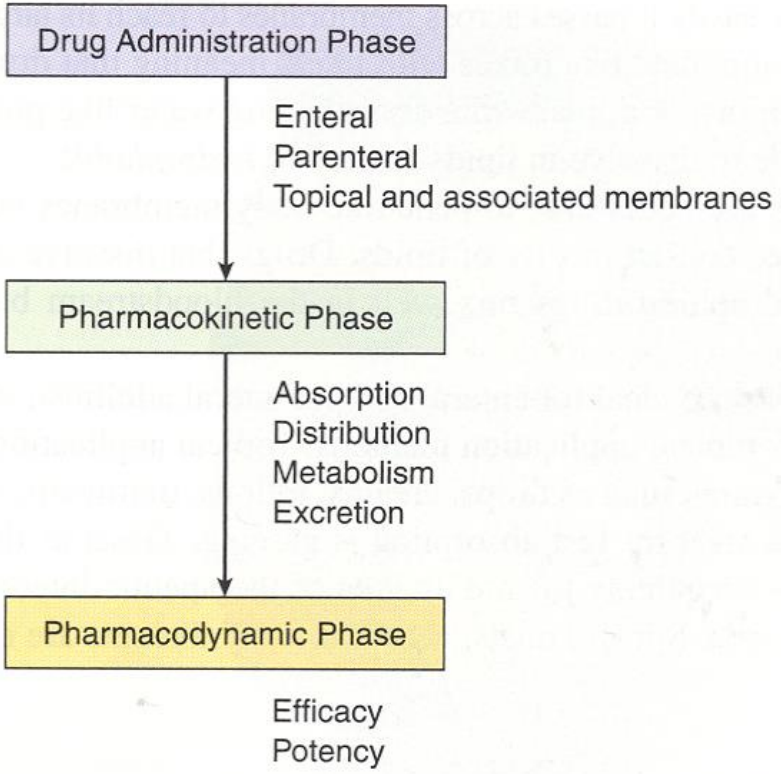
CP4163 Pharmacology and Pharmaceutical Chemistry

Topic 9 –Pharmacokinetics and Drug Administration

Drug Delivery System

- The process of delivering drugs to the body's tissues involves 3 separate phases:

- Pharmaceutical phase (Drug administration)
- Pharmacokinetic phase (ADME)
- Pharmacodynamic phase (Drug-receptor)



Drug Delivery

Drug Administration Phase **or Pharmaceutical Phase**

- **how drugs are introduced into the body**
  - drug preparations (dosage forms) depend on medication form

Pharmacokinetic Phase ***How the body handles the drug***

how administered drugs move to the target sites
- drug absorption, distribution, metabolism, elimination (ADME)
- drug bioavailability

Pharmacodynamic Phase ***What the drug does to the body***

- **drug effect at the target sites**
  - drug-receptor interaction
  - drug action at enzymes and nucleic acids
  - agonists and antagonists

Pharmaceutical Phase

Pharmaceutical Phase

- This is sometimes also called the drug administration phase, is the means by which drugs are introduced into the body. Choices vary depending on:

What form?

(i) pharmaceutical formulation /dosage form of drug

(ii) appropriate route of administration.

From where?

(i) Drug formulation/dosage form

- **Dosage Form**
  - the form in which a drug is administered
  - subdivided according to physical nature into formulations

(i) Drug formulation/dosage form

Formulations

liquids

- e.g. solutions, suspensions, emulsions

- move quickly throughout body
- but must penetrate membranes to produce effect

semisolids

- e.g. creams, ointments, gels

solids

- e.g. tablets, capsules, suppositories.

solids must disintegrate & dissolve before they can become active

slow onset of action

gases

- e.g. sprays, mists, aerosols, inhalers

- **fastest absorption rate**
  - less compacted
  - move to target site more easily

(i) Drug formulation/dosage form

- **Dosage Form**
  - active ingredient (drug, API)
  - inert ingredients (excipients)
- **Excipients**
  - serves a number of functions, e.g.
    - fillers (bulk forming)
    - lubricants (reduce frictional wear on processing equipment)
    - binders (aid adhesion of particles in formulation)
    - disintegrants (aid release of active ingredient)
    - preservatives (extend shelf life)
  - exert significant effect on release of active ingredient from dosage form

