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Dosage Form Design

By
Dr. Mohammed Sattar
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Outlines

- Pharmacokinetic principles
  - Volume of distribution
  - Half life
  - Clearance
  - Dosage regime

2

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Pharmacokinetic Principles

- **Pharmacokinetic analysis utilizes mathematical models to simplify or simulate the disposition of the drug in the body.**
- **The principal assumption is that the human body may be represented by one or more compartments in which a drug resides in a dynamic state for a short period of time.**

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Assumptions for models

1. The volume of each compartment remains constant.
2. Once a drug enters the compartment, it is instantaneously and uniformly distributed throughout the entire compartment.

4

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Volume of distribution

- Each drug has its own distinct **Vd**,
- Influenced by
  - age and disease status.
- IV, it is assumed that the drug distributes immediately to tissues and instantly attains equilibrium.
- Oral administration, the drug is absorbed at a certain rate and is characterized by the absorption rate constant K_a. Finally, the drug is eliminated from the compartment at a certain rate that is characterized by an elimination rate constant, K_{el}.

5

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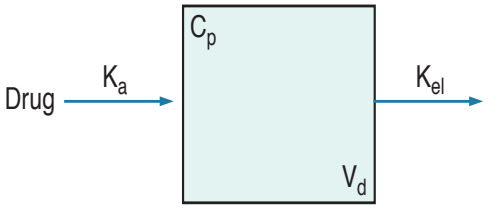
Volume of distribution

- **Vd** is a proportionality constant that refers to the volume into which the total amount of drug in the body must be uniformly distributed to provide the concentration of drug actually measured in plasma or blood.
- This term can be misleading because it does not represent a specific body fluid or volume. It is influenced by the **plasma protein binding** and **tissue binding** of a drug and **water-fat distribution** (according to log p) .
- These then influence the distribution of the drug between **plasma water**, **extracellular fluid**, **intracellular fluid**, and **total body water**.

6

- **The simplest pharmacokinetic model is the single compartment open-model system.**
- **This model depicts the body as one compartment characterized by a certain volume of distribution (Vd) that remains constant.**
- Why open?



Where:
C_p is the drug concentration in plasma
V_d is the volume of the compartment or volume of distribution

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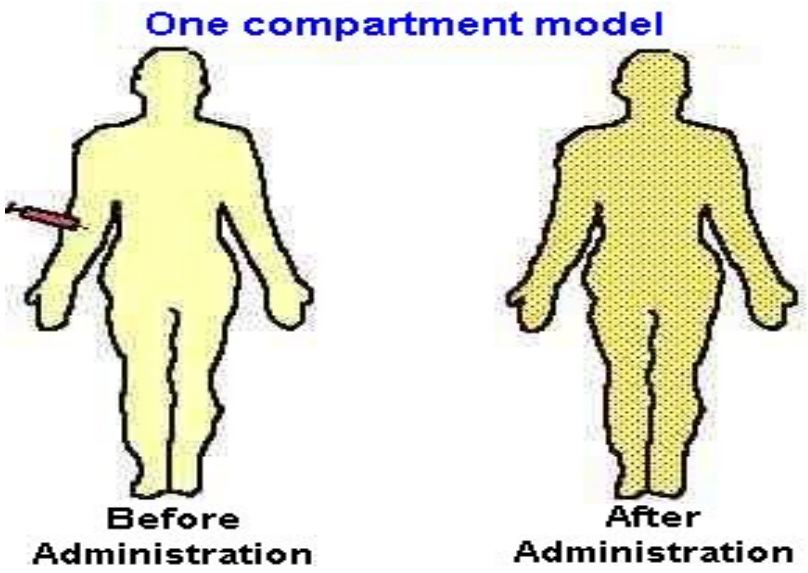

8

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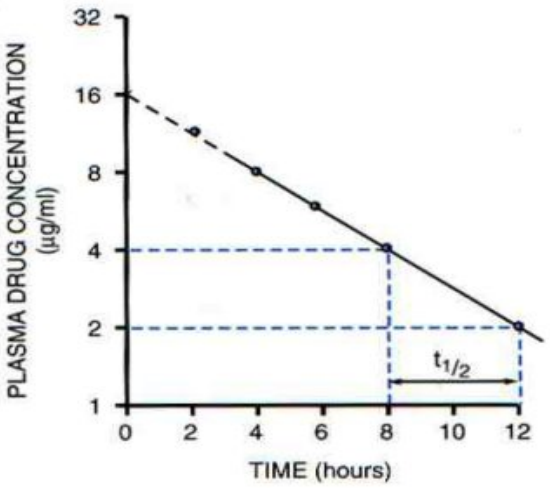
For drugs whose distribution follows first-order, one-compartment pharmacokinetics, a plot of the logarithm of the concentration of drug in the plasma (or blood) versus time will yield a straight line.



