studies last **2 years** or longer.

Carcinogenicity Studies

- Carried out in **limited number** of **rat and mouse** strains when there is information on spontaneous **tumor** incidence.
- done with **female and male animals** using high, intermediate, and low doses over a **90** day.

- Carcinogenicity studies are long term **(18 to 24 months**), with surviving animals killed and studied at defined **weeks** during the test period.
- animal death (other than killing).
- tumor incidence
- **Any preneoplastic** lesions

Reproduction Studies

- Any effect of drug on **mammalian reproduction**.
- **Embryonic, prenatal, and postnatal** development.
- Multigenerational effects; and teratology.
- Reproductive studies, on **rat.**
- In **embryo toxicity rabbit** is studied in addition to **rat**.

Genotoxicity or Mutagenicity Studies

- performed to determine effect on **gene, mutation or cause chromosome or DNA damage.**
- Strains of Salmonella typhimurium are routinely used in assays to detect mutations.

Preformulation studies

- solubility, partition coefficient, dissolution rate, physical form, and stability.

Drug Solubility

- A drug administered by any route must possess **aqueous solubility** for systemic absorption and therapeutic response.
- Poorly soluble compounds have incomplete, absorption thus produce minimal response.

- Increase aqueous solubility by:

1. prepare more soluble derivatives of parent compound, such as **salts** or **esters**, by **chemical complexation**,
2. by **reducing particle size**.

Partition Coefficient

- To produce a pharmacologic response, a drug molecule must cross biologic membrane of protein and lipid, which acts as **lipophilic barrier** to many drugs.
- The ability of a drug to penetrate this barrier based on lipids solubility(lipophilic) versus aqueous phase **(hydrophilic).** Partition coefficient is measure of distribution in **lipophilic-hydrophilic** phase system and indicates its ability to penetrate biologic multiphase systems.

Dissolution Rate

- The speed a drug substance dissolves in medium called its dissolution rate.
- dissolution constant, and partition coefficient, can provide indication of drug's absorption potential.
- For a chemical entity, its acid, base, or salt forms, as well as its physical form (e.g., particle size), may result in differences in dissolution rate.

Physical Form

- **The crystal or amorphous** forms and/or the particle size of a powdered drug can affect the dissolution rate, thus the rate and extent of absorption, for a number of drugs.
- **Reducing particle size increase surface** area of poorly soluble drug its dissolution rate in the gut is enhanced.

Stability

- Chemical and physical stability of drug alone, and when combined with formulation components, is critical to preparing a successful pharmaceutical product.
- For drugs susceptible to **oxidative** decomposition, the addition of **antioxidant** stabilizing agents to the formulation may be required to protect the potency.

- Drugs destroyed by **hydrolysis, protection against moisture** in formulation, processing, and packaging may be required to prevent decomposition.
- In every case, drug **stability testing at various temperatures, conditions of relative humidity** (RH)—as 40°C 75% RH/30°C 60% RH—durations, and environments of **light**, **air**, and **packaging** is essential in assessing drug and drug product stability. Such information is vital in developing **label instructions for use and storage**, assigning product **expiration** dating, and packaging and shipping.

- **During Phase 1 studies**: oral drugs capsules are employed containing **active ingredient alone**.(20-100 patients usually continue for several months).
- **Excipients** included in the formulation for Phase 2 trials.
- studies **drug's ADME** undertaken
- During Phase 2, the **final dosage form** is selected(several hundreds patients are used and time continue several months to two years). **Phase 3** trials; this is the formulation that is submitted to the FDA for marketing approval**(several hundreds patients to several thousands and time 1-4 years)**.

Drug effect in a population sample.

- Certain drugs may produce more than one effect, depending on dose. For example, **a low dose** of barbiturate produces **sedation, whereas a larger dose produces hypnotic effects.**
- **Age:** newborns and those born prematurely, have immature hepatic and renal function, the means by which drugs are normally inactivated and eliminated from the body.

- **Age or weight is not enough in determine pediatric dose**.
- Many pediatric doses based on **body weight or body surface area** (BSA).
- **Elderly persons:** physiologic functions decrease after 30 years. cardiac output decrease 1%/year from age 20 to 80.
- GFR falls progressively until age 80; at time it is only **half of what it was at age 20**.
- Vital capacity, immune capacity, and liver enzyme function also decrease. The decrease in renal and hepatic function in elderly slows drug clearance rate .

Accumulation and toxicity

- **Chronic disorders in old patients require concomitant drug therapy**, increasing

1. drug-drug interactions and
2. adverse effects.

- **Pharmacogenetics** varying effects among different racial populations.
- **Common genetic polymorphisms**: multiple forms of enzymes governing drug metabolism, affect clearance from blood of many drugs used in large patient populations

Body Weight

- Usual doses for drugs are suitable for **70-kg** (150 lb) individuals.
- The ratio between amount of drug administered and the size of the body influences drug concentration in body fluids. Therefore, drug dosage require adjustment heavy patients.
- Mg (drug) /kg (body weight) basis (e.g., 1 mg/kg).
- Body weight is more dependable than age
- In some instances, pediatric dose based on a combination age and weight (e.g., 6 months to 2 years of age: 3 mg/kg/day).

Body Surface Area

- Some drug doses based on (e.g., 1 mg/M^2 BSA).
- The BSA for child or adult determined using **nomogram**.
- The BSA determined at **intercept** of a **straight line drawn to connect an individual's height and weight**.
- For example, an adult measuring 67 in. in height and weighing 132 lb would have a BSA of approximately 1.7 m^2.

Sex

- Pharmacokinetic differences between women and men. important for **narrow therapeutic index**.
- Drugs with narrow therapeutic risk increase to toxic levels or decrease to ineffective levels with minimal dosing changes.
- great caution is advised for use of most drugs during **pregnancy** and in women of childbearing age. Similar caution is applicable to drug use in **nursing mothers** because transfer from mother's milk to an infant is well documented for a variety of drugs.

Pathologic State

- example, if drugs used in presence of **renal impairment**, excessive systemic accumulation occur, risking **toxicity**.
- In such conditions, lower doses are indicated, and **if therapy is prolonged**, **blood levels** should be assessed and the patient **monitored** at regular intervals to ensure the maintenance of nontoxic levels of the drug.

Tolerance

- Tolerance common with **antihistamines and narcotic analgesics**.
- After tolerance, normal response may be regained by suspending the drug's administration for a while.

Concomitant Drug Therapy

- Absorption rapid if stomach and upper part of intestine are empty.
- A dose of drug that is effective when taken before a meal less effective if administered during or after eating.
- Drug-food interactions can affect a drug's absorption.

Dosage Form and Route of Administration

- Varying rates and degrees of absorption occur from drug administration in rectum, GIT, under tongue, via skin, and to other sites.
- **Therefore, for a given drug, different dosage forms and routes of administration** are considered new by the FDA.

DRUG PRODUCT LABELING

- Drug labeling includes not only the labels placed on an immediate container but also the information on

1. the packaging,
2. in package inserts, and
3. in company literature,
4. advertising, and promotional materials.

- Description of the product
- Clinical pharmacology
- Indications and usage
- **Contraindications**
- **Warnings**
- Precautions:
- Adverse reactions
- Drug abuse and dependence
- Overdosage, including signs, symptoms
- Dosage and administration
- How supplied

- FDA REVIEW AND ACTION LETTERS
- **POSTMARKETING REPORTING OF ADVERSE DRUG EXPERIENCE**
- **ANNUAL REPORTS**

- **Failure to make required reports may lead to FDA withdrawal of approval for marketing.**

SUPPLEMENTAL NEW DRUG APPLICATION

- A change in the **method** of synthesis
- Change in the **formulation**
- Use of a **different facility** or contractor to manufacture
- Change in the **container** and **closure system**
- Extension of the **expiration date**
- Any **labeling change**

Current Good Manufacturing Practices (cGMP)

Chapter 3

Objectives

- List common terms used in the Current Good Manufacturing Practice (cGMP) for finished pharmaceuticals
- Define cGMP and its importance
- Outline Code of Federal Regulation (CFR)

Common terms

Drug product: Finished form contains active drug and inactive ingredients.

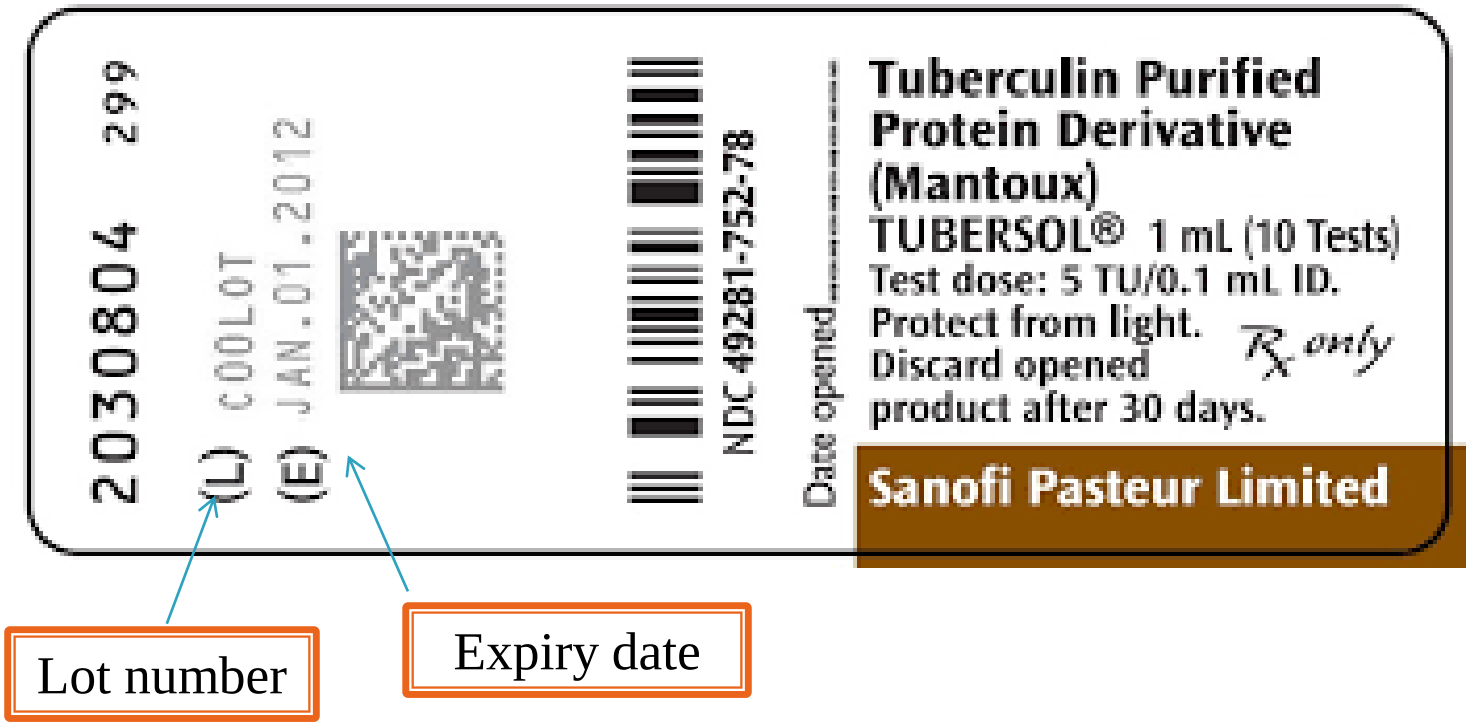
Component: Any ingredient used in manufacture of drug product.

Active pharmaceutical ingredient (API): any component have pharmacologic activity or direct effect in diagnosis, cure, mitigation, treatment or prevention of disease.

Inactive ingredient: Any component other than the active ingredients in drug product.

Batch: a specific quantity of a drug of uniform specified quality produced according to **single manufacturing order during the same cycle of manufacture.**

Lot: A batch or any portion of a batch having uniform specified quality and a distinctive identifying lot number.



Lot number, control number, or batch number: combination of letters, numbers, or symbols from which the complete history of manufacture, processing, packaging, holding, and distribution of a batch or lot of a drug product may be determined

Pop quiz

Q1)) **Regarding the pharmaceutical products production as batches, which is not true?**

A- They are useful since it is possible to make any modification to the product during the manufacturing process.

B- Batch number represents a serial number for identification complete production history of product that differs from lot number

C- The batch number is important as it may be required especially when a product is recalled

D- None of them

Common terms

Master record: **the records for** the formulation, specifications, manufacturing procedures, quality assurance requirements, and labeling of each finished product.

Master Batch record and Batch production record: contain

- Product **name**, **dosage form** and **strength**, batch size

Company logo	Batch Manufacturing Record
Product Name:	Product Code:
Batch No.:	Batch size (kg):
Manufacturing date:	Expiry date:
Prepared by:	Verified by:

MASTER BATCH FORMULA	SOP	BSCL2_2020_01
	Effective date	01/01/2016

Title: Nitrazepam Suspension 5 mg/5mL

1. Product Name

2. Batch code and number

Product License number	Batch number	Batch size	Legal category
Student id	AW3P1	100 mL	CD BENZ POM

3. Equipment

Name	Equipment Number	Calibration Status
Precision balance	QUB/EQ/01	15 Jan 2016
Analytical balance	QUB/EQ/02	15 Jan 2016
Measuring cylinder 100mL	QUB/EQ/05	20 May 2016
Graduated glass pipette 1mL	QUB/EQ/09	03 Mar 2016

Signature: *Student*	Date: *17 Apr 2016*

4. Raw materials

Name	Function	Batch number	Expiry date
Nitrazepam	*Active ingredient*	*BN00N1*	*30 Sep 2017*
Tragacanth	*Suspending agent*	*BN01T1*	*30 Sep 2017*
Conc. Cinnamon Water	*Flavouring*	*BN01C3*	*17 Apr 2016*
Amaranth	*Colouring*	*BN0104A1*	*30 Sep 2017*
D/S Chloro. Water	*Preservative*	*BN01C1*	*30 Sep 2017*
Purified Water	*Vehicle*	*QUB*	*17 Apr 2016*

Signature: *Staff*	Date: *17 Apr 2016*

-List and quantity of each component in dosage unit
-list of equipment used
-Calibration of instruments
-Specific instructions for each state in the manufacturing process.
-Statement of theoretical yield at each step in the manufacturing process
-Yield of final product
-Sampling and testing procedures (in-process control)

Parameter	Limit	Observation
Machine speed	20 rpm (15-25 rpm)	
Wt. of 20 tabs	12.00g ±2 (11.76-12.24g)	
Theoretical weight/tab	600mg	
Hardness	25Kg (20-30 Kg)	
Thickness (av. of 10 tabs)	4.10mm ±0.15mm (3.95 – 4.25mm)	
Length	10mm ± 0.1 mm (9.9 – 10.1 mm)	
Width	5 mm ± 0.1mm (4.9 – 5.1 mm)	
Disintegration time	NMT 15 mins	
Wt. variation	± 3% of Av. Wt.	
Friability (10 tabs)	NMT 1.0% w/w	

Validation Process: Establishing **documented evidence** which **provides a high degree of assurance**, that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process does what it purports to do). i.e **Action of proving .**

Phase I- Pre-validation qualification (Process Design), relate to drug development, pilot study and scale-up reliably.

Phase II- Process validation, verify that all established limits of the critical process parameter

Phase III- Validation Maintenance Phase, it requires frequent review of all process related documents

Validation protocol: a **prospective experimental plan** to produce documented evidence that the system has been validated.

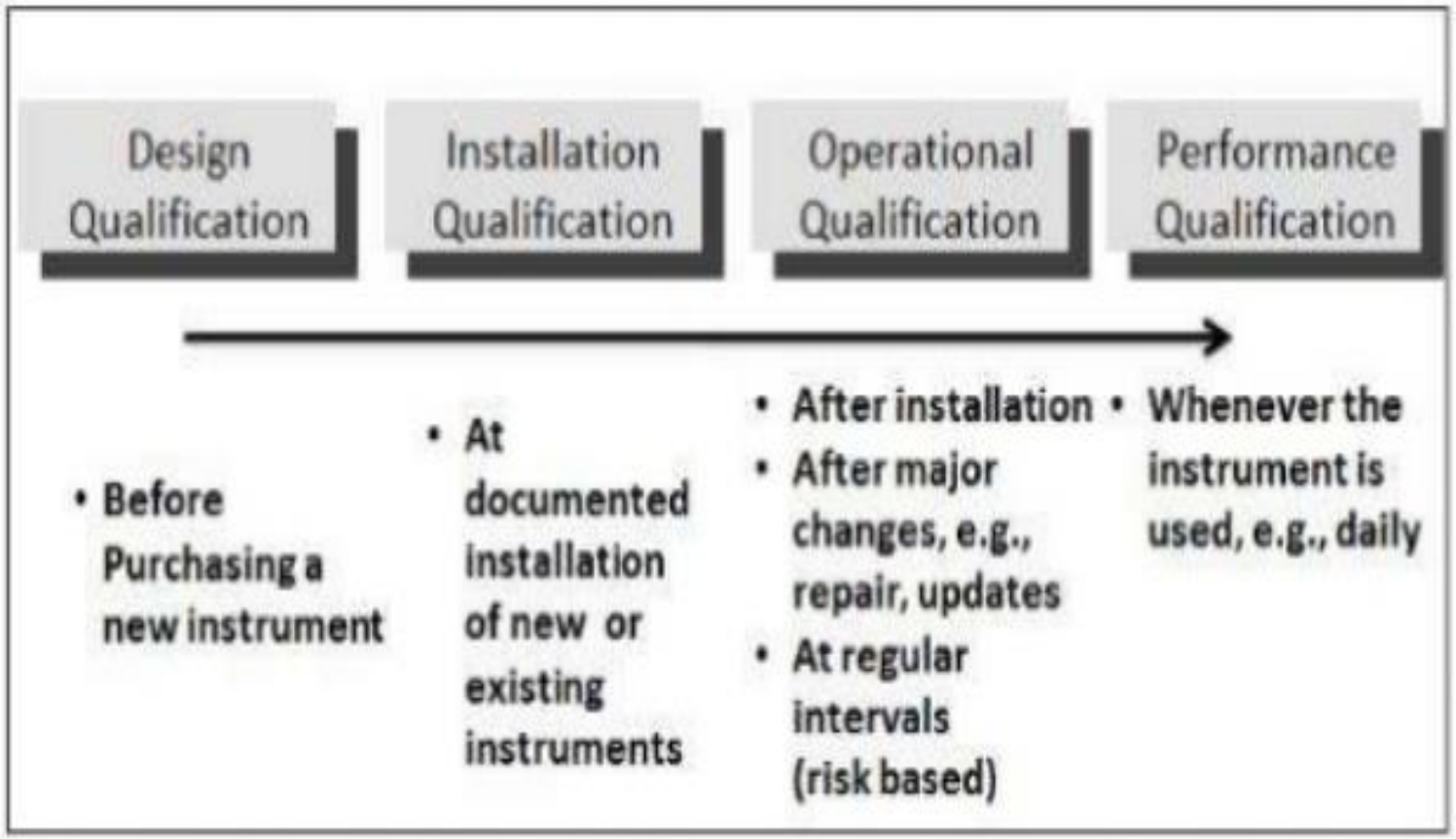
It gives idea about future performed:

- What activities are to be performed?
- Who is going to perform these activities?
- When the activities should start and when they should get over?
- What documents will be generated?
- What the policy on revalidation

Validation: Documented evidence that a system (e.g., equipment, software, controls) does what it purports to do

The major types of Validation :

- Process validation
- Cleaning validation
- Equipment validation
- Validation of analytical methods



Quality audit: A **documented activity** performed in accordance with established procedures on a planned and periodic basis to verify compliance with the procedures to ensure quality

Compliance: determine by inspection of **the extent to which the manufacturer is acting** with prescribed **regulations, standards, and practices**.

