HYPERTENSION

Hypertension has been labeled the "silent killer." It usually has minimal or no symptoms and typically is not regarded as a primary cause of death. Untreated hypertension increases the incidence and severity of cardiovascular diseases and stroke. Before 1950 there were no effective treatments for hypertension. U.S. Pres.Franklin D. Roosevelt died after a stroke in 1945, despite a large effort by his physicians to control his very high blood pressure by prescribing sedatives and rest.

When sulfanilamide was introduced into therapy, one of the side effects it produced was metabolic acidosis (acid-base imbalance). After further study, it was learned that the acidosis was caused by inhibition of the enzyme carbonic anhydrase. Inhibition of carbonic anhydrase produces diuresis (urine formation). Subsequently, many sulfanilamide-like compounds were synthesized and screened for their ability to inhibit carbonic anhydrase. Acetazolamide, which was developed by scientists at Lederle Laboratories (now a part of Wyeth Pharmaceuticals, Inc.), became the first of a class of diuretics that serve as carbonic anhydrase inhibitors. In an attempt to produce a carbonic anhydrase inhibitor more effective than acetazolamide,chlorothiazide was synthesized by a team of scientists led by Dr. Karl Henry Beyer at Merck & Co., Inc., and became the first successful thiazide diuretic. While acetazolamide causes diuresis by increasing sodium bicarbonate excretion, chlorothiazide was found to increase sodium chloride excretion. More importantly, by the mid-1950s it had been shown that chlorothiazide lowers blood pressure in patients with hypertension. Over the next 50 years many other classes of drugs that lower blood pressure (antihypertensive drugs) were added to the physician's armamentarium for treatment of hypertension. Partially as a result of effective treatment of this disease, the death rate from cardiovascular diseases and stroke decreased dramatically during this period.

The discovery of chlorothiazide exemplifies two important pathways to effective drug development. The first is screening for a biological effect. Thousands of drugs have been developed through effective screening for a biological activity. The second pathway is serendipity—i.e., making fortunate discoveries by chance. While creating experiments that can lead to chance outcomes does not require particular scientific skill, recognizing the importance of accidental discoveries is one of the hallmarks of sound science. Many authorities doubt that Fleming was the first scientist to notice that when agar plates were contaminated with *Penicillium* mold, bacteria did not grow near the mold. However, what made Fleming great was that he was the first to recognize the importance of what he had seen. In the case of chlorothiazide, it was serendipitous that sulfanilamide was found to cause metabolic acidosis, and it was serendipitous that chlorothiazide was recognized to cause sodium chloride excretion and an antihypertensive effect.

EARLY PROGRESS IN CANCER DRUG DEVELOPMENT

Sulfur mustard was synthesized in 1854. By the late 1880s it was recognized that sulfur mustard could cause blistering of the skin, eye irritation possibly leading to blindness, and severe lung injury if inhaled. In 1917 during World War I, sulfur mustard was first used as a chemical weapon. By 1919 it was realized that exposure to sulfur mustard also produced very serious systemic toxicities. Among other effects, it caused leukopenia (decreased white blood cells) and damage to bone marrow and lymphoid tissue. During the interval between World War I and World War II there was extensive research into the biological and chemical effects of nitrogen mustards (chemical analogs of sulfur mustard) and similar chemical-warfare compounds. The toxicity of nitrogen mustard on lymphoid tissue caused researchers to study the effect of nitrogen mustard on lymphomas in mice. In the early 1940s nitrogen mustard (mechlorethamine) was discovered to be effective in the treatment of human lymphomas. The efficacy of this treatment led to the widespread realization that chemotherapy for cancer could be effective. In turn, this realization led to extensive research, discovery, and development of other cancer chemotherapeutic agents.