9

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The equation that describes the plasma decay curve is

$$C_p = C_0 e^{-K_{el}t}$$

$$\text{Log}C_p = \text{Log}C_0 - (K_{el} * t)/2.303$$

- **Where**
  - K_{el} **is the first-order rate of elimination of the drug from the body,**
  - C_p **is the concentration of the drug at time equal to t,**
  - C_0 **is the concentration of drug at time equal to zero.**

- **Note:**

K_{el} **is independent of the dose, the volume of distribution, and the route of administration.**

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- Most drugs administered orally can be adequately described using a one-compartment model.
- Drugs administered by rapid intravenous infusion are usually described by a two-compartment or three compartment model system.

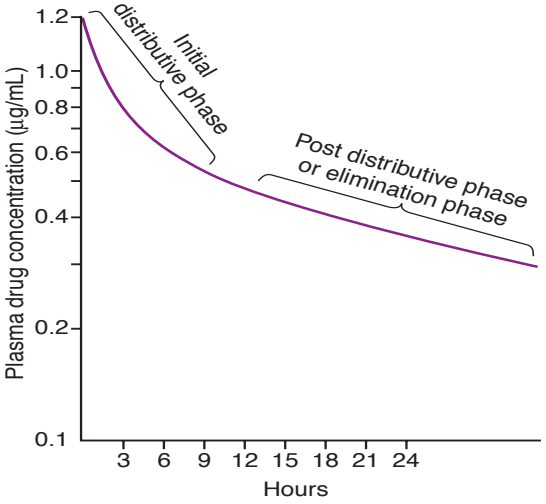

FIGURE 5.14 A semilogarithmic plot of plasma concentration versus time of an intravenous drug that follows first-order two-compartment pharmacokinetics.

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- One-compartment system : drug is confined to the plasma (or blood) and then excreted.
- Drugs that exhibit this behavior have **small Vd**.
- For example, a drug such as **warfarin sodium**, which is extensively bound to plasma albumin, will have a Vd equivalent to that of plasma water, about **2.8 L** in an average 70- kg adult.
- Some drugs, however, are initially distributed at somewhat different rates in various fluids and tissues. Consequently, these drugs' kinetic behavior can best be illustrated by considering an expansion of the one-compartment system to the *two-compartment model*

12

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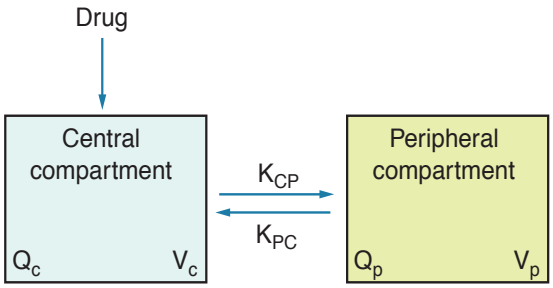
- **In the two-compartment system, a drug enters into and is instantaneously distributed throughout the central compartment.**
- **Its subsequent distribution into the second or peripheral compartment is slower.**



Where:
Q_c = Quantity of drug in central compartment
V_c = Volume of the central compartment
Q_p = Quantity of drug in peripheral compartment
V_p = Volume of the peripheral compartment

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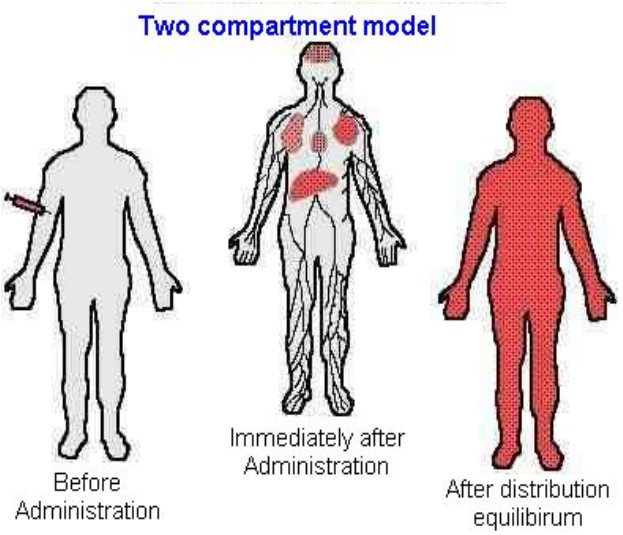
The central compartment is usually considered to include the **blood**, **the extracellular space**, and **organs with good blood perfusion**, e.g., lungs, liver, kidneys, heart.