Common terms

Certification: **Documented testimony** by **qualified authorities** that a system qualification, calibration, validation, or revalidation has been performed appropriately and that the results are acceptable.

Quarantine: An area that is marked, designated, or set aside for the holding of incoming components **prior to acceptance testing and qualification** for use

Quality Relationship

Quality assurance: all evidence needed that activities relating to quality are being performed adequately.

Quality control: process through which industry measures actual quality performance, compares it with standards.

Quality control unit:
the organizational element designated by a firm to be responsible for work related to quality control

In 1937, a public health disaster tragically (**liquid Sulfanilamide formulation** contained a poison, it killed 107 people) drove home the need for a stronger federal law

In 1941, nearly 300 people were killed or injured by one company's sulfathiazole tablets, a **sulfa drug tainted with the sedative** phenobarbital.
That incident caused FDA to drastically **revise manufacturing** and **quality control requirements**, leading to what would later be called GMPs

What are cGMPs?

GMP: regulations are established by the Food and Drug Administration (FDA) to ensure that minimum standards are met for drug product quality

In another words, Rules set up by the FDA that drug manufacturers need to follow in order to ensure that a safe , effective and high quality product is manufactured

cGMP, employ technologies and up-to-date (“current”) in order to comply with the regulation

Why GMP is important?

It is designed to saves costs, minimize risks involved in any pharmaceutical production that cannot be eliminated through testing the final product, improve the standard of drugs worldwide.

<u>Some of the main risks</u>** are

- <u>Unexpected contamination of products</u>,
- <u>Incorrect labels on containers</u>,
- <u>Insufficient or too much active ingredient</u>,

Principle of GMP

- Written step by step operating procedure and work instruction
- Carefully following written procedures
- Promptly and accurately documenting work for compliance and traceability
- Validating work ensures that system is doing what they are designed to do
- Develop a good design for the facility and the equipment from the beginning

- Properly maintaining facilities and equipment
- Clearly defining, developing and demonstrating job competence
- Protecting products against contamination by making cleanliness a continual habit Practice good Hygiene
- Design the quality in product manufacturing “effective control of quality”

- cGMP Code of Federal Regulations (CFR) **Finished Pharmaceuticals, Biologic products, Medicated articles, Medical devices**

Outline of Current Good Manufacturing Practice Regulations

- Subpart A--General Provisions
- Subpart B--**Organization and Personnel**
  - Personnel qualifications
  - Personnel responsibilities
  - Consultants
- Subpart C--**Buildings and Facilities**
  - Design and construction features
  - Lighting
  - Ventilation, air filtration
  - Plumbing Sewage and refuse warehousing
  - Washing and toilet facilities
  - Sanitation, Maintenance

- Subpart D—**Equipment**
  Equipment design, construction
  Equipment cleaning and maintenance
- Subpart E**--Control of Components and Drug Product Containers and Closures**
- Subpart F**--Production and Process Controls**
  Written procedures,
  Charge-in of components
  Calculation of yield
  In-process testing of materials and products
- Subpart G**--Packaging and Labeling Control**
- Subpart H**--Holding and Distribution**
- Subpart I**--Laboratory Controls**
- Subpart J**--Records and Reports**
- Subpart K**-- Returned and Salvaged Drug Products**

Organization and Personnel

- ✓ deals with responsibilities of **quality control unit**, **employees**, and **consultants**.
- ✓ quality control unit have responsibility for all functions that affect product quality. This includes **accepting** or **rejecting** product components, product specifications, finished products, packaging, and labeling. Adequate laboratory facilities shall be provided, written procedures followed, and all records maintained.
- ✓ All personnel required to have **education, training, and experience.** Appropriate programs of education and training, and performance evaluations are essential for maintaining quality assurance.

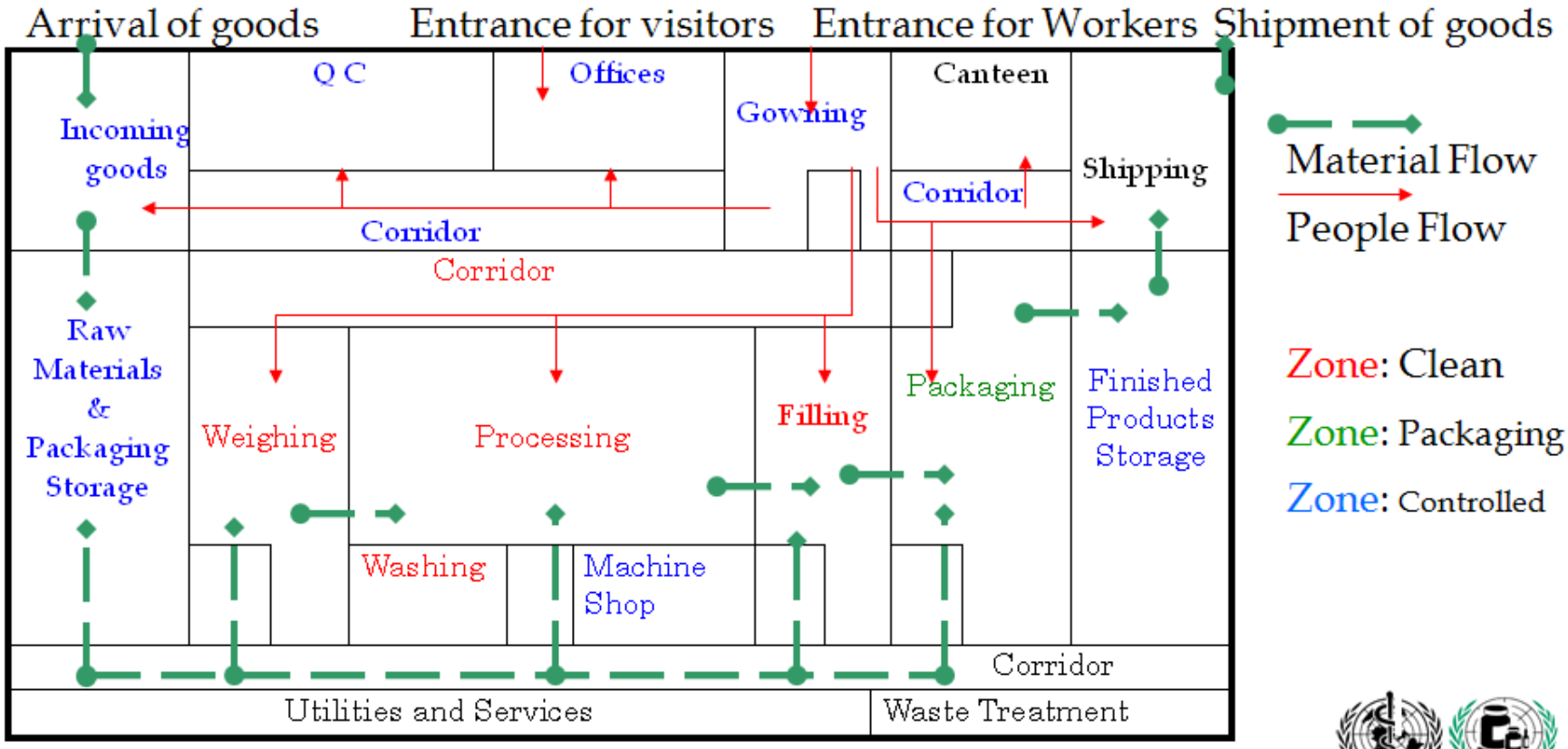
Buildings and Facilities

- Buildings and Facilities must be designed with **adequate size** and **space** for operations.
- There must be a **good flow pattern** for personnel, materials, products and waste materials (helps to eliminate mix-ups and contamination)
- The facility must be easy to clean, and sanitize (surfaces, equipment,..)
- Environmental controls must be in place (lighting, ventilation, air filtration, air heating and cooling clean rooms)

- Utilities must be validated (water systems, plumbing, electrical, …..)

Premises

Example of Materials and People Flow



Equipment

- Each piece of equipment must be: **appropriate design** and **size** to facilitate **use, cleaning, and maintenance**.
- Equipment's surfaces and parts **must not interact** with processes or products so not affect **purity**, **strength**, or **quality**.
- **Standard operating procedures (SOP)** must be **written and followed** for proper use, maintenance, and cleaning of each piece of equipment.
- Equipment and computers used in the processes must be **routinely calibrated**, maintained, and validated for accuracy.
- Filters used in the manufacture of injectable drug products **must not** release fibers into such products.

Control of components, containers and closure

- Written procedures describing: identification, storage, handling, sampling, testing, and approval or rejection of all product components, containers, and closures must be maintained and followed.

- Bulk pharmaceutical chemicals, containers, and closures must meet **the required property** (the exact physical and chemical specifications established with the supplier at the time of ordering).

- Raw materials Raw materials are **quarantined** until they are **verified** through sampling and qualitative and quantitative analysis by **quality control unit.**

- **Rejected** components, containers, and closures are **identified** and **controlled** under a **quarantine system** to prevent their use in manufacturing and processing operations.

- Mainly bulk chemicals (APIs) are synthesized in **China and India.** it is important to confirm their **identity** and **purity** with **USP** and **NF** prior to use in finished pharmaceuticals.

Production and Process Controls

- **Written procedures** are required to ensure that drug products have correct **identity**, **strength**, **quality**, and **purity**.
- In-process samples taken from production batches **periodically** for product control.

(*a*) performed by production personnel at the time of operation

(*b*) performed by the quality control laboratory personnel to ensure compliance with all product specifications and batch-to-batch consistency.

If in-process product out the standards ??????

Packaging and Labeling Control

- Written procedures are required for the issuance of labeling and packaging materials.
- Labeling for each variation in drug product— strength, dosage form, or quantity of contents—must be **stored separately** with suitable identification. Outdated labels and other packaging materials must be destroyed. Access to the storage area must be limited to authorized personnel.
- label examination shall be performed by one person and independently verified by a second person.
- Labels must meet the legal requirements for content.
- Each label must contain **expiration dating** and the **production batch** or **lot number** to facilitate product identification.
- Appropriate stability testing used to determine expiration date to assure that a drug product meets applicable standards at the time of use.

- Exception for the requirement are **homeopathic drug** products, **allergenic extracts**, and investigational drugs (**INA**) that meet the standards established during preclinical and clinical studies.

In 1982, several consumers of OTC Tylenol capsules suddenly died of cyanide poisoning. An intensive investigation of the production records showed that this was not the result of a raw materials mix-up during manufacturing. Rather, **tampering apparently** occurred on store shelves.

- A **tamper-evident package** is defined as “one having one or more **indicators or barriers to entry** which, if breached or missing, can reasonably be expected to **provide visible evidence** to consumers that tampering has occurred”. Some ex. Blister/strip pack, seal band for capsule, bottle seal, tape seal and aerosol container

Holding and Distribution

- Written procedures must be established and followed for the holding and distribution of product.
- Finished pharmaceuticals must be **quarantined in storage until released** by **the quality control unit**.
- Products must be stored and shipped under conditions that do not affect product quality.
- The oldest approved stock is distributed first.
- The distribution control system must allow the distribution point of each lot of drug product to be readily determined to facilitate its recall if necessary.

Laboratory controls

are requirements for the establishment of and conformance to: **written specifications**, **standards**, **sampling plans**, **test procedures**.

 The specifications, which apply to each batch of drug product, include:

- **sample size**
- **test intervals**
- **sample storage**
- **stability testing**

special testing requirements for parenteral, ophthalmic , controlled-release products, and radioactive pharmaceuticals.

Records and Reports

The master records of each batch must document that **each step in the production, control, packaging, labeling, and distribution** of the product was accomplished and approved by **the quality control unit**.(must be maintained for **at least a year following the expiration date** of a product batch)

- Equipment cleaning and maintainance logs.
- specifications and lot numbers of product components including, raw materials, drug product container, closure, and labeling records.
- Master production and control records for each batch.
- Batch production and control records.
- Production record review.
- Laboratory records.
- Distribution records. - Complaint files.

Records of **written and oral complaints** regarding a drug product (e.g., product failure, adverse drug experience) must also be maintained, along with information regarding **the internal disposition** of each complaint.

All records must be made available at the time of inspection by FDA officials.

Returned drug products (e.g., from wholesalers) must be identified by lot number and product quality determined through appropriate testing.

Drug products that meet specifications may be **salvaged or reprocessed**.

Those that do not, along with those that have been subjected to improper storage (e.g., extremes in temperature), shall not be returned to the marketplace.

Records for all returned products must be maintained and must include **the date and reasons for the return**; **quantity and lot number** of product returned; **procedures employed for holding**, **testing**, and reprocessing the product; and the product's disposition

Additional cGMP Regulatory Requirements

Inspection of ***Bulk Pharmaceutical Chemicals*** *(product components)* to assure that all required standards for quality are met.

Because the quality of any finished pharmaceutical product depends on the quality of the various components

GMP focuses on all elements of chemical **purity** and **quality**, including following:

- Specifications and analytical methods for components used to detect impurities or chemical residues and limits set.
- critical chemical reaction steps and handling of chemical intermediates

- Quality of water used.
- Solvent handling and recovery systems
- Effect of scale-up of chemical batches on the yield
- Stability studies of bulk pharmaceutical chemical

Biologics

the basic cGMP regulations for biologic products are similar to finished pharmaceuticals , with specific additional mandates

Medical Devices

- devices are approved for marketing when shown to be **safe** and **effective** through premarket approval.

- The regulations for "good manufacturing practice for medical devices" are similar in organizational structure to those for finished pharmaceuticals. They include **personnel**; **buildings**; **equipment**; **control of components**; production and process controls; packaging and labeling; holding, distribution, and installation; device evaluation; and records

- Medical devices are subject to the reporting of adverse events, to recall, and to termination of approval.

Devices covered by cGMP regulations include:

intraocular lenses, hearing aids, intrauterine devices, cardiac pacemakers, clinical chemistry analyzers, catheters, dental X-ray equipment, surgical gloves, condoms, prosthetic hip joints, computed tomography equipment, and wheel-chairs

Objectives

cGMP- Part 4

- Determine the similarity and difference between pharmaceutical manufacturing and extemporaneous compounding

- Describe the various types of packaging containers and their properties.

cGMP and cGCP

- Pharmaceutical **manufacturing** is large-scale production of drugs or drug products for distribution and sale.

- **Compounding** is professional preparation of prescriptions for specific patients as a part of the traditional practice of pharmacy.

The increase in preparing patient-specific medications, due to the following:

1. Many patients need **drug dosages or strengths** that are not commercially available.

2. Many patients need **dosage forms**, such as suppositories, oral liquids, or topical, that are not commercially available.

3. Many patients are **allergic to excipients** in commercially available products.

4. Children’s medications must **be prepared as liquids**, flavored to enhance compliance.

5. Some medications are **not very stable** and require preparation and dispensing every few days; they are not suitable to be manufactured products.

6. Home health and hospice care has resulted in new approaches to pain management and **higher concentrations** and **combinations of drugs** that are now used

Does the compounded drug in community pharmacy have required **quality** and meet standard specifications ?????

To ensure quality compounded products; consequently, many Standards-setting agencies since 1990 tried to establish guidelines for pharmaceutical compounding.

Chapters and monograph related to pharmacy compounding were developed and published in **U.S. Pharmacopeia–National Formulary** (USP-NP). They provide:

a **tested**, uniform **formulation** with valid beyond-use dating (Discard after).

Also, conditions and **practices to prevent harm**, including death, to patients that could possibly result from microbial contamination, excessive bacterial endotoxins, variability in the intended strength and composition, unintended chemical and physical contaminants, and ingredients of inappropriate quality

The **Good Compounding Practices** (GCP) applicable to State-Licensed Pharmacies", developed by the **National Association of Boards of Pharmacy**

(A) General Provisions and Definitions;
(B) Organization and Personnel;
(C) Drug Compounding Facilities;
(D) Equipment;
(E) Control of Components and Drug Product Containers and Closures;
(F) written procedures to ensure that the finished products are of the proper **identity**, **strength**, **quality**, and **purity**, as labeled
(H) Labeling Control of Excess Products; and Records and Reports.

Comparing and contrasting between expiry date of pharmaceutical manufacturing and extemporaneous compounding.

Expiration Date

- The date at which a manufacturer can no longer guarantee the strength or safety of a medication
- Determined by the US Food and Drug Administration
- Based on testing a drug in specific conditions related to storage containers, lighting, temperature, etc.
- Usually the date given in “years” for commercial products

Beyond-Use Date

- The date when the compounded prescription should no longer be used
- Determined by the pharmacy when they fill a prescription
- Based on **the type of drug**, how fast it degrades, **dosage**, **type of container**, **storage conditions**, **prescription length**, the likelihood of contamination
- The dates are generally given in days or months

These **maximum BUDs** are recommended for **non-sterile compounded** drug preparations in **the absence of stability information** that is applicable to a specific drug or preparation.

USP CHAPTER <795> PHARMACEUTICAL COMPOUNDING— NON–STERILE PREPARATIONS

DOSAGE FORM	BUD
Non-aqueous formulations	No later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.
Water-containing oral formulations	No later than 14 days when stored at controlled cold temperatures
Water-containing topical/ dermal and mucosal liquid and semi-solid formulations	No later than 30 days.

Proper Packaging, Labeling and storage of pharmaceuticals: are all essential for providing adequate **product stability** and **efficacious use.**

Containers:

- According to USP, a **container is** "that which **holds the article** and is **or in direct contact with article**." The immediate container is "that which is in direct contact with the article at all times."

- The closure is part of the container

❖ Depending on the intended use and type of container, among the **qualities tested** are the following:

• Physicochemical properties.(eg. sorption of diazepam onto low density plastics)
• Light transmission for glass or plastic
• Drug compatibility
• Vapor transmission for plastics
• Leaching and/or migration
• Moisture barrier
• Toxicity for plastics
• Valve, actuator, metered dose, particle size, spray characteristics, and leaks for aerosols
• Sterility and permeation for parenteral containers
• Drug stability for all packaging

The USP classifies containers according to **their ability to protect their contents from external conditions** of handling, shipment, storage, and distribution:

Containers

well-closed

- protects contents from solids and from loss under ordinary conditions.

Tight-closed

- protects contents from contamination by **liquids**, **solids** or **vapors**, or evaporation under the ordinary conditions
- It is capable of tight re-closure

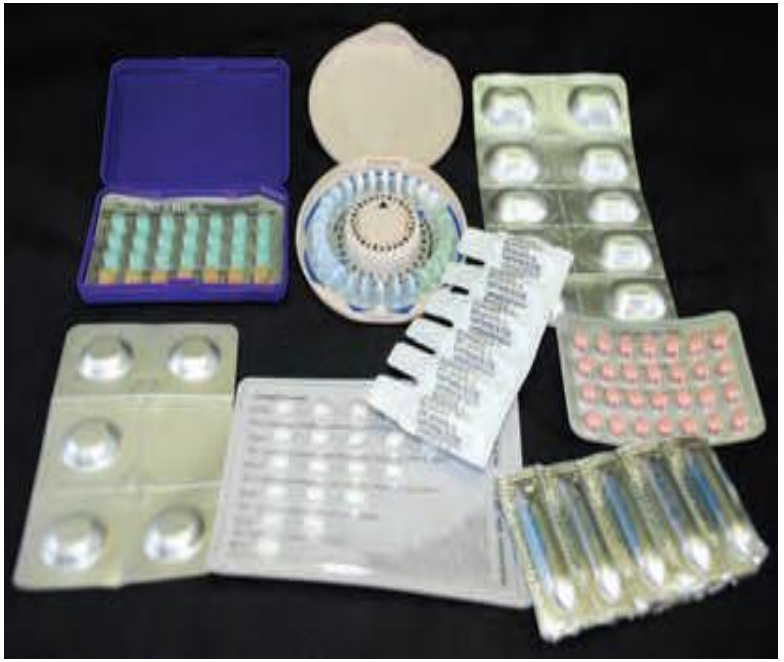
Hermetic

- is impervious to **air or any other gas** under the ordinary conditions.
- **Sterile hermetic containers** hold preparations intended for injection or parenteral administration

❑ **Unit-dose package (single-dose): (Avantages)**

positive identification of each dosage unit and **reduction of errors**, **reduced contamination** of the drug, **greater ease of inventory control** in pharmacy and nursing station, and **better management** and **less discarded medication** .