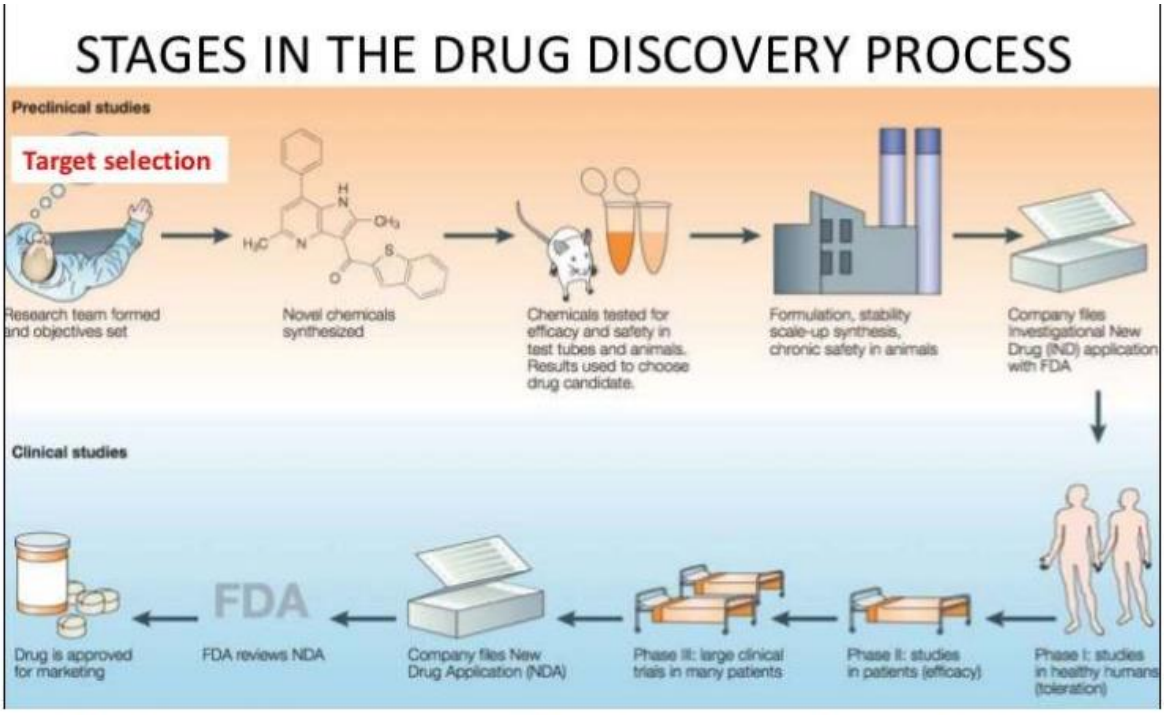
PHARMACEUTICAL INDUSTRY IN THE MODERN ERA

The pharmaceutical industry has become a large and very complex enterprise. At the end of the 20th century, most of the world's largest pharmaceutical companies were located in North America, Europe, and Japan; many of the largest were multinational, having research, manufacturing, and sales taking place in multiple countries. Since pharmaceuticals can be quite profitable, many countries are trying to develop the infrastructure necessary for drug companies in their countries to become larger and to compete on a worldwide scale. The industry has also come to be characterized by outsourcing. That is, many companies contract with specialty manufacturers or research firms to carry out parts of the drug development process for them. Others try to retain most of the processes within their own company. Since the pharmaceutical industry is driven largely by profits and competition—each company striving to be the first to find cures for specific diseases—it is anticipated that the industry will continue to change and evolve over time.

TOPIC: DRUG DISCOVERY AND DEVELOPMENT

INTRODUCTION

New drugs begin in the laboratory with scientists, including chemists and pharmacologists, who identify cellular and genetic factors that play a role in specific diseases. They search for chemical and biological substances that target these biological markers and are likely to have drug-like effects. Out of every 5,000 new compounds identified during the discovery process, approximately five are considered safe for testing in human volunteers after preclinical evaluations. After three to six years of further clinical testing in patients, only one of these compounds on average is ultimately approved as a marketed drug for treatment. The following sequence of research activities begins the process that results in development of new medicines:



- **Target Identification.** Drugs usually act on either cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease. Scientists use a variety of techniques to identify and isolate individual targets to learn more about their functions and how they influence disease. Compounds are then identified that have various interactions with the drug targets that might be helpful in treatment of a specific disease.

- **Target Prioritization/Validation.** To select targets most likely to be useful in the development of new treatments for disease, researchers analyze and compare each drug target to others based on their

association with a specific disease and their ability to regulate biological and chemical compounds in the body. Tests are conducted to confirm that interactions with the drug target are associated with a desired change in the behavior of diseased cells. Research scientists can then identify compounds that have an effect on the target selected.