14

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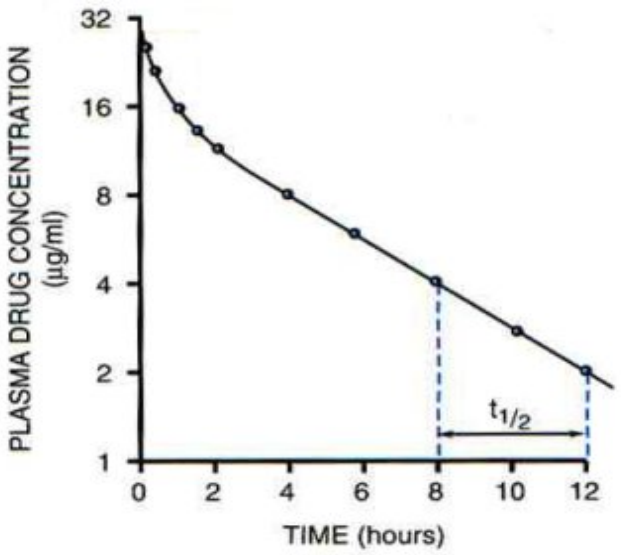
- **Note the initial steep decline of the plasma drug concentration curve.**
- **This typifies the distribution of the drug from the central compartment to the peripheral compartment.**



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Residual method

A semi-logarithmic plot of Cp vs t after rapid IV of a drug which is best described by a two-compartment model system can often be resolved into two linear components.

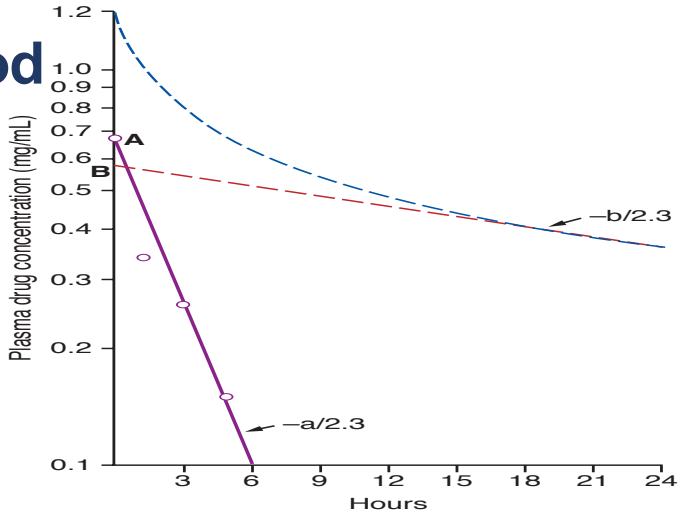

FIGURE 5.16 The logarithm of the drug concentration in plasma plotted versus time (*solid line*) after intravenous administration of a drug whose disposition can be described by a two-compartment model.

16

- The slope of the feathered line (-a/2.303) and the extrapolated line (-b/2.303) and the intercepts, A and B, are determined.

$$C_p = Ae^{-at} + Be^{-bt}$$

- This is a bi-exponential equation which describes the two-compartment system.

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Half Life

- The half-life ($T_{1/2}$) of a drug describes the time required for a drug's blood or plasma concentration to decrease by one half.

- The biological half-life of a drug in the blood may be determined graphically off of a pharmacokinetic plot of a drug's blood-concentration time plot, typically after intravenous administration to a sample population.