- The packaging materials may be combinations of paper, foil, plastic, or cellophane.
- The packaging of **solid dosage forms** in clear **plastic** or **aluminum blister** wells is perhaps the most popular single-unit packaging



Blister packaging of pharmaceuticals

- **Single-dose container:** when opened, cannot be resealed with assurance that sterility has been maintained.

- These containers include **fusion sealed ampoules** and **prefilled syringes and cartridges**.

- **Multiple-dose container:** is a hermetic container that **permits withdrawal of successive portions** of the contents **without changing** the strength or quality or purity of the remaining portion. These containers are commonly called vials.

- **Oral liquids** may be dispensed in single units in paper, plastic, or foil **cups** or prepackaged and dispensed in **glass containers** having threaded caps or crimped aluminum caps.

- **disposable plastic oral syringes** with rubber or plastic tips on the orifice for closure

- Other dosage such as, suppositories, powders, ointments, creams, and ophthalmic solutions, are also commonly found in single-unit packages.

❑ Unit–of- use packaging :

The quantity of drug product prescribed is packaged in a container Ex: if certain antibiotic capsules are prescribed to be taken 2 times a day for 10 days, unit-of-use packaging would contain 20 capsules. Other products may be packaged to contain a month's supply, such packaging "**Compliance packaging**" useful for **patients** taking **multiple medications**

❑ Light-resistant containers

- ✓ **Amber glass** or a light-resistant **opaque plastic** will reduce light transmission sufficiently to **protect** a **light-sensitive pharmaceutical**.
- ✓ **Ultraviolet absorbers (ex Tinuvin®)** may be added to transparent plastic to decrease the transmission of short ultraviolet rays.
- ✓ USP standards that define the acceptable limits of light transmission at any wavelength between 290 and 450 nm.

Recently, plastic packaging is the **coextruded two-layer high-density polyethylene (HDPE) bottle**, which has an **inner layer** of **black polyethylene coextruded** with an **outer** layer of **white polyethylene**. Increasingly being used in packaging of tablets and capsules. The container provides: **light resistance** and **moisture protection**.

- **Child-resistant & adult-senior use packaging**

a container that is fitted with a closure that is significantly difficult by children under 5 years of age to open or to obtain a harmful amount of its contents within a reasonable time and that is not difficult for “normal adults” to use properly

Material Used For Manufacture Of Containers

There are mainly four types of material: glass, plastic , metal and rubber.

Glass **used in packaging pharmaceuticals** are four categories :

Types I, II, and III intended for **parenteral products**, and type **IV: NP** is intended for other products.

- Each type tested according to resistance to water attack.
- Degree of attack is determined by **amount of alkali released** from glass in specified test conditions.
- leaching of alkali from glass to preparation could alter by pH and stability of product.
- **Type I** is **most resistant glass** of 4 categories.

Constitution and description of official glass types

Glass type	General description	Uses
TYPE 1	Highly resistant borosilicate glass	For buffered and unbuffered aqueous solutions, powders
TYPE 2	Treated (sulphur dioxide fumes) soda lime glass	For buffered aqueous solution with pH below 7 and for dry powders
TYPE 3	Soda lime glass	For dry powders and oleaginous solutions, not for aqueous preparations
TYPE 4	General purpose soda lime glass	Not for parenterals and for suspension and emulsion

Today, most products are packaged in **plastic**.

 intravenous fluids, plastic ointment tubes, plastic film-protected suppositories, and plastic tablet and capsule vials.

❖ The widespread use of **Plastic** containers arose from a number of factors:

1. The preference of plastic over glass due to: **Lightness weight** and **resistance to impact**, which **reduces transportation cost** and **losses** due to container damage

2. Versatility in container design, consumer acceptance
3. Consumer preference for plastic squeeze bottles in administration of ophthalmic, nasal sprays, and lotions
4. The popularity of blister packaging and unit-dose dispensing.

The physical and chemical alteration of the packaging material by the drug product is called modification. Example

polyethylene + **methyl groups** to every other carbon atom → **Polypropylene (can be autoclaved)**

Polyethylene —**chlorine** atom is added to every other carbon→ **Polyvinyl chloride** (PVC)

PVC is **rigid and has good clarity**, making it particularly useful in the **blister packaging** of tablets and capsules. However, it has a significant drawback for packaging medical devices (e.g.,syringes): it is **unsuitable for gamma sterilization**.

Among the newer plastics are **polyethylene terephthalate** (PET), **amorphous polyethylene terephthalate** glycol (APET), and polyethylene terephthalate glycol (PETG). Both APET and PETG have excellent **transparency** and can be **sterilized with gamma radiation.**

Among **problems** encountered in the use of **plastics** in packaging are:

(a) **Permeability of containers to atmospheric oxygen and moisture vapor**

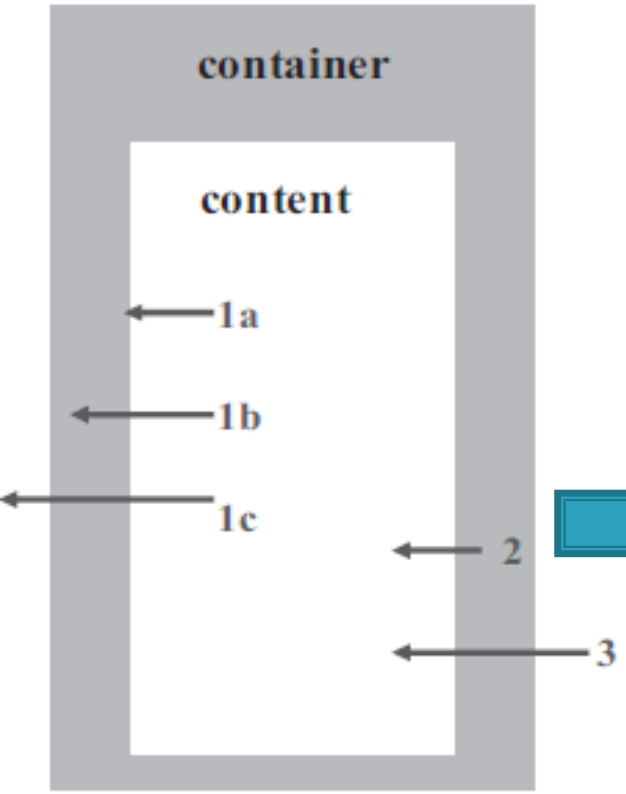
(*b*) **leaching** of the constituents of the container to the internal contents

(*c*) **absorption** of drugs from the contents to the container

(*d*) Transmission of light through the container

(*e*) Alteration of the container upon storage.

❖ Agents frequently added to alter the properties of plastic include **plasticizers**, **stabilizers**, **antioxidants**, antifungal agents, colorants, and others



(1a adsorption,
1b absorption),
1c permeation

2 leaching (release)
3 permeability

- **decrease of the activity** due to an adsorption of **the active substance**
- **active ingredient degradation** due to released substances
- content **precipitation**
- **pH change** due to a leaching of the material components
- **appearance change** (color) due to a leaching of the material components
- **analytical interference** during the determination of the active ingredient
- **safety change** due to a leaching of the material components

- The **permeability of a plastic is a function of**:

1. Nature of polymer;

2. the amounts and types of plasticizers, fillers, lubricants, pigments and other additives;

3. pressure; and temperature.

Increases in temperature, pressure, and the use of additives tend to increase permeability of plastic. Glass containers are less permeable than plastic containers.

- Many products liable to deteriorate in humidity unless
- **protected by high-barrier** packaging.
- **Desiccant silica gel** in small packets, commonly included as protection against effects of moisture vapor.

- Drug substances that are subject to **oxidative degradation** may undergo a greater degree of degradation when packaged in plastic than in glass.

- Liquid in plastic may **lose drug molecules** or solvent to the container, altering the concentration of drug in product and affecting its potency.

 Leaching is term used to describe **movement of components of container to contents**.

 Compounds leached: polymer additives, such as the plasticizers, stabilizers, or antioxidants.

 The leaching occurs when liquids or semisolids are packaged in plastic. Little leaching occurs when tablets or capsules are packaged in plastic.

 influenced **by temperature**, **excessive agitation** of the filled container, and the **solubilizing effect of liquid contents** on one or more of the polymer additives

 Sorption indicate **binding of molecules to polymer** includes both **adsorption and absorption**.

 Sorption occurs through chemical or physical means.

 Sorption may occur with **active pharmacologic agents** or with **excipients.**

 Sorption may be initiated by the **adsorption of a solute to the inner surface of a plastic container.**

 After saturation of the surface, the solute may diffuse into the container and bound within plastic container.

 Plastic materials with polar groups are prone to sorption. Because **sorption depends on penetration or diffusion of a solute into plastic.**

 un-ionized species of solute has greater tendency to bound than ionized species. The degree of ionization of a solute affected by pH of solution, the pH may influence sorption of particular solute.

 The sorption of excipients :colorants, preservatives, or stabilizers would likewise alter the quality of product.

 Methylparaben may be sorbed to some types of plastics, resulting in a decrease in the available concentration of preservative.

Deformations, **softening**, **hardening**, and other physical changes in plastic containers can be caused by the action of container's contents or external factors, including changes in temperature and physical stress placed upon the container in handling and shipping.

Pharmaceuticals labeling

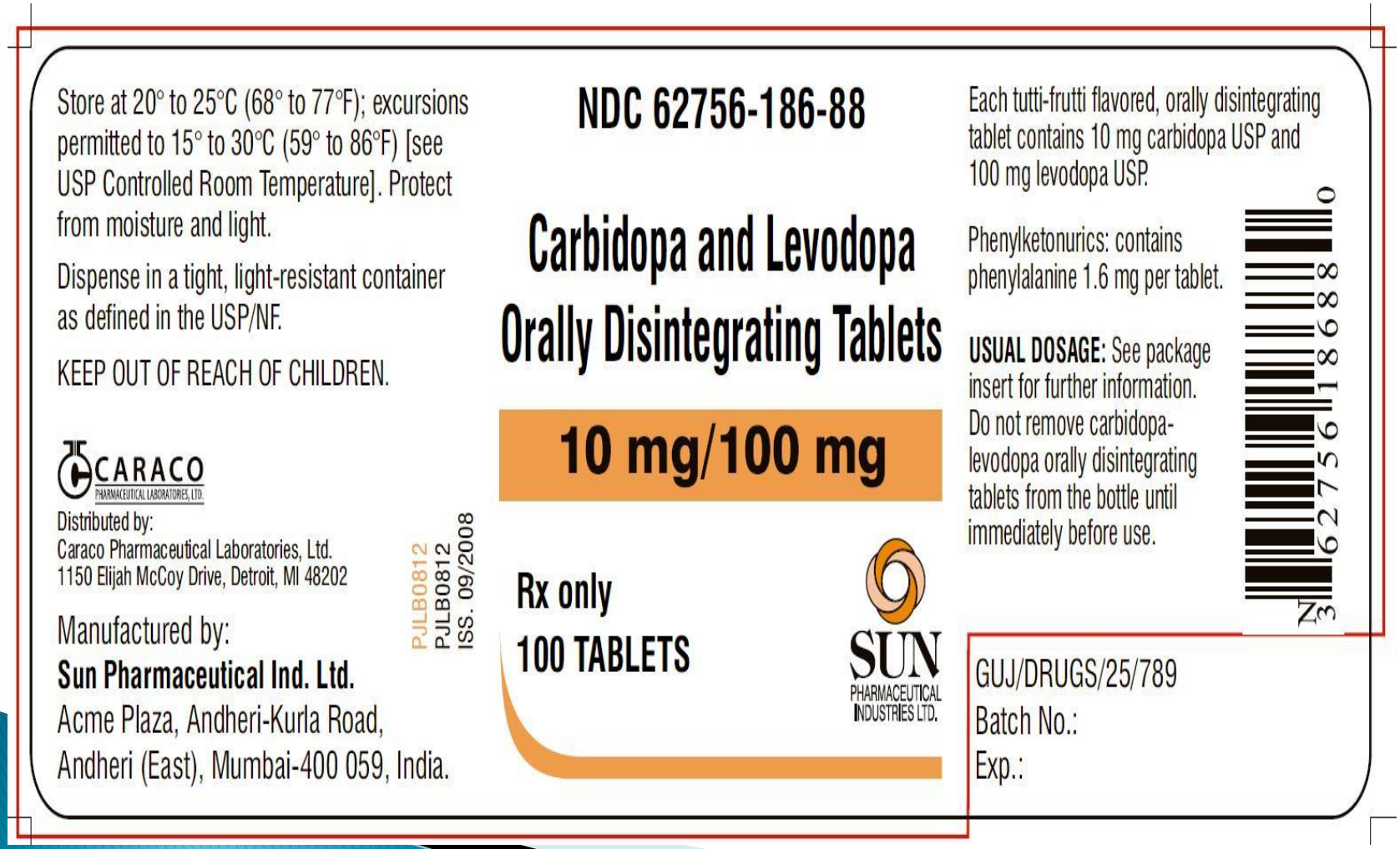
All drug products distributed must **meet labeling requirements**: Investigational drugs, Manufacturer's prescription drugs, Controlled substances, Dispensed prescription medication, OTC products, Products for animals, Medical devices.

In addition of labeling on the immediate container and packaging, **manufacturers' drug product insert**:

- Company literature
- Advertising and promotional material (brochures, booklets, bulletins, sound recordings, price lists, catalogs, sound recordings, motion picture films, exhibits, and computer-accessed information etc.)
- Important information for a prescription-only drug is provided to health professionals

Manufacturer's Product Label

The information usually appearing on label affixed to the container is the following