- **Lead Identification.** A lead compound or substance is one that is believed to have potential to treat disease. Laboratory scientists can compare known substances with new compounds to determine their likelihood of success. Leads are sometimes developed as collections, or libraries, of individual molecules that possess properties needed in a new drug. Testing is then done on each of these molecules to confirm its effect on the drug target.

- **Lead Optimization.** Lead optimization compares the properties of various lead compounds and provides information to help biopharmaceutical companies select the compound or compounds with the greatest potential to be developed into safe and effective medicines. Often during this same stage of development, lead prioritization studies are conducted in living organisms (*in vivo*) and in cells in the test tube (*in vitro*) to compare various lead compounds and how they are metabolized and affect the body.

In the preclinical stage of drug development, an investigational drug must be tested extensively in the laboratory to ensure it will be safe to administer to humans. Testing at this stage can take from one to five years and must provide information about the pharmaceutical composition of the drug, its safety, how the drug will be formulated and manufactured, and how it will be administered to the first human subjects.

- **Preclinical Technology.** During the preclinical development of a drug, laboratory tests document the effect of the investigational drug in living organisms (*in vivo*) and in cells in the test tube (*in vitro*).

- **Chemistry Manufacturing and Controls (CMC)/Pharmaceutics.** The results of preclinical testing are used by experts in pharmaceutical methods to determine how to best formulate the drug for its intended clinical use. For example, a drug that is intended to act on the sinuses may be formulated as a time-release capsule or as a nasal spray. Regulatory agencies require testing that documents the characteristics -- chemical composition, purity, quality and potency -- of the drug's active ingredient and of the formulated drug.

- **Pharmacology/Toxicology.** Pharmacological testing determines effects of the candidate drug on the body. Toxicology studies are conducted to identify potential risks to humans.

The results of all testing must be provided to the Food and Drug Administration (FDA) and/or other appropriate regulatory agencies to obtain permission to begin clinical testing in humans. Regulatory agencies review the specific tests and documentation required to proceed to the next stage of development.

Testing of an investigational new drug begins with submission of information about the drug and application for permission to begin administration to healthy volunteers or patients.

- **Investigational New Drug (IND)/Clinical Trial Exception (CTX)/Clinical Trial Authorization (CTA) Applications.** INDs (in the U.S.), CTXs (in the U.K.) and CTAs (in Australia) are examples of requests submitted to appropriate regulatory authorities for permission to conduct investigational research. This research can include testing of a new dosage form or new use of a drug already approved to be marketed.

  In addition to obtaining permission from appropriate regulatory authorities, an institutional or independent review board (IRB) or ethical advisory board must approve the protocol for testing, as well as the informed consent documents that volunteers sign prior to participating in a clinical study. An IRB is an independent committee of physicians, community advocates and others that ensures a clinical trial is ethical and the rights of study participants are protected.

  Clinical testing is usually described as consisting of Phase I, Phase II and Phase III clinical studies. In each successive phase, increasing numbers of patients are tested.

- **Phase I Clinical Studies.** Phase I studies are designed to verify safety and tolerability of the candidate drug in humans and typically take six to nine months. These are the first studies conducted in humans. A small number of subjects, usually from 20 to 100 healthy volunteers, take the investigational drug for short periods of time. Testing includes observation and careful documentation of how the drug acts in the body -- how it is absorbed, distributed, metabolized and excreted.

- **Phase II Clinical Studies.** Phase II studies are designed to determine effectiveness and further study the safety of the candidate drug in humans. Depending upon the type of investigational drug and the condition it treats, this phase of development generally takes from six months to three years. Testing is conducted with up to several hundred patients suffering from the condition the investigational drug is designed to treat. This testing determines safety and effectiveness of the drug in treating the condition and establishes the minimum and maximum effective dose. Most Phase II clinical trials are randomized, or randomly divided into groups, one of which receives the investigational drug, one of which gets a placebo containing no medication and sometimes a third group that receives a current standard treatment to which the new investigational drug will be compared. In addition, most Phase II

studies are double-blinded, meaning that neither patients nor researchers evaluating the compound know who is receiving the investigational drug or placebo.