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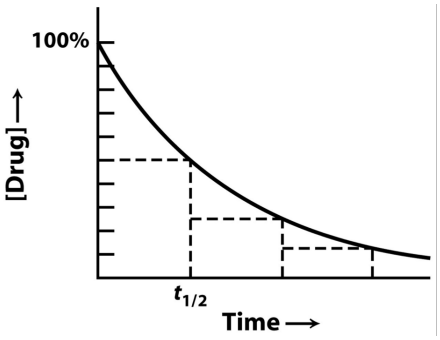
Half life of drugs

- Time required for the drug reach its half concentration in the body after administration



19

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Half life of drugs

$$\frac{K_{el}t}{2.303} = \text{Log } C_p^0 - \text{Log } C_p = \frac{\text{Log } C_p^0}{C_p}$$

$$\frac{K_{el}t}{2.303} = \frac{\text{Log } C_p^0}{0.5\ C_p^0} = \text{Log } 2$$

$$t_{1/2} = \frac{2.303\ \text{Log } 2}{K_{el}} = \frac{0.693}{K_{el}}$$

20

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Half life of drugs

- Half life measurement gives an idea about the elimination capacity of the body.
- Data on a drug's biologic half-life are useful in determining the most appropriate dosage regimen.

21

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Half life of drugs

- Exceptions are in case of renal or hepatic abnormal function.
  - Digoxin half life when renal function is normal is 1.5-2 days.
  - Digoxin half life in anuric patient is 4-6 days.

22

Half life of drugs

- For theophylline:

Physiological condition	Half life
Premature with immature liver enzyme systems	14-58 hrs
Children aged 1-4 years	2-5.5 hrs
Adult non-smokers	6.1-12.8 hrs
Adult smokers	4.3 hrs

23

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Half life of drugs

- Smoking induces theophylline metabolism.
- Smokers may require a 50% to 100% increase in theophylline dose.
  - The time required to normalize the effect of smoking on theophylline metabolism in the body once the patient stops smoking may range from 3 months to 2 years.

24

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Clearance

The three main mechanisms by which a drug is removed or cleared from the body include

1. The hepatic metabolism, i.e., **hepatic clearance**, Cl_h, of a drug to either an active or inactive metabolite,
2. The renal excretion, i.e., **renal clearance**, Cl_r, of a drug unchanged in the urine,
3. Elimination of the drug into **the bile** and subsequently into the intestines for excretion in feces.

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Clearance

Fraction of the total volume of distribution that can be cleared from the drug per unit of time.

In the one compartment model described earlier, total body clearance is the product of the volume of distribution, V_d, and the overall rate of elimination, k_{el}:

$$Cl_B = V_d \; k_{el}$$

$$t_{1/2} = 0.693 V_d / Cl_B$$

$$t_{1/2} = 0.693 V_d / (Cl_h + Cl_r)$$

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Dosage regimen considerations

• Approaches to the development of a dosage regimen

1. Empirical approach.

2. Use of pharmacokinetics, or the kinetic approach .

27

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Dosage regimen considerations

• Empirical approach

- Administration of a drug in a certain quantity.
- Noting the therapeutic response.
- Modifying the amount and interval of dosage accordingly.

28

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Dosage regimen considerations

- Empirical therapy is usually employed when:
  - the drug concentration in serum or plasma does not reflect the concentration of drug at the receptor site
  - the pharmacodynamic effect of the drug is not related (or correlated) with drug concentration at the receptor site.

29

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Dosage regimen considerations

- Empirical therapy is used for many anticancer drugs.
  - ➢Demonstrate effects long after they have been excreted from the body.
  - ➢It is difficult to relate the serum level of these drugs with the desired therapeutic effect.

30

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Dosage regimen considerations

- Use of pharmacokinetics, or the kinetic approach .
- **It is based on the assumption that the therapeutic and toxic effects of a drug are related to the amount of drug in the body or to the plasma concentration of drug at the receptor site.**
- **Through careful pharmacokinetic evaluation of a drug's absorption, distribution, metabolism and excretion in the body from a single dose, the levels of drug attained from multiple dosing can be estimated.**

31

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When one considers the development of a dosage regimen, a number of factors that should be considered

1) **Inherent activity, i.e., pharmacodynamics, and toxicity, i.e., toxicology of the drug.**
2) **The pharmcokinetics of the drug, which are influenced by the dosage form in which the drug is administered to the patient, e.g., biopharmaceutical considerations.**

3) The patient to whom the drug will be given and encompasses the clinical state of the patient and how the patient will be managed.

4) Atypical factors may influence the dosage regimen.