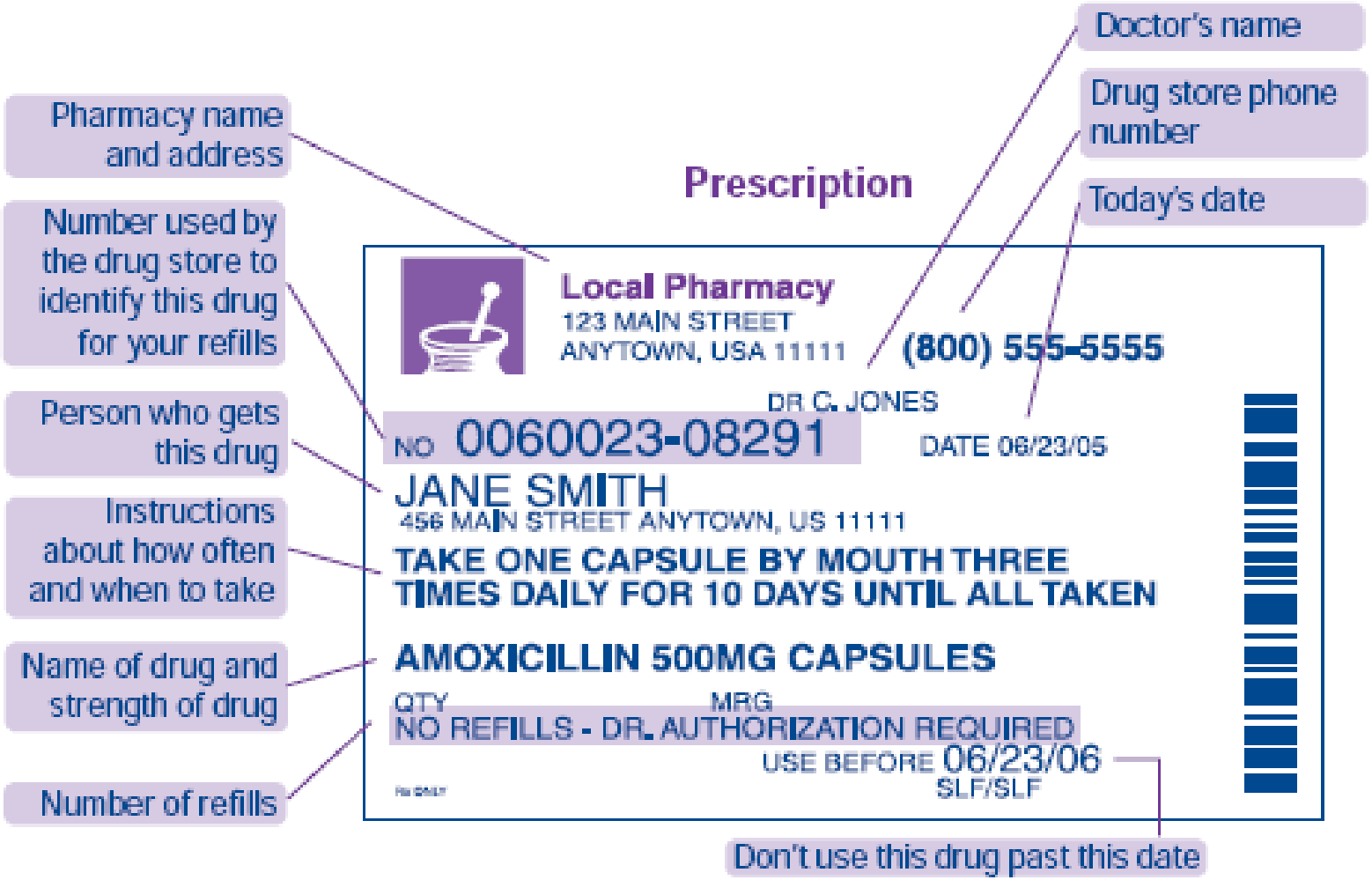


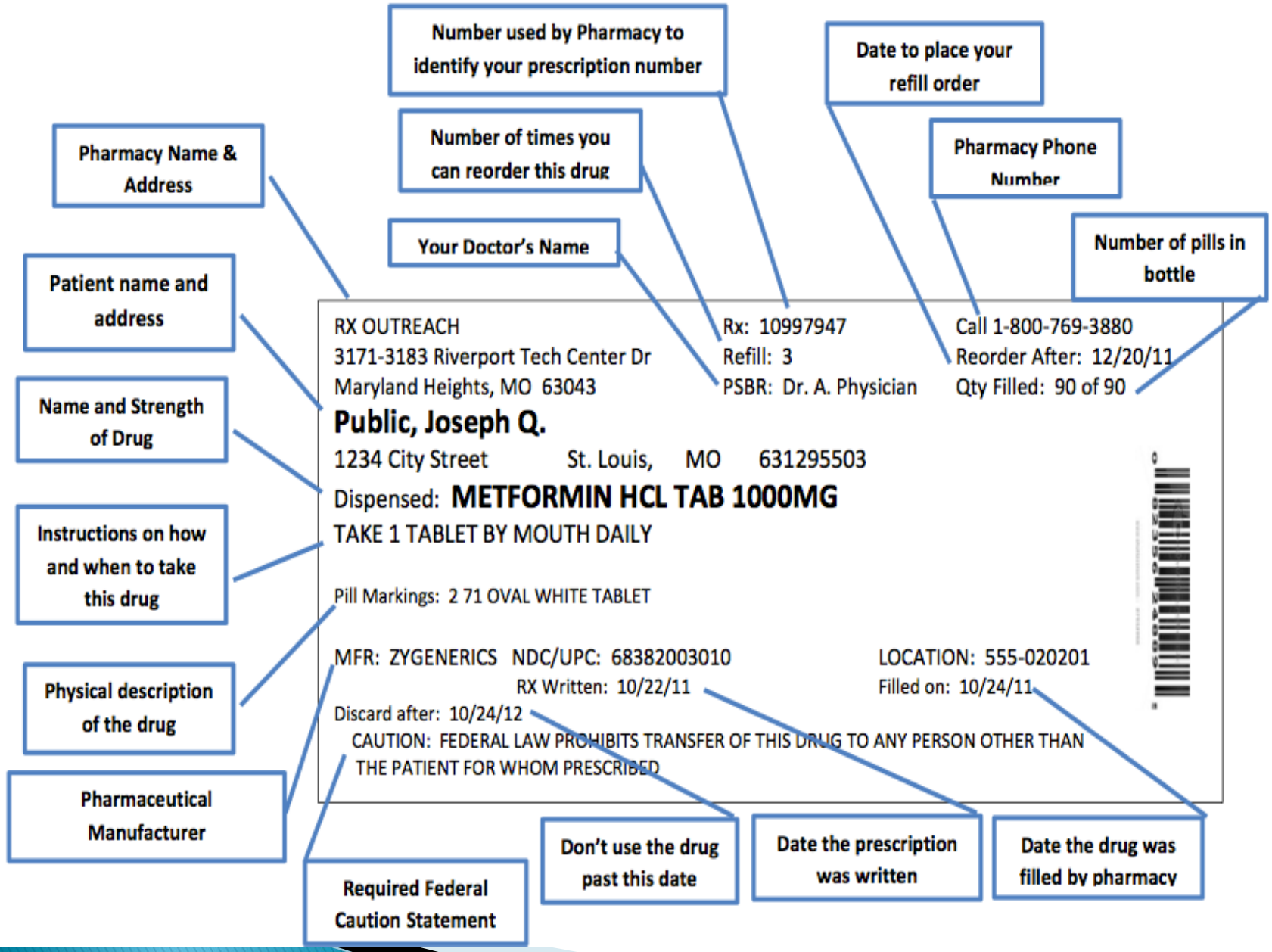
- The **nonproprietary name** of drug
- The **name of the manufacturer**, or distributor of the product
- A quantitative statement of **the amount of each drug per unit of weight**, volume, or dosage unit, whichever is most appropriate
- The pharmaceutical **type of dosage form** constituting the product
- The **net amount of drug product** contained in the **package**, in units of weight, volume, or number of dosage units, as appropriate
- The **logo "Rx only"** or the federal legend "Caution—Federal law prohibits dispensing without prescription" or a similar statement

- A **label reference** to refer to the accompanying **package insert** or other product literature for dosage and other information
- Special **storage instructions** when applicable
- The **National Drug Code identification** number for the product and a bar code
- An identifying lot or control number
- An **expiration date**
- “Warning—May be habit forming” may also appear.

Prescription Label

When dispensing a prescription include the following information on the label of the dispensed medication:




Number used by Pharmacy to identify your prescription number
Date to place your refill order
Pharmacy Name & Address
Number of times you can reorder this drug
Pharmacy Phone Number
Your Doctor's Name
Number of pills in bottle
Patient name and address
RX OUTREACH
3171-3183 Riverport Tech Center Dr
Maryland Heights, MO 63043
Rx: 10997947
Refill: 3
PSBR: Dr. A. Physician
Call 1-800-769-3880
Reorder After: 12/20/11
Qty Filled: 90 of 90
Public, Joseph Q.
1234 City Street St. Louis, MO 631295503
Name and Strength of Drug
Dispensed: METFORMIN HCL TAB 1000MG
Instructions on how and when to take this drug
TAKE 1 TABLET BY MOUTH DAILY
Pill Markings: 2 71 OVAL WHITE TABLET
Physical description of the drug
MFR: ZYGENERICS NDC/UPC: 68382003010
LOCATION: 555-020201
RX Written: 10/22/11
Filled on: 10/24/11
Discard after: 10/24/12
CAUTION: FEDERAL LAW PROHIBITS TRANSFER OF THIS DRUG TO ANY PERSON OTHER THAN THE PATIENT FOR WHOM PRESCRIBED
Pharmaceutical Manufacturer
Required Federal Caution Statement
Don't use the drug past this date
Date the prescription was written
Date the drug was filled by pharmacy

- The name and address of the pharmacy
- The serial number of the prescription
- The date of the prescription or the date of its filling or refilling (state law often determines which date is to be used)
- The name of the prescriber
- The name of the patient
- Directions for use, including any precautions, as indicated on the prescription

In addition, state laws may require additional information:

• The address of the patient

- The initials or name of the dispensing pharmacist
- The telephone number of the pharmacy
- The drug name, strength, and **manufacturer's lot or control number**
- The expiration date of the drug
- The **name of the manufacturer or distributor**
- In an effort to decrease medication errors, there is thought to include the **"indication"** on the prescription label to help the pharmacist assure the prescribed drug is appropriate

Over- The-Counter Labeling

the name of the product, the name and address of the manufacturer or distributor, the quantity of net contents, the bar code and other product-identifying items, the expiration date, and the other drug-specific required information

Drug Facts

Active ingredient (in each capsule) — **Purpose**

Diphenhydramine HCl 25 mg ..... Antihistamine

Uses ■ temporarily relieves these symptoms of the common cold: ■ runny nose ■ sneezing ■ temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ runny nose ■ sneezing ■ itching of the nose or throat ■ itchy, watery eyes

Warnings

Do not use with any other product containing diphenhydramine, even one used on skin.

Ask a doctor before use if you have ■ a breathing problem such as emphysema or chronic bronchitis ■ glaucoma ■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers.

When using this product ■ excitability may occur, especially in children ■ marked drowsiness may occur ■ avoid alcoholic drinks ■ alcohol, sedatives, and tranquilizers may increase drowsiness ■ be careful when operating machinery or driving a motor vehicle

Drug Facts (continued)

If pregnant or breast-feeding, ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

■ take every 4 to 6 hours, not more than 6 doses in 24 hours

adults and children 12 years of age and over	take 1 or 2 capsules
children 6 to under 12 years of age	take 1 capsule
children under 6 years of age	consult a doctor
children under 4 years of age	**do not use**

Other information

■ store at room temperature 15°-30°C (59°-86°F) in a dry place ■ protect from light ■ do not use if imprinted safety seal under cap is broken or missing ■ do not use if red band around capsule is broken or missing ■ *This product is not manufactured or distributed by McNeil Consumer Healthcare, Division of McNeil-PPC, Inc., owner of the registered trademark Benadryl® Allergy Kapgels®.

Inactive ingredients

D&C Red #28, FD&C Blue #1, FD&C Red #40, gelatin, lactose and starch.

Over- the-counter labeling

Additional information, “drug facts” must appear in label

 Names and quantities of all active ingredients /dosage unit. Inactive ingredients also listed.

 Statement of pharmacologic category (e.g., antacid, antihistaminic, analgesic, etc….)

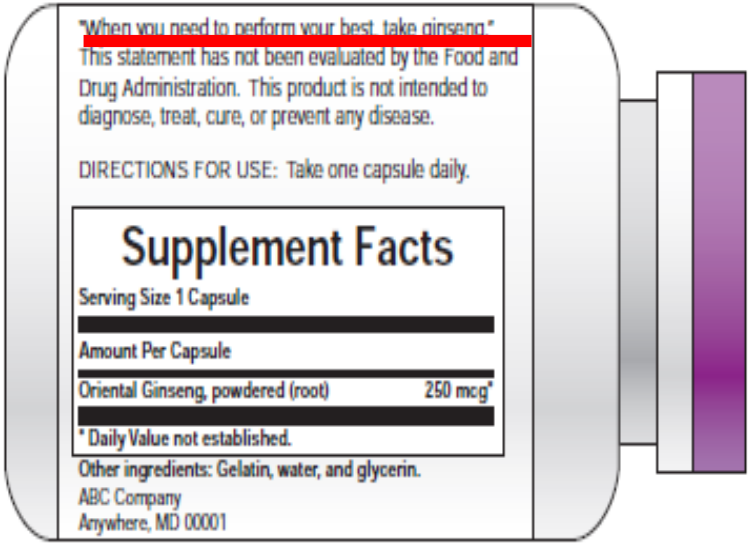
 adequate directions for safe and effective use. Ex. dose, frequency of dose, dose and age considerations, route of administration, and preparation for use, such as shaking before use or dilution.

 Name of any substances in the preparation. Ex. sodium content for certain orally ingested product that contains 5 mg of sodium or more/single dose or 140 mg or more in maximum daily dose. Storage conditions

Dietary Supplement Labeling

- A vitamin
- A mineral
- An herb or other botanical
- An amino acid
- A dietary substance for use
- A concentrate, metabolite, constituent, extract, or a combination of any above ingredient

- Disallows "**disease claims**" that infer or imply that the product can be used to prevent, treat, cure, mitigate or diagnose a disease



Dietary Supplement Labeling

Storage

 The product must be stored in proper conditions to ensure product stability during its shelf life.

 The labeling of product includes **the desired storage conditions,** and such terms employed (USP):

 Cold: Any temperature **not exceeding 8°C.**

-A **refrigerator** is a cold place in which the temperature is maintained thermostatically **between 2° and 8°C**.

-A freezer is a cold place in which the temperature is maintained thermostatically **between -25° and -10°C.**

 Cool: Any temperature **between 8° and 15°C**.

 Room temperature: The temperature prevalent in a working area which is ranged **20°C to 25°C**. (but also allows for temperature variations between 15°C and 30°C.

- **Warm:** Any temperature **between 30° and 40°C**.
- **Excessive heat: Above 40**°C.

- Protection from freezing: freezing subjects products to the **risk of container breakage**, **loss of strength** or **potency,** or to **destructive alteration of dosage form**
- Transportation to and within geographic areas of extreme temperatures and humidity requires special consideration

Dosage form design: pharmaceutical and formulation consideration

Chapter 4

Dosage forms are needed to get safe and effective dose and for additional reasons:

1- To protect drug from **destructive influences of atmospheric oxygen or humidity** (coated tablets, sealed ampules).

2- To protect the drug substance from **destructive influence of gastric acid** after oral administration (enteric-coated tablets).

3- **To mask bitter, salty, or odor** of a drug substance (capsules, coated tablets, flavored syrups).

4- To **provide liquid** preparations of drug substances, either as dispersions (suspensions) or as clear preparations (solutions).

5-To provide **rate controlled drug** action (controlled-release tablets, capsules, and suspensions).

6- To provide **topical** administration sites (ointments,

creams, transdermal patches, and ophthalmic, ear, and nasal preparations).

7- To provide for **insertion of a drug into body's orifices** (rectal or vaginal suppositories).

8-To provide for **placement of drugs directly in blood** stream or body tissues (injections).

9-To provide for **optimal drug action** through **inhalation** therapy (inhalants and inhalation aerosols)

General concideration for dosage form design

- If drug is intended for **systemic use** and **oral** administration is desired, **tablets** and/or **capsules** are usually prepared.
- If drug used in emergency in patient with **coma**, **injectable** form of medication may be prepared.
- motion sickness, nausea, and vomiting, for which **tablets and skin patches** are used for prevention and suppositories and injections for treatment.
- **The age of patient plays a role in dosage form design:**
- For **infants and children** younger than 5 years of age, pharmaceutical **liquid**s are preferred for oral administration.
- These liquids, which are flavored aqueous solutions, syrups, or suspensions, are usually administered directly into the infant's or child's mouth by drop, spoon, or oral dispenser or incorporated into the child's food. The palatability of some commercial products may not be acceptable to some patients so different flavoring additives may be indicated to enhance compliance; an example would be the FLAVORx flavoring
- system.

- A single liquid paediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered.
- Medications intended for the elderly are commonly formulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist. In many patient-care facilities, as nursing homes, tablet-crushing devices are utilized by the nursing staff preparatory to mixing with food (as applesauce) for administration. However, certain tablets and capsules that are designed for controlled release should not be crushed or chewed, because that would interfere with their integrity and intended performance.
- person with difficulty in swallowing tablet can use chewable tablets or orodispersible tablets that dissolve in mouth in about 10 to 15 seconds; this allows patient to take a tablet but actually swallow a liquid.

- Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and color of solid dosage forms, the easier is proper identification of the medications. Errors in taking medications among the elderly occur frequently because of their multiple drug therapy and impaired eyesight. Dosage forms that allow reduced frequency of administration without sacrifice of efficiency are particularly advantageous.

- Capsules have been found by many to be more **easily swallowed than whole tablets**. If a capsule is moistened in the mouth before it is swallowed, it becomes slippery and readily slides down the throat with water.
- Also, a teaspoonful of gelatin dessert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowing them.
- Medications intended for **elderly** are commonly formulated into **oral liquids.**

- Formulating a drug substance into a proper dosage form, research pharmacists employ knowledge gained through experience with other chemically similar drugs and through the proper use of the physical, chemical, biologic, and pharmaceutical sciences. The early stages of any new formulation include studies to collect basic information on the physical and chemical characteristics of the drug substance. These basic studies are the preformulation work needed before actual product formulation begins.

Excipients

- **flavors** and **sweeteners.**
- **Colorants**
- **Preservatives**
- **Antioxidant**s
- **chelating agents**
- lubricants

There is some psychologic basis to drug therapy, and the odor, taste, and color of a pharmaceutical preparation can play a part.

- An appropriate drug has its most beneficial effect when it is accepted and taken properly by the patient. The proper combination of flavor, fragrance, and color in a pharmaceutical product contributes to its acceptance.

- An “electronic tongue” is used to aid in providing a global “taste fingerprint” during formulation development. It provides information on bitterness levels and the stability of flavours in terms of taste

FIGURE 4.4 Electronic tongue to assist in formulation development. (Courtesy of Alpha MOS.)

- **Acidifying agent** Used in liquid preparations to provide acidic medium for product stability:Citric acid, Acetic acid,Fumaric acid, Hydrochloric acid, Nitric acid.
- **Alkalinizing agent** Used in liquid preparations to provide alkaline medium for product stability: Ammonia solution, Ammonium carbonate, Diethanolamine, Monoethanolamine, Potassium hydroxide, Sodium bicarbonate, Sodium borate, Sodium carbonate, Sodium hydroxide.
- **Adsorbent** An agent capable of holding other molecules onto its surface by physical or chemical (chemisorption)means: Powdered cellulose, Activated charcoal.
- **Aerosol** propellantAgent responsible for developing the pressure within an aerosol container and expelling the product when the valve is opened:Carbon dioxide, Dichlorodifluoromethane, Dichlorotetrafluoroethane, Trichloromonofluoromethane
- **Air displacement** Agent employed to displace air in a hermetically sealed container to enhance product stability: Nitrogen,Carbon dioxide

- **Antifungal preservative** Used in liquid and semisolid preparations to prevent growth of fungi. Effectiveness of parabens is usually enhanced by use in combination Butylparaben, Ethylparaben, Methylparaben, Benzoic acid, Propylparaben, Sodium benzoate, Sodium propionate.
- **Antimicrobial preservative** Used in liquid and semisolid preparations to prevent growth of microorganisms: Benzalkonium chloride.
- **Antioxidant** Used to prevent deterioration of preparations by oxidation: Ascorbic acid, Ascorbyl palmitate, Butylated hydroxyanisole.
- **Buffering agent** Used to resist change in pH upon dilution or addition of acid or alkali: Potassium metaphosphate, Potassium phosphate, monobasic Sodium acetate, Sodium citrate, anhydrous and dihydrate
- **Chelating agent** Substance that forms stable water-soluble complexes (chelates) with metals; used in some liquid pharmaceuticals as stabilizers to complex heavy metals that might promote instability. In such use, they are also called sequestering agents: Edetic acid Edetate disodium.

- **Colorant** Used to impart color to liquid and solid (e.g., tablets and capsules) preparations: FD&C Red No. 3, FD&C Red No. 20, Caramel, Ferric oxide, red.
- **Flavorant** Used to impart a pleasant flavor and often odor to a preparation. In addition to the natural flavorants listed, many synthetic ones are used: Anise oil, Cinnamon oil, Cocoa, Menthol, Orange oil,Peppermint oil.
- **Humectant** Used to prevent drying of preparations, particularly ointments and creams: Glycerin, Propylene glycol, Sorbitol.
- **Sweetening** agent Used to impart sweetness to a preparation: Aspartame, Dextrose, Glycerin2, Mannitol, Saccharin sodium, Sorbitol, Sucrose.
- **Tablet antiadherents** Prevent tablet ingredients from sticking to punches and dies during production: Magnesium stearate.
- **Tablet binders** Substances used to cause adhesion of powder particles in tablet granulations: Acacia, Alginic acid, Carboxymethylcellulose sodium, gelatin.
- **Tablet and capsule diluent** Inert filler to create desired bulk, flow properties, and compression characteristics of tablets and capsules: Dibasic calcium phosphate, Kaolin, Lactose, Mannitol, Microcrystalline cellulose, Powdered cellulose, Precipitated calcium carbonate, Sorbitol, Starch.

- **Tablet-coating agent** Used to coat a tablet to protect against decomposition by atmospheric oxygen or humidity, to provide a desired release pattern, to mask taste or odor, or for aesthetic purposes. Coating may be sugar, film, or thick covering around a tablet. Sugarcoated tablets generally start to break up in the stomach. Film forms a thin cover around a formed tablet or bead. Unless it is enteric, film dissolves in the stomach. Enteric coating passes through the stomach to break up in the intestines. Some water insoluble coatings (e.g., ethylcellulose) are used to slow the release of drug in the gastrointestinal tract:
- **Sugar coating**: Liquid glucose, Sucrose.
- **Film coating:** Hydroxyethyl cellulose, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Methylcellulose (e.g., Methocel) ,Ethylcellulose (e.g., Ethocel).
- **Enteric coating**:Cellulose acetate phthalate, Shellac (35% in alcohol.
- **Tablet or capsule opaquant:** Used to render a coating opaque. May be used alone or with a colorant:Titanium dioxide.
- **Tablet polishing agent** Used to impart an attractive sheen to coated tablets:Carnauba wax, White wax.

- **Not all salts are salty but their taste is function of both cation and anion.**

- Salty tastes :NaCl, KCl, NH_4Cl and by NaBr, KBr.
- ammonium give bitter and salty sensations.
- **potassium iodide** and **magnesium sulfate** (epsom salt) are predominantly bitter.

- In general, low-molecular-weight salts are salty, and high-molecular-weight salts are bitter.

- With organic compounds, increase number of hydroxyl groups (—OH) increase the sweetness of the compound.

Flavoring Pharmaceuticals

- The flavour sensation of a food or pharmaceutical is actually a complex blend of taste and smell, with lesser influences of texture, temperature, and even sight. In flavour formulating a pharmaceutical product, the pharmacist must give consideration to the color, odor, texture, and taste of the preparation. It would be incongruous, for example, to color a liquid pharmaceutical red and give it a banana taste and a mint odor. The color of a pharmaceutical must have a psychogenic balance with the taste, and the odor must also enhance that taste. Odor greatly affects the flavor of a preparation or foodstuff. If one's sense of smell is impaired, as during a head cold, the usual flavor sensation of food is similarly diminished.