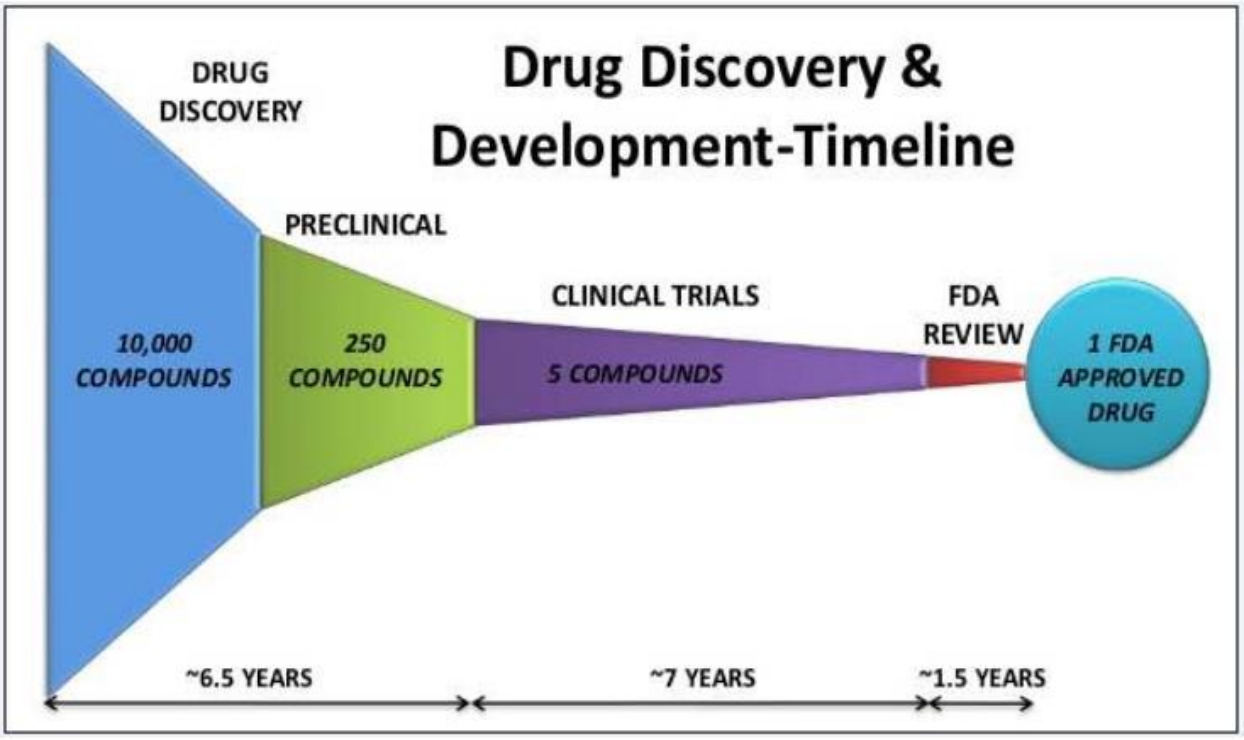
- **Phase III Clinical Studies.** Phase III studies provide expanded testing of effectiveness and safety of an investigational drug, usually in randomized and blinded clinical trials. Depending on the type of drug candidate and the condition it treats, this phase usually requires one to four years of testing. In Phase III, safety and efficacy testing is conducted with several hundred to thousands of volunteer patients suffering from the condition the investigational drug treats.

- **New Drug Application (NDA)/Marketing Authorization Application (MAA)**NDAs (in the U.S.) and MAAs (in the U.K.) are examples of applications to market a new drug. Such applications document safety and efficacy of the investigational drug and contain all the information collected during the drug development process. At the conclusion of successful preclinical and clinical testing, this series of documents is submitted to the FDA in the U.S. or to the applicable regulatory authorities in other countries. The application must present substantial evidence that the drug will have the effect it is represented to have when people use it or under the conditions for which it is prescribed, recommended or suggested in the labeling. Obtaining approval to market a new drug frequently takes six months to two years.