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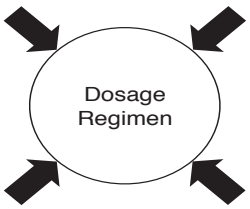
Factors that determine a dosage regimen

ACTIVITY, TOXICITY
Minimum therapeutic dose
Toxic dose
Therapeutic index
Side effects
Dose–response relationships



PHARMACOKINETICS
Absorption
Distribution
Metabolism
Excretion

CLINICAL FACTORS

Clinical State of Patient
Age, weight, urine pH
Condition being treated
Existence of other disease states

Management of Therapy
Multiple drug therapy
Convenience of regimen
Compliance of patient

OTHER FACTORS
Tolerance–dependence
Pharmacogenetics–idiosyncrasy
Drug interactions
Life style factors, for example, diet, recreational drug use

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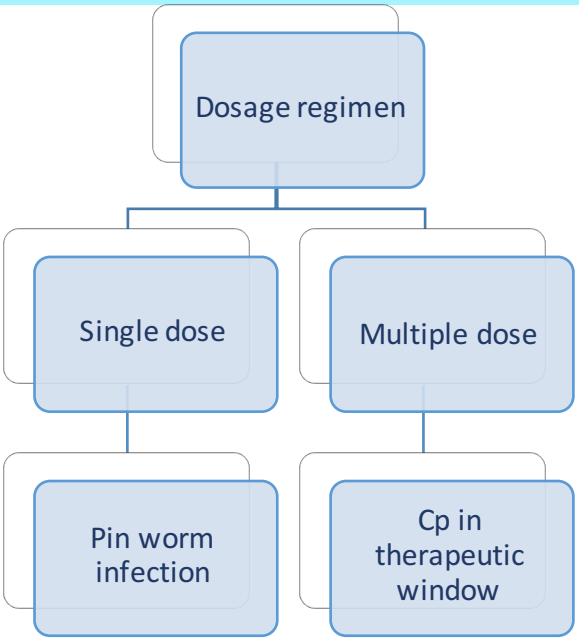

35

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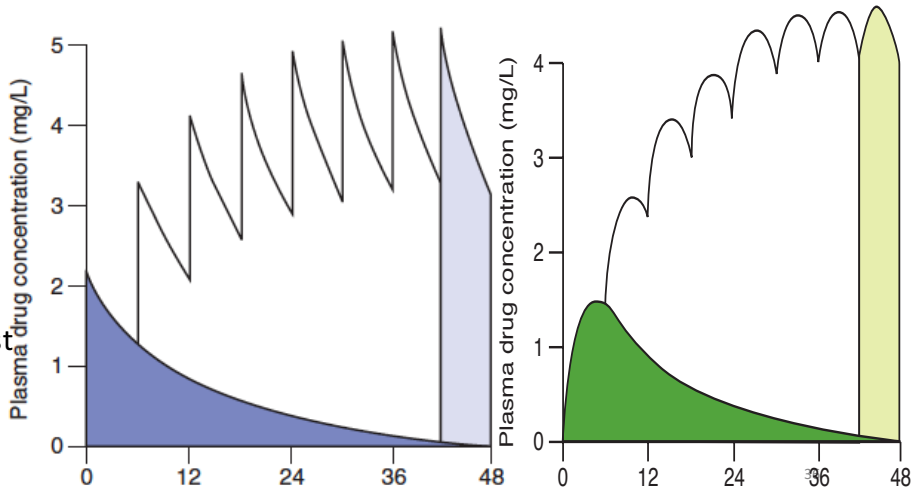
Example on dosage regimen

- 50mg of the drug was given.
- In a 8 hr interval.
- Half life is 12 hrs.
- Amount of drug lost per interval is replenished when the drug is dosed again.



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Theophylline dosage regimen

- Theophylline plasma conc in asthmatic patient must be between 10 and 20 μ g/mL.
- It is preferable to give theophylline around the clock four times daily to sustain levels at least above the MEC.

37

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Theophylline dosage regimen

- If this medicine is administered only every 4 hours during the waking hours, it is possible that the minimum concentration will fall below MEC between the bedtime dose and the morning dose.
- Asthma attacks at night

38

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Pharmacokinetic dosing services?

- Maximize drug efficacy,
- Minimize toxicity,
- Keep health care costs at a minimum.

39

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Pharmacokinetic dosing services?

- After physician prescribes the drug:
  - Pharmacist determines the sampling time
  - Interprets the results
  - Consults with the physician regarding subsequent dosages.

40

Questions

1. What are general principles of drug absorption ?
2. Write Henderson-Hasselbalch equation and explain it.
3. What is Noyes-Whitney equation?
4. What factors could affect drug absorption?
5. Describe the routes of drug administration and their characteristics ?
6. What is biotransformation ? What are the biochemical mechanisms of biotransformation?
7. Explain shortly about one compartment model and two compartment model ?
8. How to develop dosage regimens ?