Flavoring Pharmaceuticals

- **Added to liquid** mask **taste**.
- **Chewable tablets**, such as antacid and vitamin products, usually are **sweetened and flavored** to improve acceptance.
- Organic compounds: Increase number of **hydroxyl** groups (-OH) **increase sweetness** of compound.
- **Sucrose**(**8 -**OH), sweeter than **glycerin**(3-OH)
- In general: organic esters, alcohols, and aldehydes are pleasant to the taste
- volatile, affect odor and flavor of preparations

- **Many nitrogen-containing** (e.g., quinine) **bitter**, but other nitrogen-containing (e.g., **aspartame**) are **sweet**.
- Even **simple structural change alter taste**.
- D-Glucose is **sweet**, but L-glucose has slightly **salty.**

- **saccharin** is very **sweet** but **N-methyl-saccharin** is **tasteless**.

- **Selection of appropriate flavor depends on several factors:**

A: Taste of drug: Certain flavoring materials are more effective than others in masking bitter, salty, sour, or otherwise undesirable taste of medicinal agents. Although individuals' tastes and flavor preferences differ, **cocoa-flavored** vehicles are considered effective for masking the taste of **bitter drugs**. **Fruit or citrus** flavors are frequently used to combat **sour or acid**-tasting drugs, and **cinnamon, orange, raspberry**, and other flavors have been successfully used to make preparations of **salty** drugs more palatable.

- B: The age of patient:
- The age of the intended patient should also be considered in the selection of the flavoring agent, because certain age groups seem to prefer certain flavors.

1. **Children prefer sweet candy-like with fruity flavors.**
2. **Adults prefer less sweet with tart rather than a fruit flavor.**

Flavors can consist of oil- or water-soluble liquids and dry powders; most are diluted in carriers. Oil-soluble carriers include soybean and other edible oils; water-soluble carriers include water, ethanol, propylene glycol, glycerin, and emulsifiers. Dry carriers include maltodextrins, corn syrup solids, modified starches, gum arabic, salt, sugars, and whey protein. Dry carriers include maltodextrins, corn syrup, modified starches, gum, salt, sugars, and whey protein.

Flavors can degrade as a result of exposure to light, temperature, headspace oxygen, water, enzymes, contaminants, and other product components, so they must be carefully selected and checked for stability.

Flavoring agents may be derived from natural sources (e.g., fruit components) or prepared artificially. They may be either water soluble or oil soluble.

Artificial flavor: Any substance used to give flavor that is not derived from spice, fruit or fruit juice, vegetable or vegetable juice, herb, bark, bud, root, leaf eggs, dairy

- Their selected use in pharmaceutical products is based on desired **flavor**, their **solubility** characteristics, and their **chemical and physical compatibility** with the active therapeutic agent and other components of the formulation.
- Flavoring agents in liquid pharmaceutical products are added to the **solvent or vehicle** component of the formulation in which it is most soluble or miscible. That is, water soluble flavorings are added to the aqueous component of a formulation and oil-soluble flavorings are added to the nonaqueous components. In general, artificial flavors are used in liquid pharmaceutical at levels of 0.1% to 0.2%, whereas natural flavors are used within the 1% to 2% range.

Sweetening Pharmaceuticals

In addition to sucrose, a number of artificial sweetening agents have been used in foods and pharmaceuticals over the years. Some of these, including aspartame, saccharin, and cyclamate, have faced challenges over their safety by the FDA and restrictions to their use and sale.

At the present time, the following artificial sweeteners are approved by the FDA with, in parenthesis, the number of times (×) each one

is sweeter than table sugar:

- Acesulfame potassium (~200 ×)
- Aspartame (~180 to 200 ×)
- Sucralose (~600 ×)
- Saccharin (~300 ×)
- **saccharin** excreted **unchanged** by kidneys but it has bitter after taste sensation.
- **Cyclamate**, is **metabolized**, in GIT, and excreted by kidneys.
- **Aspartame** breaks down to three basic components: amino acids **phenylalanine** and **aspartic acid**, and **methanol**. **So aspartame** are metabolized through regular pathways in the body.

- metabolism to phenylalanine.
- So the use of aspartame by persons with **phenylketonuria** (PKU) is discouraged.Why?

Any diet foods and drinks that contain aspartame must have a label **warning** not be consumed by phenyl ketone urea individuals because they cannot metabolize phenylalanine adequately, so they undergo an increase in the serum levels of the amino acid (hyperphenylalaninemia will happen). result in **mental retardation** and can affect the fetus of a pregnant woman who has PKU.

Other arteficial sweetners

- Acesulfame potassium, a non nutritive sweetener Structurally similar to saccharin, it is 130 times as sweet as sucrose and is excreted unchanged in urine.
- **Acesulfame is more stable than aspartame at elevated temperatures** use in candy, chewing gum, and instant coffee and tea.
- Stevia powder30 times as sweet as sucrose.used in both hot and cold preparations.

Coloring Pharmaceuticals

Coloring agents are used in pharmaceutical preparations for esthetics. A distinction should be made between agents that have inherent color and those that are employed as colorants. An example of a natural substance with inherent color that is employed as a colorant is red ferric oxide. It is mixed in small proportions with zinc oxide powder to give calamine its characteristic pink color, which is intended to match the skin tone upon application.

- sulfur (yellow), riboflavin (yellow), cupric sulfate (blue), ferrous sulfate (bluish green), cyanocobalamin (red), and red mercuric iodide (vivid red).
- **most pharmaceutical colorants in use synthetic, a few are natural mineral and plant sources**.
- ferric oxide mixed with zinc oxide to give calamine pink color.
- 0.0005% to 0.001% FD&C, D&C, dyes or lake.
- **30 to 60 coats:tablet dyes**. With **lakes, fewer** color coats are used

- ointments, suppositories, and ophthalmic and parenteral products **assume the color of their ingredients and do not contain color additives.**

PRESERVATIVES

- **Ophthalmic and injectable preparations, sterilized by physical methods (autoclaving for 20 minutes at 15 lb pressure and 121°C, or dry heat in oven at 180°C for 1 hour, or bacterial filtration for drugs which is sensative to high teperatures) during manufacture.**
- **syrups, emulsions, suspensions, and some semisolid creams** protected by addition of antimicrobial preservative.
- **hydroalcoholic and most alcoholic preparations not require addition of preservative** when the alcoholic content is sufficient to prevent microbial growth.

- **15% V/V alcohol will prevent microbial growth in acidic media and 18% V/V in alkaline media.**
- elixirs, spirits, and tinctures, are self-sterilizing and do not require additional preservation.

Preservative selection should do the followings:

1. **prevents growth** of microorganisms.
2. **Soluble in water** to achieve adequate concentrations in aqueous phase.
3. Concentration of preservative does not affect the safety of patient.
4. has **adequate stability** and not reduced in concentration by **decomposition** during desired shelf life of preparation.
5. **compatible** with all formulative ingredients.
6. The preservative **does not adverse**ly affect container or closure.

General Preservative Considerations

- intravenous preparations given in large volumes as blood replenishers or nutrients **not contain bacteriostatic additives**.
- Microorganisms **molds, yeasts it prefere acidic** medium while **bacteria** favoring slightly **alkaline** medium.
- few microorganisms grow **below pH 3 or above pH 9**
- Aqueous preparations are within favorable pH range must be protected against microbial

- Preservative must **dissolve in sufficient concentration** in **aqueous phase** of preparation. (The preservative is soluble enough in water to achieve adequate concentrations in the aqueous phase of a system with two or more phases).
- , only **undissociated fraction** of preservative possesses preservative capability, because the ionized portion is incapable of penetrating the microorganism.
- preservative selected must be largely undissociated at pH of the formulation prepared.

- Acidic preservatives **benzoic** acid, **boric acid, and sorbic acids** more **undissociated** more effective as the medium is made more **acid.** Conversely,
- **alkaline preservatives** are less effective in acid or neutral media and more effective in **alkaline media**.
- if formula interfere with solubility or availability of preservative t, its chemical concentration may **misleading**, because it may not be a true measure of the effective concentration.

- tragacanth, **attract and hold preservative**, such as the **parabens and phenolic** rendering them unavailable for preservative function.
- preservative **must not interact with container**, such as a metal ointment tube or a plastic medication bottle, or closure, such as a rubber or plastic cap or liner.

Mode of Action of preservatives

1. **Modification of cell membrane permeability**.
2. **Lysis and cytoplasmic leakage** Irreversible coagulation of cytoplasmic constituents (e.g., protein precipitation)
3. **Inhibition of cellular metabolism**, such as by interfering with enzyme systems or inhibition of cell wall synthesis
4. **Oxidation** of cellular constituents
5. **Hydrolysis**

Preservatives concentrations

- benzoic acid (**0.1% to 0.2%).**
- sodium benzoate (**0.1% to 0.2%)**
- alcohol (15% to 20%),
- phenol (0.1% to 0.5%),
- cresol (0.1% to 0.5%),
- benzalkonium chloride (**0.002% to 0.01%)**
- combinations of methylparaben and propylparaben (0.1% to 0.2)against fungus.

- **Preservative in ophthalmic preparation**

must have **low degree of irritant** qualities, like **chlorobutanol**, **benzalkonium** chloride.

- Single dose eye drop not contain preservative.

Preformulation studies

Preformulation Studies

- Before the formulation of a drug substance into a dosage form, it is essential that it be chemically and physically characterized. The following preformulation studies and others provide the type of information needed to define the nature of the drug substance. This information provides the framework for the drug's combination with pharmaceutical ingredients in the fabrication of a dosage form.

Physical Description

Most drug substances in use today are solid materials so

Solid drugs :are pure chemical compounds of either crystalline or amorphous constitution.

The **purity of chemical substance** is essential for its identification and for evaluation of its chemical, physical, and biologic properties.

Chemical properties include **structure**, **form**, and **reactivity**.

Physical properties include: **physical description**, **particle size**, **crystalline structure**, **melting point**, and **solubility**.

Biologic properties relate to its **ability to get to a site of action** to give **biologic response**.

- Drugs can be used therapeutically as solids, liquids, and gases. Liquid drugs are used to a much lesser extent than solid drugs, gases even less frequently.
- Liquid drugs pose an interesting problem in the design of dosage forms and delivery systems. Many liquids are volatile and must be physically sealed from the atmosphere to prevent evaporation loss.

Liquid drugs

- Many liquids are **volatile** and must be **physically sealed from atmosphere** to prevent evaporation loss.

- **Amyl nitrite**, for example, is a clear yellowish liquid that is volatile even at low temperatures and highly flammable. It is kept in small sealed glass cylinders wrapped with gauze.
- When amyl nitrite is administered, the glass is broken between the fingertips, and the liquid wets the gauze covering, producing vapors that are inhaled by patient requiring vasodilation.

Other example

Propyl hexedrine is volatile liquid that must be contained in a closed system. This drug is used as a nasal inhalant for vasoconstrictor action.

A cylindrical roll of fibrous material is impregnated with

Propyl hexedrine, and the saturated cylinder is placed in a suitable, **plastic, sealed nasal inhaler**. The inhaler's cap must be securely tightened each time it is used.

Even then, the inhaler maintains its effectiveness for only a **limited time** because of the volatility of the drug.

Another problem associated with **liquid drugs** is that those intended for oral administration **cannot generally be formulated into tablet** without chemical modification.

An exception to this is liquid drug **nitroglycerin**, which is formulated into **sublingual tablets** that **disintegrate within seconds** after placement under the tongue.

However, because the drug is volatile, it has a tendency to escape from the tablets during storage,

the tablets sould be **stored in a tightly sealed glass container**.

when a liquid drug is to be administered orally and a solid dosage form is desired, one of two approaches is used.

First, liquid sealed in soft gelatin capsule. Vitamins A, D, and E are liquids available in capsule form.

Second, liquid drug developed into solid ester or salt so will be suitable for tablets or capsules.

Example: **scopolamine hydrobromide** is a solid salt of liquid drug scopolamine and is easily pressed into tablets.

Another approach to formulate liquids into solids is by **mixing drug with a solid or melted semisolid material**, such as a high molecular weight PEG. The melted mixture is poured into hard gelatin capsules to harden, and the capsules are sealed.

liquid drugs, that **taken orally in large doses** or **applied topically**, their liquid nature may have some advantage in therapy.

For example, 15-mL doses of mineral oil may be administered conveniently as such.

However, for pharmacists **prefer solid** materials in formulation work because they can easily form them into tablets and capsules.

- **Formulation and stability difficulties** arise less frequently with **solid dosage forms** than with **liquid preparations**, and for this reason, many new drugs first reach the market as tablets or dry-filled capsules.
- Later, when the pharmaceutical problems are resolved, liquid form of the same drug may be marketed. This procedure is doubly advantageous, because for the most part, physicians and patients alike prefer small, generally tasteless, accurately dosed tablets or capsules to the analogous liquid forms.
- Therefore, marketing a drug in solid form first is more practical for the manufacturer and suits most patients. It is estimated that tablets and capsules constitute the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules.

Microscopic Examination

Microscopic examination of raw drug substance is important step in preformulation work. It gives an indication of particle size and size range of the raw material along with the crystal structure.

. Photomicrographs of the initial and subsequent batch lots of the drug substance can provide important information in case of problems in formulation processing attributable to changes in **particle or crystal** characteristics of the drug.

During some processing procedures, the solid drug powders must **flow freely**. Spherical and oval powders flow more easily than needle-shaped powders and make processing easier.

Heat of Vaporization

- The use of **vapor pressure** is important in the operation of **implantable pumps** delivering medications as well as in aerosol dosage forms.
- Another application is the use of **nasal inhalants** (propylhexedrine with menthol and lavender oil—Benzedrex) for treating nasal congestion. In this latter dosage form, the quantity of drug required for effectiveness and a reasonable estimate of time of usefulness can be determined. Also, in the case of spills in inaccessible places, the time to evaporation of a substance can also be calculated.

Some **volatile** drugs can **migrate within a tablet** dosage form so the distribution may not be uniform any longer. So drug in one portion may be higher or lower than in the other portion.

- heat of vaporization of liquid: is the **amount of heat absorbed when 1 g of liquid vaporizes** and measured in calories.
- The heat of vaporization of water at 100°C is 540 cal/g or about 9.720 cal/mole. T

Melting Point Depression

A characteristic of a pure substance is a defined melting point or melting range.

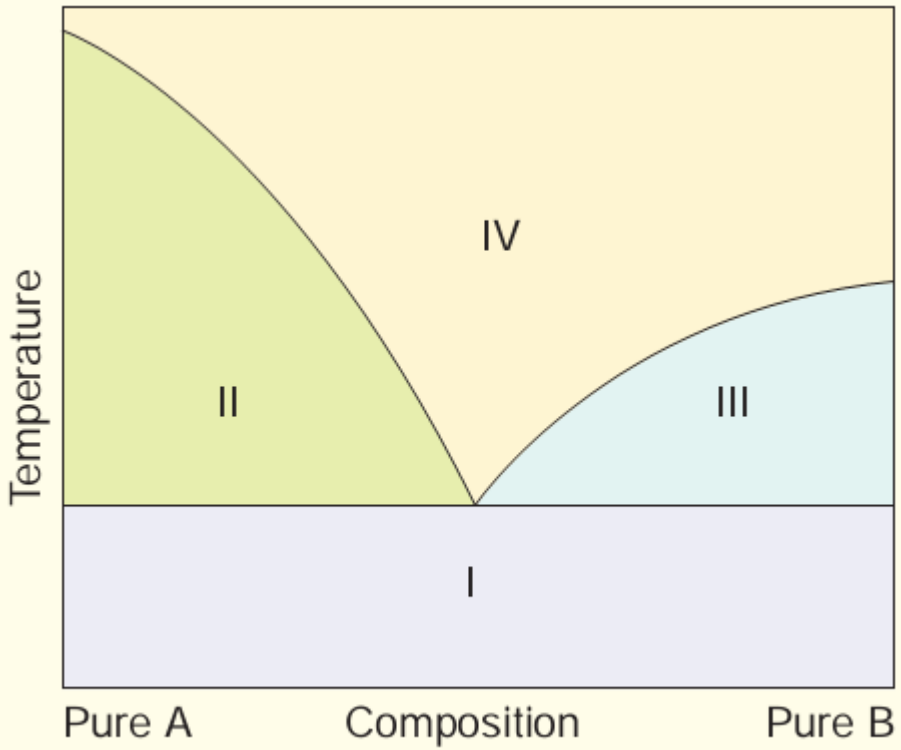
If **not pure**, the substance will exhibit a **change in melting point**.

This phenomenon is commonly used to determine the purity of a drug and compatibility of various substances before inclusion in the same dosage form.

The Phase Rule

Phase diagrams are used to **provide visual picture of the existence and extent of the presence of solid and liquid phases in binary, ternary**, and other **mixtures.**

I. Solid A + solid B
II. Solid A + melt
III. Solid B + melt
IV. Melt



The Phase Rule

A phase diagram, or temperature composition diagram, represents the melting point as a function of composition of two or three component systems.

The figure is an example of such a representation for a two-component mixture. This phase diagram depicts a two component mixture in which the components are completely miscible in the molten state and no solid solution or addition compound is formed in the solid state. As is evident, starting from the extremes of either pure component A or pure component B, as the second component is added, the melting point of the pure component decreases.

Particle Size

physical and chemical properties of drug are affected by particle size which are :**dissolution rate**, **bioavailability**, **content uniformity**, **taste**, **texture, color, stability**.

In addition**, flow ch**aracteristics and **sedimentation rates**, are important factors related to particle size.

particle size affect absorption profiles of certain drugs, including **griseofulvin, nitrofurantoin, spironolactone, and procaine penicillin.**

Also, satisfactory **content uniformity** in solid dosage forms depends on **particle size** and the equal distribution of the active ingredient through-out the formulation.

Polymorphism

An important factor on formulation is crystal or amorphous form of drug.

Polymorphic forms usually exhibit different physicochemical properties, including **melting point** and **solubility**.

Polymorphic forms in drugs are relatively common. It has been estimated that at least **one third** of all organic compounds **exhibit polymorphism**

In addition to polymorphic forms, compounds may occur in non crystalline or amorphous forms. The energy required for a molecule of drug to escape from a crystal is much greater than is required to escape from an amorphous powder. Therefore, amorphous form is **always more soluble than crystal form**.

- The changes in crystal characteristics can influence **bioavailability** and **chemical and physical stability**. For example, it can be a significant factor relating to tablet formation because of flow and compaction behaviors.

Various techniques are used to determine crystal properties:

1. **hot stage microscopy**,
2. **thermal analysis**,
3. **infrared spectroscopy**, and
4. **x-ray diffraction**

Solubility

- important especially **aqueous solubility**. A drug must possess some aqueous solubility for therapeutic efficacy.

For a drug to **enter the systemic circulation** and exert a **therapeutic** effect, it must first be in solution.

- Relatively **insoluble compounds exhibit incomplete absorption**.

If the solubility of the drug substance is less than desirable, should improve solubility. The methods used depend on chemical nature of drug and type of drug product under consideration.

- Chemical modification of the drug into **salt or ester** forms is frequently used to increase solubility.

Equilibrium solubility method

A drug's solubility is usually determined by the equilibrium solubility method, by which an excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained. Then chemical analysis of the drug content in solution is performed to determine degree of solubility.