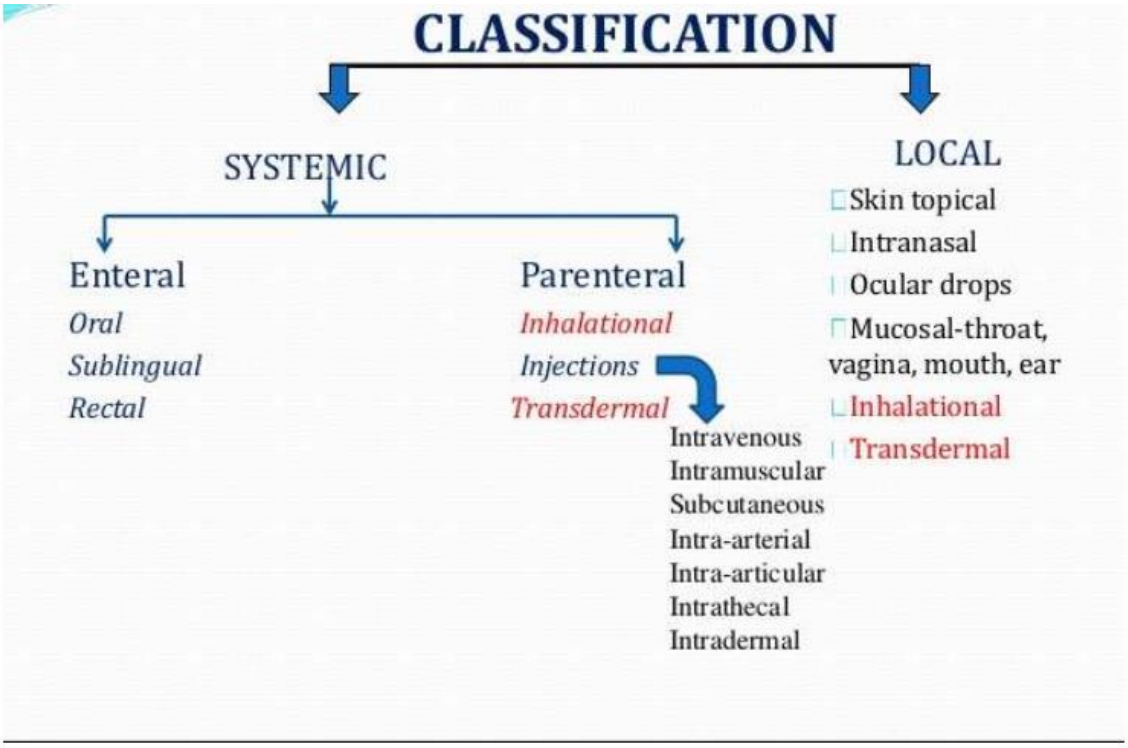
  After the FDA (or other regulatory agency for drugs marketed outside the U.S.) approves a new drug, pharmaceutical companies may conduct additional studies, including Phase IIIb and Phase IV studies. Late-stage drug development studies of approved, marketed drugs may continue for several months to several years.

- **Phase IIIb/IV Studies.** Phase IIIb trials, which often begin before approval, may supplement or complete earlier trials by providing additional safety data or they may test the approved drug for additional conditions for which it may prove useful. Phase IV studies expand testing of a proven drug to broader patient populations and compare the long-term effectiveness and/or cost of the drug to other marketed drugs available to treat the same condition.

- **Post-Approval Studies.** Post-approval studies test a marketed drug in new age groups or patient types. Some studies focus on previously unknown side effects or related risk factors. As with all stages of drug development testing, the purpose is to ensure the safety and effectiveness of marketed drugs.



Routes of drug administration



1. Enteral—Entering Intestinal/Digestive Tract

Oral

The mouth route is the most commonly used route of drug administration due to the ease in which the drugs can be taken. This method also provides the most difficult pathway for the drug to reach the targeted area. Drugs which are taken orally have a high chance of incurring the first-pass effect—also known as first-pass metabolism, which refers to the drug concentration being reduced before arriving at the systemic circulation.