Solubility and Particle size

The **particle size** and **surface area** of a drug exposed to a medium can affect actual solubility within reason, for example, in the following relationship:

$$\log \frac{S}{S_0} = \frac{2\gamma V}{2.303\ RTr}$$

where

S is the solubility of the small particles,
S_0 is the solubility of the large particles,
γ is the surface tension,
V is the molar volume,
R is the gas constant,
T is the absolute temperature, and
r is the radius of the small particles.

The equation can be used to estimate the decrease in particle size required to increase solubility. For example, a desired increase in solubility of 5% would require an increase in the S/S_0 ratio to 1.05; that is, the left term in the equation would become log 1.05. If a powder has a surface tension of 125 dynes/cm, molar volume of 45 cm^3, and temperature of 27°C, what is the particle size required to obtain the 5% increase in solubility?

$$\log 1.05 = \frac{(2)(125)(45)}{(2.303)(8.314 \times 10^7)(300)r}$$

$$r = 9.238 \times 10^{-6} \text{ cm or } 0.0238\ \mu$$

A number of factors are involved in actual solubility enhancement, and this is only an introduction to the general effects of particle size reduction.

Solubility and pH

- To formulate liquid product, should adjust the pH of solvent to enhance solubility.

for many drug substances, pH adjustment is not an effective means of improving solubility.

- Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or that may cause stability problems with formulation ingredients.

Adjustment of pH usually has little effect on the solubility of substances other than electrolytes. In many cases, it is desirable to improve aqueous solubility by:

1-use cosolvents

2-complexation,

3-micronization,

4-solid dispersion.

Dissolution

dissolution rate, or the time it takes for the drug to dissolve in the fluids at the absorption site, is the rate-limiting step in absorption.

This is true for drugs administered orally in **solid forms**, such as **tablets**, **capsules**, or **suspensions**,

and for those administered **intramuscularly**.

When the dissolution rate is the rate-limiting step, anything that affects it will also **affect absorption**. Consequently, **dissolution rate** can affect the **onset**, **intensity**, and **duration of response** and **control the overall bioavailability** of the drug from the dosage form

- The dissolution rate of drugs increased by:

1. decreasing drug's particle size.
2. Increase solubility in diffusion layer.
3. Use **highly water-soluble salt** of parent substance.

Dissolution rates of chemical compounds determined by two methods:

1. **The constant surface method**, which provides intrinsic dissolution rate of the agent.
2. **Particulate dissolution**, in which a suspension of the agent is added to a fixed amount of solvent without exact control of surface area.

fick's laws of diffusion and Noyes-Whitney equation

- All drugs must diffuse through various barriers when administered to the body.

- Ficks low govern **absorption** through membrane
- Noyes-Whitney equation govern **dissolution** rate.

Membrane Permeability

- **passage of drug molecules across biologic membranes to produce a biologic response.**

- The biologic membrane acts as a **lipid barrier** to most drugs and permits the absorption of **lipid-soluble substances** by **passive diffusion**.
- while **lipid-insoluble** substances cannot diffuse across the barrier.

technique using **everted intestinal sac used to evaluate absorption of drug:**

In this method, a **piece of e intestine** is removed from intact animal, is **everted, and is filled with a solution** of drug, and the degree and rate of passage of the drug through the membrane sac are determined.

- In the latter stages of preformulation testing or early formulation studies, **animals and humans** must be studied to **assess absorption efficiency** and **pharmaco kinetic** parameters and to establish possible **in vitro and in vivo correlation** for dissolution and bioavailability.

Partition coefficient

$$P = \frac{(\text{Concentration of drug in octanol})}{(\text{Concentration of drug in water})}$$

P depends on drug concentration only if drug molecules have a tendency to associate in solution.

The oil–water partition coefficient is a measure of a molecule's **lipophilic character**; that is, its preference for the hydrophilic or lipophilic phase.

- If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and reach an equilibrium at a constant temperature.

pKa /Dissociation constant

The extent of dissociation or ionization is highly dependent on **pH of medium** containing drug.

- In formulation, the vehicle is adjusted to a certain pH to obtain a certain level of ionization of drug for solubility and stability.
- In pharmacokinetic area, the extent of ionization of a drug has a strong effect on its extent of absorption, distribution, and elimination.
- dissociation constant, or pKa , is usually determined by potentiometric titration.

Hydrates and Solvates

Many active pharmaceutical agents exist as hydrates or solvates; some are hygroscopic, deliquescent, and/or efflorescent.

Hygroscopic powders are those that will tend to **absorb moisture** from the air.

Deliquescent powders are those that will absorb moisture from the air and even liquefy.

Efflorescent powders are those that may give up their water of crystallization and may even become damp and pasty.

When working with these powders, extra care must be taken.

if a hygroscopic or deliquescent powder is being weighed on a balance, the powder may absorb moisture from air and weigh heavier than it should. Therefore, weighings should be made quickly after opening the bulk chemical containers and then resealing them.

Solvates and hydrates must be packaged in "tight" containers to prevent the loss or gain of moisture.

In fact, it is best to have **all chemicals stored** in "tight" containers and to keep them closed at all times except for the short time when a weighing step is involved. Storage at the indicated temperatures is also important and to minimize any exposure to very high humidity levels.

organic Salt considerations

Because many drugs are either weak acids or weak bases and have limited water solubility, they are often used as their "salts" to increase their aqueous solubility.

For example: sodium salicylate is salt of weak acid, salicylic acid, and sodium hydroxide).

Also, ephedrine hydrochloride can be prepared between a weak base, ephedrine, and hydrochloric acid.

Generally, the "**unionized" portion of drug in solution that will be absorbed for systemic effect**.

This is described by the "dissociation constant" or "pKa " of the drug.

Active pharmaceutical ingredient (API) in a salt form is not 100% active drug, it is important to know whether or not the dose of drug is based upon drug salt or drug base form.

The purpose of “salt” form is usually **to enhance solubility** of drug; but it may also **enhance stability** and change other attributes of the drug that **make it easier to handle** and manipulate for producing dosage forms.

the “unionized” portion of drug will exert effect in body

Potency–Designated active Pharmaceutical ingredients

API, is not 100% active drug in all cases. It is important to know the assayed potency designation of the ingredient so that appropriate allowances can be made to obtain the correct amount. This may be on the label or on the Certificate of Analysis.

Some APIs, including some antibiotics, endocrine products, biotechnology-derived products, biologics, etc., have potencies that are based on "activity" and are expressed in terms of "**units** of activity," "**micrograms per milligram**," or other standard terms of measurements. These are described for each API in USP.

drug and drug Product stability

Stability studies conducted in preformulation phase include:

1- **solid-state stability of drug alone**

2- **solution-phase stability**

3-stability in presence of excipients.

Initial investigation begins with knowledge of the drug's **chemical structure**, which allows the preformulation scientist to anticipate possible degradation reactions.

Drug Stability: Mechanisms of Degradation

Chemical : Chemically, drug substances are **alcohols**, **phenols**, **aldehydes**, **ketones**, esters, ethers, acids, salts, alkaloids, glycosides, and others, each with **reactive chemical groups** having different susceptibilities to chemical instability.

Chemically, the most frequently encountered destructive processes are **hydrolysis** and **oxidation**.

Hydrolysis is a **solvolysis** process in which (**drug) interact with water** to yield **breakdown products**.

For example, aspirin, or acetylsalicylic acid, combines with a water molecule and hydrolyzes into one molecule of salicylic acid and one molecule of acetic acid.

Hydrolysis is probably the most important single cause of drug decomposition, mainly because a **great number of medicinal agents are esters** or contain such other groupings as substituted **amides**, **lactones**, and **lactams**, which are susceptible to the hydrolytic process.

Another destructive process is **oxidation**,

which destroys many drug, including: **aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils.**

Chemically, oxidation is loss of electrons from atom or molecule. Each electron lost is accepted by some other atom or molecule, reducing the recipient.

In inorganic chemistry, oxidation is accompanied by

increase in positive valence of an element: for example, ferrous (+ 2) oxidizing to ferric (+ 3).

In organic chemistry, oxidation is frequently considered synonymous with **loss of hydrogen dehydrogenation**) from molecule.

Drug and Drug Product Stability: Kinetics and Shelf Life

Stability is the extent to which a product retains within specified limits and through out its period of storage and use (i.e., its **shelf life**) the same properties and characteristics that it possessed at the time of its manufacture.

Five types of stability concern pharmacists:

1. **Chemical:** Each active ingredient retains its chemical integrity and labeled potency within the specified limits.
2. **Physical:** The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.
3. **Microbiologic:** Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents retain effectiveness within specified limits.
4. **Therapeutic:** The therapeutic effect remains unchanged.
5. **Toxicologic:** No significant increase in toxicity occurs.

Chemical stability is important for **selecting storage conditions** (temperature, light, humidity), selecting the proper container for dispensing (glass versus plastic, clear versus amber or opaque, cap liners), and anticipating interactions when mixing drugs and dosage forms.

Stability and expiration dating are based on reaction kinetics, that is, the study of the rate of chemical change and the way this rate is influenced by concentration of reactants, products, and other chemical species and by factors such as solvent, pressure, and temperature.

In considering chemical stability of a pharmaceutical, one must know the **reaction order and reaction rate**. The reaction order may be the overall order (the sum of the exponents of the concentration terms of the rate expression) or the order with respect to each reactant (the exponent of the individual concentration term in the rate expression).

Reaction rate: The reaction rate is a description of drug concentration with respect to time. Most commonly, zero-order and first-order reactions are encountered in pharmacy.

Zero-order rate reactions

- If the loss of drug is independent on concentration of reactants and constant with respect to time (i.e., 1 mg/mL/h), the rate is called zero order. The mathematical expression is

$$\frac{-dC}{dt} = k_0$$

where k_0 is the zero-order rate constant [concentration (C)/time (t)].

The integrated and more useful form of the equation:

$$C = -k_0 t + C_0$$

where C_0 is the initial concentration of the drug.

- **units for zero rate constant** K_0 are concentration per unit time such as:
- **Mole/liter/ second** or **mg/ml/min**

- It is meaningless to attempt to describe the time required for all material in a reaction to decompose that is infinity therefore reaction rate are commonly described by K or by their half life $t_{1/2}$
- The half life equation for a zero order reaction
- $\mathbf{t_{1/2} = ½ (C_0/K_0)}$
- If the C_0 changes the $t_{1/2}$ changes . There is inverse relationship between $t_{1/2}$ and K

Example1

- A drug suspension (125 mg/mL) decays by zero-order kinetics with a reaction rate constant of 0.5 mg/mL/h. What is the concentration of intact drug remaining after 3 days (72 hours), and what is its $t_{1/2}$?

$$C = -(0.5\,mg/mL/h)(72\,h) + 125\,mg/mL$$
$$C = 89\,mg/mL \text{ after } 3\,d$$
$$t_{1/2} = 1/2(125\,mg/mL)/(0.5\,mg/mL/h)$$
$$t_{1/2} = 125\,h$$

EXAMPLE 2

How long will it take for the suspension to reach 90% of its original concentration?

$$90\% \times 125\ \text{mg/mL} = 112.5\ \text{mg/mL}$$

$$t = \frac{C - C_0}{-k_0} = \frac{112.5\ \text{mg/mL} - 125\ \text{mg/mL}}{-0.5\ \text{mg/mL/h}} = 25\ \text{h}$$

Drug suspensions are examples of pharmaceuticals that ordinarily follow zero-order kinetics for degradation.

First order reactions

- If loss of drug is **directly proportional to concentration** remaining with respect to time, it is called a first-order reaction and has the units of **reciprocal time**, that is, time^{-1}. The mathematical expression is:

$$\frac{-dC}{dt} = kC$$

where

C is the concentration of intact drug remaining,
t is time,
(dC/dt) is the rate at which the intact drug degrades, and
k is the specific reaction rate constant.

The integrated and more useful form of the equation:

$$\log C = \frac{-kt}{2.303} + \log C_0$$

where C_0 is the initial concentration of the drug.
In natural log form, the equation is

$$\ln C = -kt + \ln C_0$$

The units of k for a first-order reaction are per unit of time, such as per second.
The half-life equation for a first-order reaction is

$$t_{1/2} = 0.693 / k$$

and can be easily derived from first-order equation by substituting values of C = 50% and C0 = 100%, representing a decrease in concentration by 50%.

Example 3

An ophthalmic solution of a mydriatic drug at 5 mg/mL exhibits first-order degradation with a rate of 0.0005/day. How much drug will remain after 120 days, and what is its half-life?

$$\ln C = -(0.0005/\text{d})(120) + \ln(5\ \text{mg/mL})$$
$$\ln C = -0.06 + 1.609$$
$$\ln C = 1.549$$
$$C = 4.71\ \text{mg/mL}$$
$$t_{1/2} = 0.693 / 0.0005/\text{d}$$
$$t_{1/2} = 1,386\ \text{d}$$

- Example 4

In Example 3, how long will it take for drug to degrade to 90% of its original concentration?

$$90\%\ \text{of}\ 5\ \text{mg/mL} = 4.5\ \text{mg/mL}$$
$$\ln 4.5\ \text{mg/mL} = -(0.0005/\text{d})t + \ln(5\ \text{mg/mL})$$
$$t = \frac{\ln 4.5\ \text{mg/mL} - \ln 5\ \text{mg/mL}}{-0.0005/\text{d}}$$
$$t = 210\ \text{d}$$

Enhancing Stability of Drug Products

- Many pharmaceutical ingredients used to prepare the desired dosage form of a drug substance. Some of these agents used to achieve the desired physical and chemical characteristics of the product or enhance its appearance, odor, and taste. Other substances used to increase the stability of drug substance, against hydrolysis and oxidation.

There are several **approaches** to **stabilize pharmaceutical** preparations containing drugs subject to **hydrolysis**:

1-reduction or elimination of water from pharmaceutical system.

2- solid dosage forms containing water-labile drugs must be protected from humidity in the atmosphere. This may be accomplished by applying a waterproof protective coating over tablets or by keeping the drug in a tightly closed container. It is fairly common to detect hydrolyzed aspirin by noticing odor of acetic acid upon opening a bottle of aspirin tablets.

3-In liquid preparations, **water can frequently be or reduced in the formulation through the use of substitute liquids such as glycerin, propylene glycol**, and **alcohol**.

- In certain injectable products, anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.
- 4- hydrolysis prevented in liquid drugs by suspending them in nonaqueous vehicle rather than dissolving them in aqueous solvent. Particularly for unstable antibiotic drugs, when aqueous preparation is desired, the drug supplied in a dry form for reconstitution by adding a specified volume of purified water just before dispensing. The dry powder is mixture of antibiotic, suspending agents, flavorants, and colorants; when reconstituted by the pharmacist, it remains stable for the period of use.

5-Refrigeration is advisable for most preparations considered subject to hydrolysis. Together with temperature, pH is a major determinant of the stability of drug prone to hydrolytic decomposition. Hydrolysis of most drugs depends on relative concentrations of the hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined. For most hydrolysable drugs, optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, through use of buffering agents, the stability can be increased.

Buffers are used to maintain a certain pH

Buffer Capacity

$$pH = pK_a + \log(base / acid)$$

pH, buffers, and buffer capacity are especially important in drug product formulation, since they affect the drug's solubility, activity, absorption, and stability and the patient's comfort.

A buffer is a system, usually an **aqueous solution, that can resist changes in pH upon addition of acid or a base**. Buffers are composed of a **weak acid and its conjugate base or a weak base and its conjugate acid**. Buffers are prepared by one of these processes:

1. **Mixing a weak acid and its conjugate base or a weak base and its conjugate acid**
2. Mixing a **weak acid and a strong base** to form the conjugate base or a **weak base and a strong acid to form the conjugate acid**

Using the Henderson-Hasselbalch equation:

Remember that **acid is the proton donor** and the **base is the proton acceptor.**

Example1

A buffer is prepared by mixing 100 mL of 0.2 M phosphoric acid with 200 mL of 0.08 M sodium phosphate monobasic. What is the pH of this buffer? (K_a of phosphoric acid = 7.5×10^{-3})

Moles acid = (0.2 mol/1,000 mL) (100 mL) = 0.02 mol; (0.02 mol)/(0.3 L) = 0.067 M

Moles base = (0.08 mol/1,000 mL) (200 mL) = 0.016 mol; (0.016 mol)/(0.3 L) = 0.053 M

$pKa = -\log 7.5 \times 10^{-3} = 2.125$

pH = 2.125 + log (0.016 mol/0.02 mol) = 2.028

Pharmaceutically, **oxidation** of a susceptible drug substance is most likely to occur when it is **not kept dry in the presence of oxygen** or when it is **exposed to light** or **combined with other chemical agents** without proper regard to their influence on oxidation.

Oxidation of a chemical in a pharmaceutical preparation is usually accompanied by an **alteration in the color** of that preparation. It may also result in **precipitation** or a change in **odor**.

The oxidative process is inhibited by agents called antioxidants, which react with one or more compounds in drug to prevent progress of reaction.

- antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. Various antioxidants are employed in pharmacy.
- Among those, most frequently used in aqueous preparations are sodium sulfite (Na2 SO3 , at high pH values), sodium bisulfite (NaHSO3 , at intermediate pH values), sodium metabisulfite (Na2 S2 O5 , at low pHvalues), hypophosphorous acid (H3PO2), and ascorbic acid. In oleaginous (oily or unctuous) preparations, alpha-tocopherol, butyl hydroxy anisole, and ascorbyl palmitate find application.

- In its labeling regulations for pharmaceutical products containing sulfites, the FDA requires a warning about possible allergictype reactions, including possible life-threatening anaphylaxis symptoms and/or asthma episodes, in susceptible persons.
- Sulfites are used as preservatives in many injectable drugs, such as antibiotics and local anesthetics. Some inhalants and ophthalmic preparations also contain sulfites, but relatively few oral drugs contain these chemicals. The purpose of the regulation is to protect the estimated 0.2% of the population who are subject to allergic reactions to the chemicals. Many sulfite-sensitive persons have asthma or other allergic conditionsPrevious to the regulations dealing with prescription medication, the FDA issued regulations for the use of sulfites in food. Asthmatics and other patients who may be sulfite sensitive should be reminded to read the labels of packaged foods and medications to check for the presence of these agents.

- Sulfite agents covered by the regulations are potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide. The FDA permits the use of sulfites in prescription products, with the proper labeling, because there are no generally suitable substitutes for sulfites to maintain potency in certain medications. Some but not all epinephrine injections contain sulfites.

- The proper use of antioxidants permits their specific application only after appropriate biomedical and pharmaceutical studies.
- In certain instances, other pharmaceutical additives can inactivate a given antioxidant.
- In other cases, certain antioxidants can react chemically with the drugs they were intended to stabilize without a noticeable change in the appearance of the preparation.

- Because oxygen may adversely affect their **stability**, certain pharmaceuticals require an **oxygen-free atmosphere** during preparation and storage.
- Oxygen may be present in pharmaceutical liquids in the airspace within the container or may be dissolved in the liquid vehicle.
- To avoid these exposures, oxygen-sensitive drugs may be prepared in the **dry state** and packaged in **sealed containers** with the **air replaced by an inert gas** such as nitrogen, as may liquid preparations. This is a common practice in commercial production of vials and ampules of easily oxidizable preparations intended for parenteral use.

- Trace metals originating in the drug, solvent, container, or stopper are a constant source of difficulty in preparing stable solutions of oxidizable drugs. The rate of formation of color in epinephrine solutions, for instance, is greatly increased by the presence of ferric, ferrous, cupric, and chromic ions. Great care must be taken to eliminate these trace metals from labile preparations by thorough purification of the source of the contaminant or by chemically complexing or binding the metal through the use of specialized agents that make it chemically unavailable for participation in the oxidative process. These chelating agents are exemplified by calcium disodium edetate and EDTA.

Light can also **act as a catalyst to oxidation** reactions, , transferring its energy (photons) to drug molecules, making the latter more reactive through increased energy capability.

As a precaution against acceleration of oxidation, sensitive preparations are packaged in light-resistant or opaque containers.

Because most drug degradations proceed more rapidly as **temperature increases**, it is advisable to maintain oxidizable drugs in a cool place. Another factor that can affect stability of oxidizable drug in solution is the pH of the preparation. Each drug must be maintained in solution at pH most favorable to its stability. This varies from preparation to preparation and must be determined on an individual basis for the drug in question.

- Potassium iodide in solution is prone to photocatalyzed oxidation and the release of free iodine, with a resultant yellow to-brown discoloration of the solution.
- The use of light-resistant containers is essential to its stability.
- As a further precaution against decomposition if the solution is not to be used within a short time, the USP recommends the addition of 0.5 mg of sodium thiosulfate for each gram of potassium iodide. In the event, free iodine is released during storage, and the sodium thiosulfate converts it to colorless and soluble sodium iodide.
- Product containers, closures, and other packaging features must be considered in stability testing. For instance, tablets or capsules packaged in glass or plastic bottles require different stability test protocols from those for blister packs or strip packaging.

- Drug instability in pharmaceutical formulations detected by change in physical appearance, color, odor, taste of formula, whereas in other instances chemical changes may not be self-evident and may be ascertained only through chemical analysis.

In summary, for easily oxidizable drugs, the formulation pharmacist may stabilize the preparation by the selective **exclusion from the system:** of **oxygen**, **oxidizing agents**, **trace metals**, **light**, **heat**, and other **chemical catalysts** to oxidation process.

Antioxidants, **chelating agents**, and **buffering agents** may be added to create and **maintain a favorable pH**.

In addition to oxidation and hydrolysis, destructive processes include:

- **polymerization**,
- **chemical decarboxylation**, and
- **deamination**. However, these processes occur less frequently and are peculiar to only small groups of chemical substances.

Stability Testing

Drug and drug product stability testing during every stage of development is critical to the quality of the product.

Drug stability is important during preclinical testing and in clinical (human) trials to obtain a true and accurate assessment of the product being evaluated.

For a **marketed drug product**, assurance of stability is vital to its safety and effectiveness during the course of its shelf life and use.

FDA-required demonstration of drug stability is necessarily different for each stage of drug development, such as for a **2-week preclinical study**, an early **phase I study**, a **limited phase II trial**, **a pivotal phase III clinical study**, or for a new drug application.

As a drug development program progresses, so do the requisite data to demonstrate and document the product's **stability profile**.

- Drug product: The dosage form in the final immediate packaging intended for marketing.
- Drug substance: The unformulated drug substance that may subsequently be formulated withexcipients to produce the dosage form.
- Excipient: Anything other than the drug substance in the dosage form.
- Expiration date: The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.

- Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.
- Stress testing (drug substance): Studies undertaken to elucidate the intrinsic stability of a drug substance. Such testing is part of the drug development process and is normally carried out under more severe conditions than those used for accelerated testing.
- Stress testing (drug product): Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing as well as the specific testing of certain product types (e.g., metered dose inhalers, creams, emulsions).

- For the drug substance, the testing should evaluate its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension.
- Photostability testing should be an integral part of stress testing.
- Data should be obtained from at least three pilot-scale batches of the drug substance, manufactured by the method and procedures that mirror the process to be used for final full-scale production batches.
- Stability studies also should be conducted on the drug substance packaged in the container closure system that is the same or simulates the packaging proposed for the final product.

Accelerated testing

- Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of long-term, intermediate, and accelerated studies. Data from these studies are used to assess degradation that might occur under normal (nonexaggerated) or slight deviations in storage conditions as during shipping and storage. Results allow the development of product labeling with regard to expiration dating and recommended conditions for storage

Before approval for marketing a product's stability must be assessed with regard to its formulation;

1. influence of its pharmaceutical ingredients;
2. influence of container and closure;
3. manufacturing and processing conditions (e.g., heat);
4. packaging components;
5. conditions of storage;
6. conditions of shipping,
7. temperature,
8. light, and
9. humidity; and
10. duration and conditions of pharmacy shelf life and patient use.
11. Holding intermediate product components (such as drug granulations for tablets) for long periods before processing into finished pharmaceutical products can affect the stability of

Both intermediate component and finished product.

Therefore, **in-process stability testing**, including **retesting of intermediate components**, is important.

Product containers, closures, and other packaging features must be considered in stability testing.

For instance, **tablets or capsules packaged in glass or plastic bottles** require **different stability test protocols from those for blister packs or strip packaging**.

Drugs particularly subject to **hydrolysis** or **oxidative** decomposition must be evaluated accordingly.

And sterile products must meet **sterility test** standards to ensure **protection against microbial contamination**. All **preservatives** must be tested for effectiveness in the finished product.

- **Study stability of drug products** by:

1. **long-term storage at room temperature and relative humidity**.
2. **accelerated stability studies** as indication of shelf life stability.

Drug instability in pharmaceutical formulations may be detected by change in physical appearance, color, odor, taste, or texture of formulation, whereas in other instances, chemical changes may not be self-evident and may be ascertained only through chemical analysis.

Scientific data pertaining to stability of formulation can lead to prediction of **expected shelf life** of proposed product, and when necessary to redesign of drug (e.g., into more stable salt or ester form) and to reformulation of the dosage form. Obviously, the rate at which a drug product degrades is important.

- **study of rate of chemical change** and the way it is influenced by such factors as:

1. **concentration of drug or reactant**,
2. the **solvent,**
3. **temperature and**
4. **pressure**, and
5. **other chemical agents** in the formulation .

In general, a kinetic study begins by measuring:
the concentration of drug at given intervals under a specific set of conditions, including **temperature, pH, ionic strength, light intensity, and drug concentration.**

The measurement of the drug's concentration at the various times reveals the stability or instability of the drug under the specified conditions with the passage of time.

From this starting point, each of the original conditions may be varied to determine the influence of such changes on drug's stability.

For example, the **pH of the solution may be changed** while the **temperature, light intensity, and original drug concentration** are held **constant**.

accelerated Stability Studies

stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of environmental factors, such as **temperature**, **humidity, oxidation, light and microbial exposure**. Stability testing is also used to establish the shelf life for a drug product and recommended storage conditions

Accelerated testing:

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of long-term, intermediate, and accelerated studies.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance: The unformulated drug substance that may subsequently be formulated with excipients to produce dosage form.

Excipient: Anything other than the drug substance in dosage form.

Expiration date: **The date placed on container label** of drug product designating the time prior to which a batch of the product is expected to remain within approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Shelf life (also referred to as **expiration dating** period):The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on container label.

Stress testing (drug substance):

Studies undertaken to elucidate the **intrinsic stability of a drug** substance. Such testing is part of the drug development process and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product):**Studies undertaken to assess the effect of severe conditions on drug product**. Such studies include photostability testing as well as the specific testing of certain product types (e.g., metered dose inhalers, creams, emulsions).

For the drug substance, the testing should evaluate its **susceptibility to hydrolysis across a wide range of pH values** when **in solution or suspension**.

Photo stability testing should be an integral part of stress testing.

Data should be obtained from at least **three pilot-scale batches** of the drug substance, manufactured by the method and procedures that mirror the process to be used for final full-scale production batches.

Stability studies also should be **conducted on drug substance packaged in the container closure system** that is the same or simulates the packaging proposed for final product.

Table 4.2 EXAMPLE PROTOCOL FOR DRUG AND/OR DRUG PRODUCT STABILITY STUDIES[a]

STUDY TYPE	STORAGE CONDITION	MINIMUM TIME PERIOD
Long term	25°C ± 2°C @ 60% RH[b] ± 5% RH	12 mo
Intermediate	30°C ± 2°C @ 65% RH[a] ± 5% RH	6 mo
Accelerated	40°C ± 2°C @ 75% RH[a] ± 5% RH	6 mo

[a]For chemical entities. Adapted from Stability and Testing of New Drug Substances and Products. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf. (Accessed September 28, 2012).
[b]RH, relative humidity.

on at least **three batches of manufactured dosage** form, packaged in the container and closure system, including all secondary packaging (e.g., outer carton) proposed for marketing.

The studies should include testing product that susceptible to change during storage, thereby affecting quality and efficacy.

The testing should cover, as appropriate, the **physical, chemical, biological, and microbiological** attributes;

preservative content (e.g., **antioxidant, anti-microbial preservative**); and functionality tests (e.g., metered-dose delivery system).

Table 4.2 presents an example protocol for long-term, intermediate, and accelerated stability studies for a chemical drug entity and dosage form product.

Protocols vary for products intended to be maintained under conditions of refrigeration, for those to be

frozen, for products known to be destined for geographic areas of temperature extremes, and for biotechnological /biological products, which have separate protocols for stability studies.

Following FDA product approval and initial marketing, pharmaceutical manufacturers retain production samples of drug/drug product for **5 years or longer** and continue studies for signs of degradation under various conditions of storage.

Pharmacy practitioners should also observe **signs of product instability** (e.g., color change, distorted capsules, softened tablets, etc.) and report such findings.

Prescriptions requiring compounding by pharmacist do not require extended shelf life that commercially manufactured and distributed products do because they are intended to be **used immediately** by patient and used only during immediate course of prescribed treatment.

These compounded prescriptions must remain stable and efficacious during the course of use, and compounding pharmacist must employ formulative components and techniques that will result in a stable product.

Today, there are a number of literature sources for the pharmacist to utilize in compounding of high quality and stable prescriptions.

- Following FDA product approval and initial marketing, pharmaceutical manufacturers retain production samples of drug/drug product for 5 years or longer and continue studies for signs of degradation under various conditions of storage. Pharmacy practitioners should also observe signs of product instability (e.g., color change, distorted capsules, softened tablets, etc.) and report such findings.

- Prescriptions requiring extemporaneous compounding by the pharmacist do not require the extended shelf life that commercially manufactured and distributed products do because they are intended to be used immediately on receipt by the patient and used only during the immediate course of the prescribed treatment. However, these compounded prescriptions must remain stable and efficacious during the course of use, and the compounding pharmacist must employ formulative components and techniques that will result in a stable product. Today, there are a number of literature sources for the pharmacist to utilize in the compounding of high quality and stable prescriptions.

USP guidelines on stability

USP guidelines on stability of extemporaneous compounded formulations state that in the absence of stability information applicable to a specific drug and preparation, the following guidelines can be used:

non aqueous liquids and solid formulations when manufactured drug is the source of the active ingredient, not later than 25% of the time remaining until the product's expiration date or 6 months until the product's expiration date or 6 months, whichever is earlier.

nonaqueous liquids and solid formulations in which a USP or National Formulary (NF) substance is the source of active ingredient, a beyond-use date of 6 months.

for water-containing formulations prepared from ingredients in solid form, a beyond-use date **not later than 14 days** in storage at cold temperatures.

for all other formulations, a beyond-use date of the intended duration of therapy or 30 days, whichever is earlier .

Thus, if oral aqueous liquid preparation is made from a tablet or capsule formulation, the pharmacist should make up only at most 14 days' supply, and it must be stored in a refrigerator.

- Furthermore, the pharmacist must dispense the medication in a container conducive to stability and use and must advise the patient of proper method of use and conditions of storage of the medication.
- Finally, when compounding on the basis of extrapolated or less than concrete information, the pharmacist is well advised to keep the formulation simple and not to shortcut but use the necessary pharmaceutical adjuvants to prepare the prescription.
-

Dosage Form Design: Biopharmaceutical and Pharmacokinetic Considerations

Chapter 5

Biopharmaceutics

- Is the science that study relation of **physicochemical properties of drug**, **dosage form**, & **route of administration** on **rate and extent** of drug absorption.

pharmacokinetics

- It is the study of the kinetics of absorption, distribution, metabolism, and excretion (ADME) of drugs and their pharmacologic, therapeutic, or toxic effects in animals and man.

- drugs given IV go directly into blood.
- **elimination refers to both metabolism and. excretion.**

- **drug in blood exists in equilibrium with drug in tissues.**
- In equilibrium **concentration of the drug in blood different** (greater or lesser) than the **concentration** of the drug in tissues. This is due to the **physicochemical** properties of the drug.
-
- the rate of transfer of a drug from one compartment to another is **proportional to concentration of the drug in the compartment from which it exits**; the greater the concentration, the greater is the amount of drug transfer.

- During metabolism a drug substance may be biotransformed into:

1. pharmacologically active,
2. inactive metabolites,
3. or both.

For example, anticonvulsant drug carbamazepine is metabolized in the liver to active epoxide metabolite.

- **metabolism of drug to inactive products is irreversible process.**
- In some instances, a pharmacologically inactive drug (termed a prodrug) administered for known effects of its active metabolites.
- (k_{el}) : elimination rate constant for drug describe its rate of elimination from body.

PRINCIPLES OF DRUG ABSORPTION

Passive Diffusion:

1. From high to low concentration
2. depends on the molecule's **lipid solubility**, particle **size**, **degree of ionization**, and **area** of absorptive surface.
3. Primary mechanism for most drugs
4. No need for energy or carrier.

- ***Fick's law of Absorbtion***, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

$$\frac{dQ}{dt} = \frac{DAK}{h}(C_{GI} - C_p)$$

- Where dQ/dt = rate of diffusion, D = diffusion coefficient,
- K = lipid water partition coefficient
- A = surface area of membrane;
- h = membrane thickness, and
- $C_{GI} - C_p$ = difference between the concentrations of drug in the gastrointestinal tract and in the plasma.

- Because *D*, *A*, *K*, and *h* are constants under usual conditions for absorption, a combined constant *P* or permeability coefficient may be defined.

$$P = \frac{DAK}{h} \qquad (13.2)$$

- drug concentration in plasma, C_p, is extremely small compared to the drug concentration in the gastrointestinal tract, C_{GI}. If C_p is negligible and *P* is substituted

$$\frac{dQ}{dt} = P(C_{GI}) \qquad (13.3)$$

2-Facilitated Passive Diffusion:

1. From high to low concentration
2. Need **Carrier** in the membrane combines reversibly with the substrate molecule outside the cell membrane
3. No need for energy.
4. specific molecular configuration
5. Limited number of carrier

3-Active Transport:

1. Against concentration gradient.
2. selective,
3. requires energy
4. limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids).
5. These drugs are usually **absorbed from specific sites in the small intestine**.

Many body nutrients, such as **sugars** and **amino acids**, are transported across the membranes of the gastrointestinal tract by **carrier** processes.

Certain **vitamins**, such as **thiamine, niacin, riboflavin, and pyridoxine**, and drug substances, such as **methyldopa** and **5-fluorouracil**, require **active transport** mechanisms for their absorption.

DISSOLUTION

- The process by which a drug particle dissolves.

For a drug to be absorbed, it must first dissolved in the fluid at absorption site.

- As a drug particle undergoes dissolution, the drug molecules on the surface are the first to enter into solution, creating a saturated layer of drug solution that envelops the surface of the solid drug particle. This layer of solution is the **diffusion layer**.
- From diffusion layer the drug molecules pass throughout the dissolving fluid and make contact with biologic membranes, and absorption ensues.

- **If dissolution is rapid** or if the drug is administered as a solution the rate at which the drug becomes absorbed depends mainly on its ability **to traverse the membrane barrier**.
- **If dissolution slow** because of the physicochemical characteristics of the drug substance or dosage form, **dissolution is a rate-limiting step in absorption**.

- Drug remain in stomach :2 to 4 hours.
- In small intestine: 4 to 10 hours.

Various techniques used to determine gastric emptying time like:

- **Gamma scintigraphy**: tracking dosage forms labeled with gamma-emitting radionuclides.
- **The gastric emptying time for a drug is rapid with fasting stomach**.

1. slower as food content is increased.

Changes in gastric **emptying time** or **intestinal motility** can affect drug transit time and thus opportunity for drug dissolution and absorption.

a. **anticholinergic drug, slows gastric emptying**. Which increases drugs absorption from stomach and reduce drugs absorption from small intestine.

b. drugs that **enhance gastric motility**, for example, laxatives, **reduce** amount of drug absorbed.

c. **Aging** decrease absorption (geriatrics)

- **decrease in gastric emptying time** is advantageous for **drugs absorbed** from stomach but disadvantage for **drugs prone to acid degradation**, like penicillins and erythromycin, or **inactivated by stomach enzymes**, like L-dopa.

The rate of dissolution

- Rate of dissolution described by **Noyes-Whitney equation** :

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$

- where
- **dw/dt is the rate of dissolution,**
- **D** is the **dissolution rate constant**,
- **A** is the **surface area** of dissolving solid,
- c_s is **saturation concentration of drug** in diffusion layer (which may be approximated by the maximum solubility of the drug in the solvent, because the diffusion layer is considered saturated), and
- **c_t is the concentration of the drug in dissolution medium** at time t ($c_s - c_t$ is concentration gradient).
- **L: length of diffusion layer.**

- **rate of dissolution governed by rate of diffusion of solute through diffusion layer.**

dissolution rate increased by:

1. **increasing surface area** (reducing the particle size),
2. **by increasing the solubility of drug in diffusion layer**, by factors embodied in dissolution rate constant, D, including the **intensity of agitation of the solvent** and **diffusion coefficient of dissolving drug**. For a given drug, the diffusion coefficient and usually concentration of the drug in diffusion layer will increase with **increasing temperature.**
3. **Increasing rate of agitation of the dissolving medium** will increase the rate of dissolution.
4. **reduction in the viscosity** of solvent enhance dissolution rate of a drug.
5. **Changes in pH** or nature of solvent that influence the solubility of the drug may be used to increase dissolution rate.

Henderson–Hasselbalch equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$ **for** acidic drugs

$$pH = pKa + \log \frac{unionized}{ionized}$$ for basic drugs

- Drug movement **not always affected by pH.**
- Very weak acids and bases completely **non ionized** at physiological p H ,their transfer rapid and independent of p H. .
- strong acids and bases are completely ionized and so their transfer is usually slow and pH-independent.

- drugs include acids within the pK range 3 to 7.5 and bases in the pK range 7 to 11
- **Stomach pH: 1-2**
- **Duodenum pH: 2-4**
- **Small intestine pH: 4-6**
- **Large intestine 6-7.8**

Bases	pK_a
Amphetamine	9.8
Apomorphine	7.0
Atropine	9.7
Caffeine	0.8
Chlordiazepoxide	4.6
Cocaine	8.5
Codeine	7.9
Guanethidine	11.8
Morphine	7.9
Procaine	9.0
Quinine	8.4
Reserpine	6.6

Acids	pK_a
Acetylsalicylic acid	3.5
Barbital	7.9
Benzylpenicillin	2.8
Boric acid	9.2
Dicoumarol	5.7
Phenobarbital	7.4
Phenytoin	8.3
Sulfanilamide	10.4
Theophylline	9.0
Thiopental	7.6
Tolbutamide	5.5
Warfarin sodium	4.8

Surface area

- When a drug particle is broken up, surface area increased. For drug substances that are poorly or slowly soluble, this generally results in increase in the rate of dissolution.

- **To increase surface are**a, use **micronized** powders in their solid products. micronized powders consist of drug particles reduced in size to about **5 µm** and smaller.