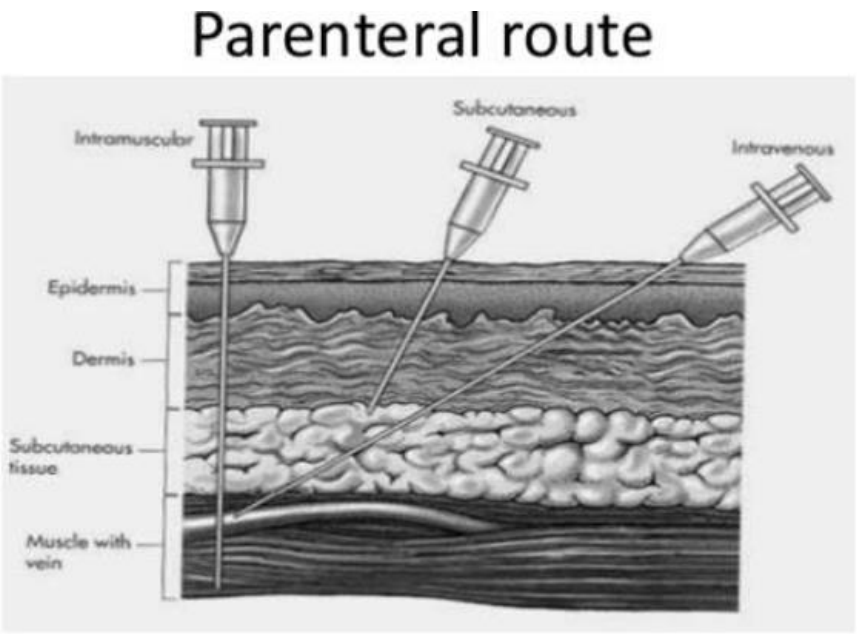
Rectal

Rectal administration can deliver both systemic and local effects, although it has proven to be rather ineffective at times. This type of administration can be useful for those who find it difficult to swallow, or keep down medication, for example, people with vomiting condition.

Sublingual

Although this type of administration does not lead to the drug entering the gastrointestinal tract, it is placed under the tongue, therefore, it is considered oral and enteral. The medication rapidly diffuses into the network of capillaries, directly entering the system circulation.

2. Parenteral—Medication That Avoids the Gastrointestinal Tract



Intravenous (IV)

This is the most common parenteral route of drug administration, which is often administered when a quick effect is required from the drug. This method involves injecting the medication straight

into systemic circulation. However, there are numerous drawbacks to this method, including giving too high a concentration of the medication.

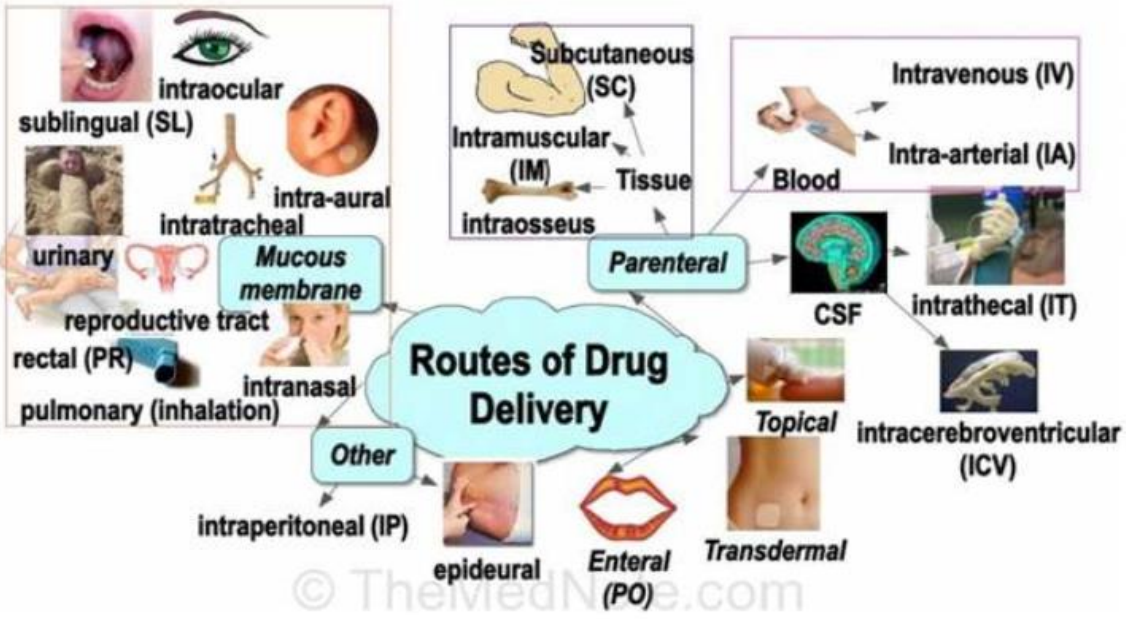
Intramuscular (IM)

This method of drug administration offers patients with a faster effect than medication that is taken orally. Through this route, the drug can be in aqueous or depot form. But the aqueous can be absorbed faster than depot form. Besides, the amount and rate of absorption are highly dependent on local blood flow and where the injection is made.