Crystal or Amorphous Drug form

- Solid drug materials may occur as crystalline or amorphous.
- Amorphous usually more soluble than crystalline form, different extents of drug absorption :
- **antibiotic chloramphenicol** palmitate, are inactive when administered in crystalline, but when administered **amorphous**, absorption from GIT rapidly, with good therapeutic response.

- **In other instances:** crystalline forms of drugs may be used because of greater stability than amorphous forms.

For example, **the crystalline forms of penicillin G** as potassium salt or sodium salt are **more stable than amorphous forms**. Thus, in formulation work on penicillin G, the **crystalline forms are preferred** and result in excellent therapeutic response.

- The **amorphous**, or **Prompt Insulin Zinc Suspension**, USP, is **rapidly absorbed** upon intramuscular. The larger **crystalline** material, called **ultralente insulin** or Extended Insulin Zinc Suspension, USP, is more **slowly absorbed** and has a resultant longer duration of action.
- By combining the two types in various proportions, a physician can provide patients with intermediate-acting insulin of varying degrees of onset and duration of action. A physical mixture of **70% of the crystalline form and 30% of the amorphous** form, **called lente insulin** or Insulin Zinc Suspension, USP, is **intermediate acting** and meets the requirements of many diabetics.

- **Polymorphism:**
- Only one form of a pure drug is **stable**, the other is **metastable forms**, converting in time to the stable crystalline form. It is therefore fairly common for a metastable form of a medicinal agent to change form even in a completed pharmaceutical preparation.
- **time required for a complete change may exceed the normal shelf life of the product.**
- **any change in crystal structure of agent affect the stability and therapeutic efficacy of the product** .

- **Salt forms**
- The dissolution rate of a salt of a drug is different from that of the parent compound.
- Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve more than free acids or bases.
- The **addition of the ethylenediamine** moiety to **theophylline increases the water solubility** of theophylline **fivefold.**

- The use of the ethylenediamine salt of theophylline has allowed the development of oral aqueous solutions of theophylline.

Other factor

The state of hydration of a drug molecule can affect its solubility and pattern of absorption.

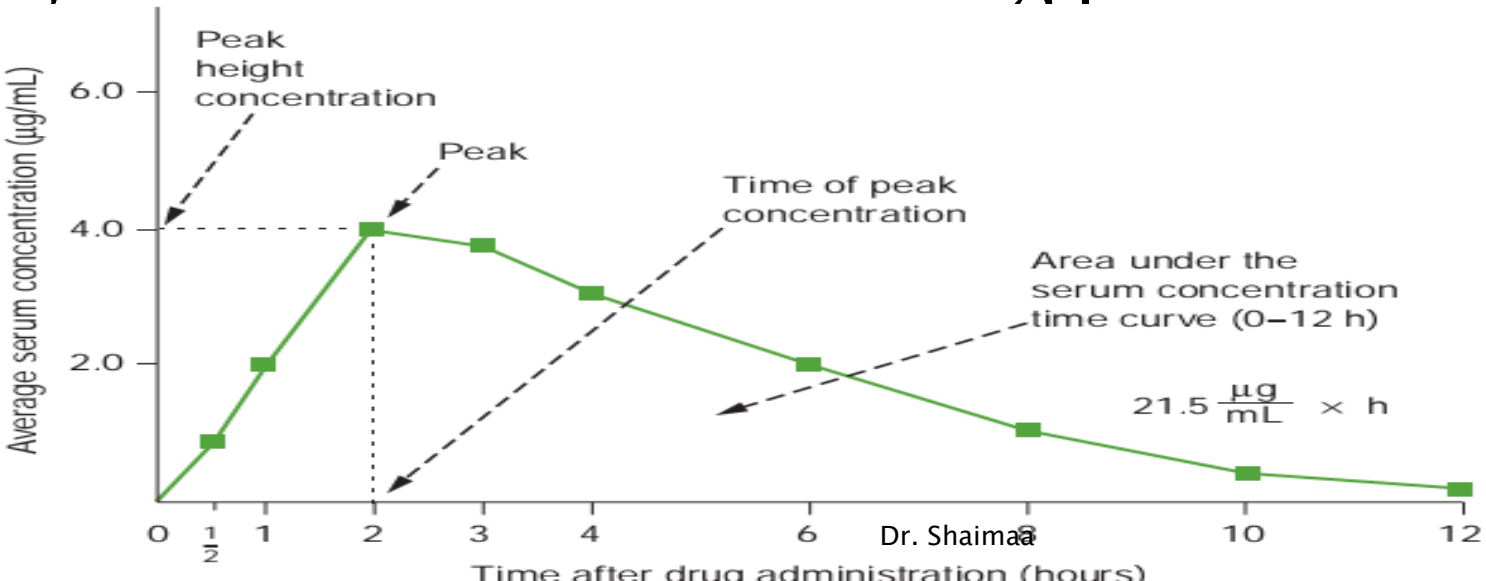
Usually, the anhydrous form of an organic molecule is more readily soluble than the hydrated form. This characteristic was demonstrated with the drug ampicillin, when the anhydrous form was found to have a greater rate of solubility than the trihydrate. The rate of absorption for the anhydrous form was greater than that for the trihydrate form of the drug.

Other factors

- A drug's solubility in GIT can be affected by **pH** also by **food**. A drug may interact with agents present to form a **chemical complex** that result in reduced drug solubility and decreased absorption.
- The classic example of this **complexation: between tetracycline and calcium, magnesium, and aluminum**, resulting in non absorbable complex so decreased absorption of the tetracycline.

Bioavailability and Bioequivalence

- **bioavailability** is the **rate and extent** of drug absorption from site of administration to the general circulation.
- The term **bioequivalence** refers to a comparison of bioavailabilities of different formulations, drug products, or batches of the same drug product.



- **Bioavailability used to determine**

1. **amount of drug absorbed** from a formulation or dosage form,
2. **rate at which the drug was absorbed**,
3. **duration of the drug's** presence in biologic fluid or tissue correlated with the patient's response, and
4. **relationship between drug blood levels and clinical efficacy and toxicity**.

During product development stage:

1. **studies bioavailability** to **compare different formulations** of the drug substance to ascertain which one allows the most desirable absorption pattern.
2. Later **bioavailability studies** used to compare the **availability of the drug** substance **in different production batches**.
3. They may also be used to compare **the availability of the drug substance in different dosage forms** (e.g., tablets, capsules, elixirs),
4. or in the **same dosage form produced by different (companies) manufacturers.**

Blood, Serum, or Plasma Concentration time curve

- Following oral administration of drug, blood samples are withdrawn at specific time intervals and analyzed for drug content.
- The vertical presents the concentration of drug in blood, and horizontal axis presents time the samples were obtained following drug administration.
- **time zero the blood concentration of drug should be zero**.
- As the drug passes into the stomach and/or intestine, dissolves, and absorbed. As the sampling and analysis continue, the blood samples reveal increasing concentrations of drug until maximum (peak) concentration (C_{max}) is reached. Then the blood level of the drug decreases.
- Absorption does not terminate after the peak blood level is reached; it may continue for some time.
- process of drug elimination is continuous. It begins as soon as the drug first appears in the blood stream and continues until all the drug has been eliminated.
- The positive or negative slope of the curve indicates which process is faster.

Parameters for assessment and comparison of bioavailability

- Following oral administration of single doses of two formulations of the same drug :
- **The peak height concentration (C_{max})**
- The time to peak concentration (T_{max})
- The area under the blood (or serum or plasma) concentration time curve (AUC)
- **C_{max} observed in blood following a dose of the drug, indicating a slope of zero**, meaning the **rates of absorption and elimination are equal**.

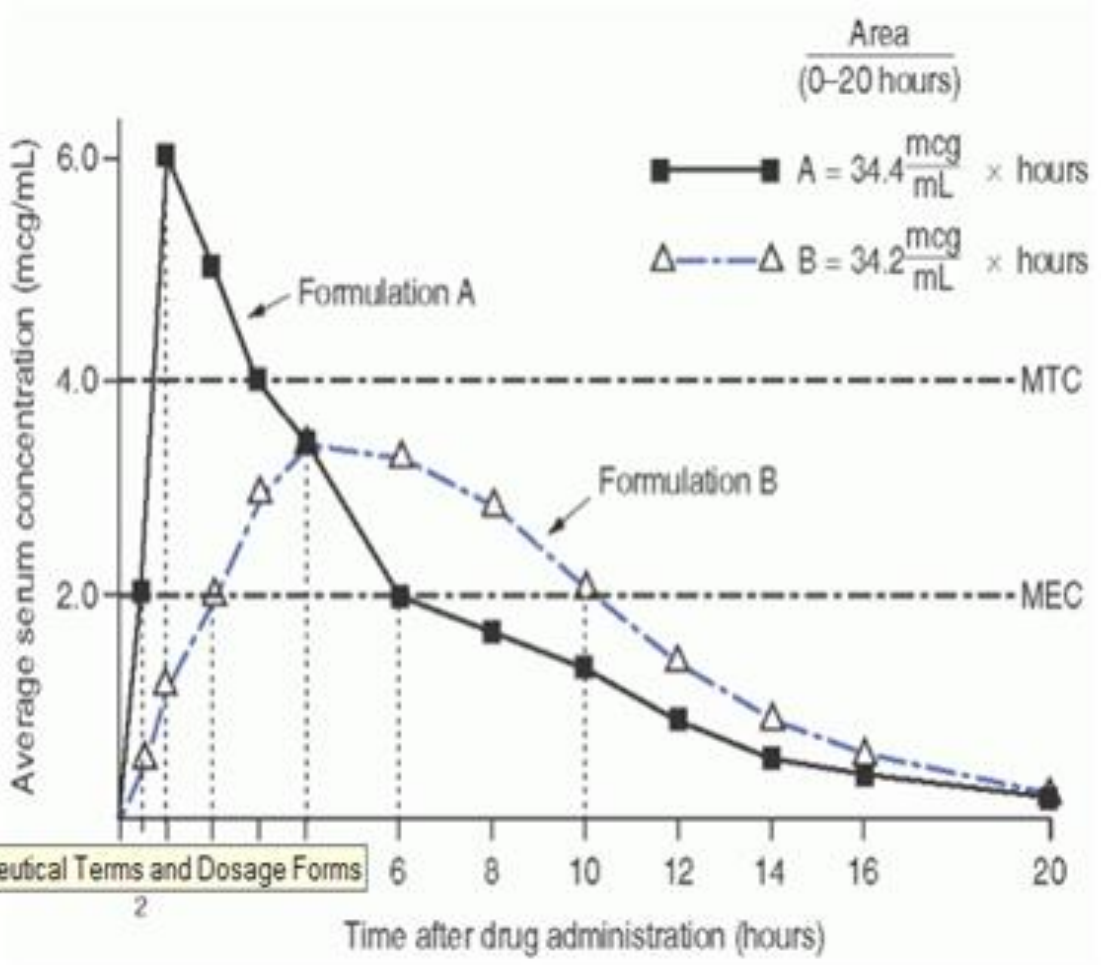


FIGURE 5.7 Serum concentration-time curve showing peak height concentrations, peak height times, times to reach MEC and areas under the curves for equal amounts of drug from two different formulations following oral administration. MEC, minimum effective concentration; MTC, minimum toxic concentration. (Courtesy of D. I. Chodos and A. R. Disanto, Upjohn.)

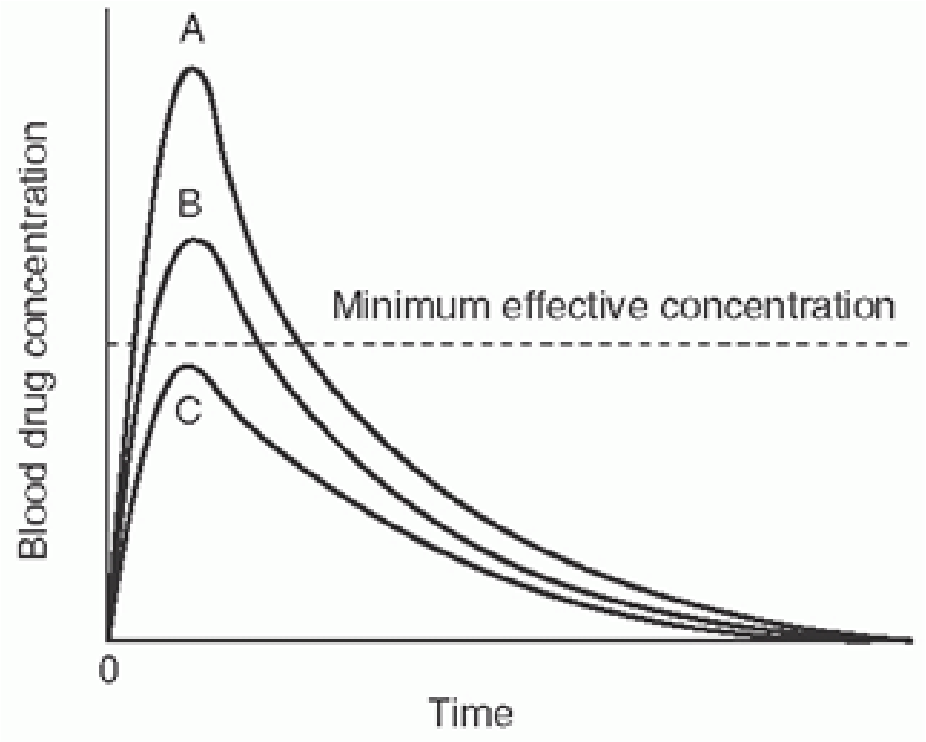


FIGURE 5.8 The influence of dose size on the blood drug concentration-time curves when three different doses of the same drug are administered and the rates of drug absorption and elimination are equal after the three doses. A, 100 mg; B, 80 mg; C, 50 mg. (Adapted with permission from Ueda CT. Concepts in Clinical Pharmacology: Essentials of Bioavailability and Bioequivalence. Upjohn, 1979.)

When the rate of absorption is decreased, the C_{max} is lowered and T_{max} occurs at a later time.

Area under the Serum Concentration Time Curve

- The AUC of concentration-time curve) represent **total amount of drug absorbed** following administration of a single dose of that drug.
- If similar doses of drug in **different formulas produce different AUC values**, differences exist in **extent of absorption** between formulations.
- In general, the smaller AUC, the lesser drug absorbed.

- F: bioavailability of orally administered drug calculated by comparison of AUC after oral administration with that obtained after intravenous administration:
- **$F = (AUC)_{oral}/(AUC)_{IV} \times DOSE\ IV/DOSE\ oral$**

- The absolute bioavailability following oral dosing is generally compared to intravenous dosing.

Bioequivalence of drug products

- Bioavailability: rate and extent to which a drug in a dosage form becomes available for biologic absorption.
- the **same drug** when formulated in **different dosage forms** have **different bioavailability** and exhibit **different clinical effectiveness**.
- Furthermore, two identical or equivalent products of **same drug** in the **same dosage strength** and in the **same dosage form** but **differing in formulative** materials or **method of manufacture** may vary widely in bioavailability and thus, in clinical effectiveness.

- **FDA uses the following terms to define type or level of equivalency between drug products.**

- **Pharmaceutical equivalents:** are drug products that **contain identical amounts of identical active ingredient**, that is, the **same salt** or ester of the **same therapeutic moiety**, in **identical dosage forms** but **not necessarily containing the same inactive ingredients**.
- **Pharmaceutical alternatives** are **drug products** that contain the **identical therapeutic moiety** or its precursor but **not necessarily in the same amount or dosage form** or as **the same salt or ester.**

- bioequivalent drug products **are pharmaceutical equivalents or pharmaceutical alternatives** whose **rate and extent of absorption are similar**.
- Some **pharmaceutical equivalents** or **pharmaceutical alternatives** equivalent in **extent absorption but not in rate of absorption** and yet may be considered **bioequivalen**t. because such differences in rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered **medically insignificant** for the drug product studied.

- **therapeutic equivalents:** used to indicate pharmaceutical equivalents that provide **same therapeutic effect** when administered to **same individuals in same dosage regimens.**

- **The most common experimental plan to compare the bioavailability of two drug products :is simple crossover design study.**
- 12 to 24 individuals carefully matched subjects (usually healthy men aged 18 to 40 years and having similar height and weight) is administered both products under fasting conditions.
- each test subject is randomly assigned one of the two products for the first phase of the study.
- Once the first assigned product is administered, samples of blood or plasma are drawn from the subjects at predetermined times and analyzed for the active drug moiety and its metabolites as a function of time.
- The same procedure is then repeated (crossover) with the second product after an appropriate interval, that is, a washout period to ensure that there is no residual drug from the first administered product that would artificially inflate the test results of the second product. Afterward, the patient population data are tabulated and the parameters used to assess and compare bioavailability; that is, C_{max}, T_{max}, and AUC are analyzed with statistical procedures. Statistical differences in bioavailability parameters may not always be clinically significant in therapeutic outcomes.
- The value in the crossover experiment is that each individual serves as his own control by taking each of the products. Thus, inherent differences between individuals are minimized.

- **Absolute bioequivalency** between drug products **rarely occurs**. Such absolute equivalency would yield serum concentration-time curves for the products that would be exactly superimposable.
- This simply is not expected of products that are made at different times, in different batches, or indeed by different manufacturers.
- In most studies of bioavailability, the originally marketed product (**brand name drug product**) is recognized as the established product of the drug and is used as the **standard for the bioavailability** comparative studies.

- According to the FDA: generic drug is considered **bioequivalent if the rate and extent of absorption do not show a significant difference from that of standard drug when administered at the same molar dose of the therapeutic ingredient under the same experimental conditions**.
- Because in the case of a systemically absorbed drug blood levels even if from identical product may **vary in different subjects**, in bioequivalence studies each subject receives both the standard and the test drug and thus serves as his own control.

Under the **1984** act, to gain FDA **approval a generic drug product** must have these characteristics:

1. **The same active ingredients** as the standard drug .
2. **Identical strength**, **dosage form**, and **route of administration**
3. The **same indications** and **precautions** for use .

- **<u>Bioequivalency</u>**
- The same batch-to-batch requirements for **identity**, **strength**, **purity**, and **quality**
- If a standard manufacturer reformulates an FDA-approved product, the subsequent formulation must meet the same bioequivalency standards that are required of generic manufacturers of that product .

- The sampling time for blood and/or urine is usually at least three times the half-life of the active drug ingredient or therapeutic moiety, its metabolite(s), or at least three times the half-life of the acute pharmacological effect.
- Measured are the peak concentration in the blood and the total area under the curve

Multiple-dose bioavailability studies

Multiple dose bioavailability studies compare **test product** and **reference** after **repeated** administration to determine steady-state levels (Css) of drug in the body. Studies are conducted in human subjects in fasting or nonfasting state, depending upon the conditions reflected in the proposed labeling of the test product.

A multiple-dose study may be required for a test product if :

(a) there is a difference in **rate of absorption** but not in extent of absorption

(b) (b) there is excessive **variability in bioavailability** from subject to subject

(c) (c) the concentration of drug or its metabolites, in blood resulting from a single dose is too low

(d) (d) the drug product is an extended-release dosage form.

A multiple-dose study is generally **crossover in design** unless scientific reasons dictate otherwise (e.g., if the study is designed to establish pharmacokinetic profile of a **new drug product**, a **new drug delivery** system, or an **extended-release** dosage form). At least **five times the half-life** of active drug ingredient, its therapeutic moiety or its active metabolite(s) is measured in the blood or urine.


THANK
YOU