Subcutaneous (SC)

Much like IM injections, SC injections need similar absorption. This route of drug administration is slower to take effect than IV, but also has reduced risks.

3. Other Routes



- **Inhalation:** This route is typically used for drugs that are gaseous, or for medications that can be given in aerosol, such as an asthma pump. This form of administration offers almost instantaneous effects.
- **Intranasal:** This is the term given to medications that are administered through the nose.
- **Topical:** Medication that is supplied exactly when and where it is required or desired.
- **Transdermal:** This is the term given to medication that is absorbed through the skin, the rate of absorption, however, is dependent upon an individual's skin characteristics.

- **Intrathecal/Intravetricular:** For this route, the medication is administered into cerebrospinal fluid.

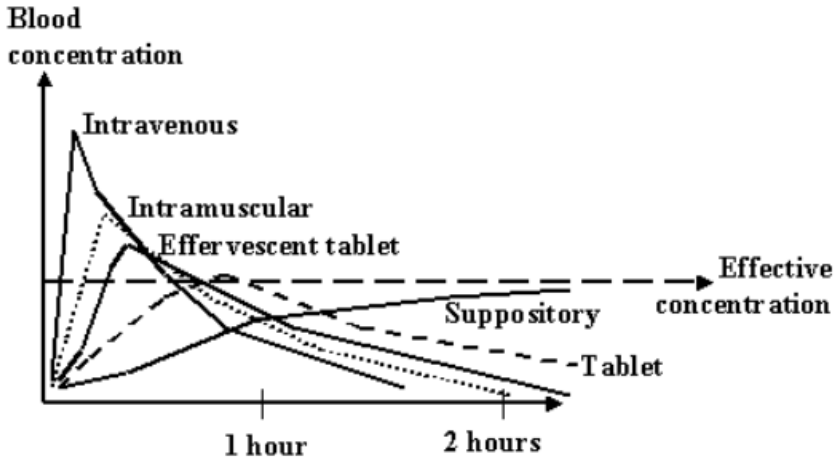
Drug Administration on Dosage and Time

Dosage

To correctly determine how much of a medication you should be taken, you should always seek advice from a medical professional. Although most medications advise the recommended dosage within the instructions, you should still have a consultation with your doctor before proceeding. It can be very difficult to determine the correct dosage of medication when treating many illnesses and many factors can affect your required dosagesuch as your age and physical state, etc.

Time

It is also important to know when to take the medication. Many types of treatments require the medication to be taken consistently at precises times, or with precise intervals between each dosage. If these strict guidelines are not followed, then the treatment may prove to be ineffective.



Pros & Cons of Different Routes of Drug Administration

1. Oral

Pros: Easily administered; preferable to patients; slow-release medications may extend the duration of the effect; medications are formulated to avoid stomach acids and digestive enzymes.

Cons: Unsuitable for those who are experiencing severe vomiting or have difficultyswallowing. Also, because it is absorbed slowly, this route is not fast acting. And unpredictable effect due to stomach acids and digestive enzymes should be noticed.

2. Rectal

Pros: Absorption rate is good as the haemorrhoidal veins connect and drain straight into the inferior vena cava.

Cons: Disliked by some patients; not suitable for those who have undergone anal or rectal surgery/injury.

3. Subcutaneous or Intramuscular

Pros: Absorption is good; effect of medication happens quicker than many other routes of drug administration; can have extended duration of medicinal effect, depending on formulation.

Cons: Absorption can be unpredictable; injections may hurt or scare patients (especially children).

4. Intravenous

Pros: Offers a very dependable effect, drugs reaches the systemic circulation instantaneously.

Cons: Requires specialist equipment; requires more work from health care professionals than other routes; can be unnerving to some patients; disposed to t infection; may cause adverse reactions.

5. Topical

Pros: Easy to administer; extremely un-invasive; high rate of patient satisfaction.

Cons: Very slow rate of absorption.

6. Inhaled

Pros: Extremely high rate of absorption.

Cons: Effectiveness depends upon the patient's inhaler, and their technique when using it.