(i) Drug formulation/dosage form

- **Dosage Regimen**
  - **dose of a drug and how it is administered**
  - vary
    - from single dose
    - to regular daily doses
    - to continuous IV infusions
  - designed to maintain the drug concentration within the **therapeutic window or range** at site of action

(i) Drug formulation/dosage form

Example:

Amoxicillin, 50mg
1 Capsule, 3 times daily

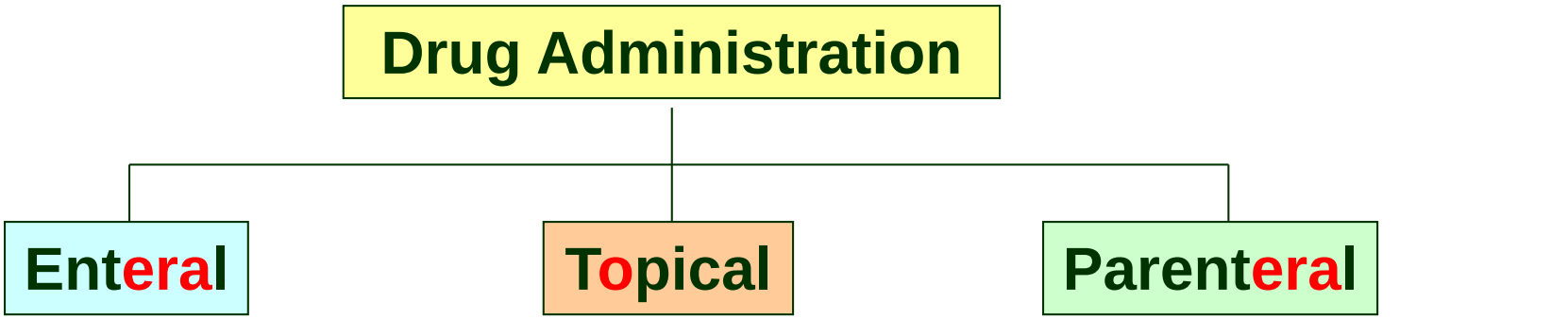
(Given 12 capsules in packet)

It means dose of drug = 50mg. 2 capsules – Dose = 100mg

It is administered orally, 1 capsule , 3 times a day for 4 days

(ii) Routes of Drug administration

3 Main Routes of Administration



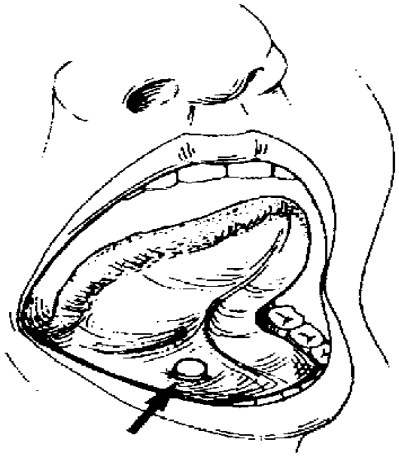
Note common spelling **errors**

(ii) Routes of Drug administration

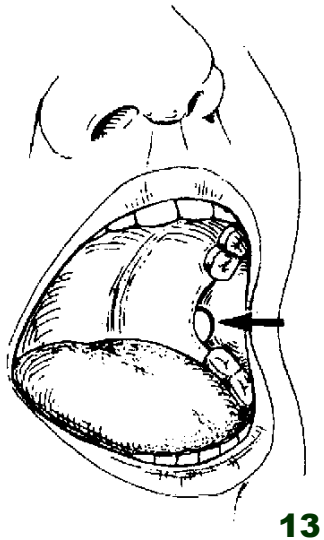
- **Enteral Administration**
  - **Advantage**
    - **large absorptive surfaces of oral mucosa (mouth), stomach or small intestine**
  - Oral e.g. tablets, capsules
    - most common, most convenient, usually least costly
    - skin's protective barrier not broken $\Rightarrow$ safe
  - **Disadvantages**
    - some drugs get **inactivated** by gastric acid & digestive enzymes
    - drugs must first travel to the liver (**1st pass effect**) before entering the general circulation to reach the target site

(ii) Routes of Drug administration

- **Enteral Administration**
  - **Sublingual**
    - placed under the tongue & allowed to dissolve slowly
    - rich blood supply under tongue ⇒ **rapid onset of action**
    - formulations
      - rapidly disintegrating tablets, soft gelatin capsules filled with liquid drug

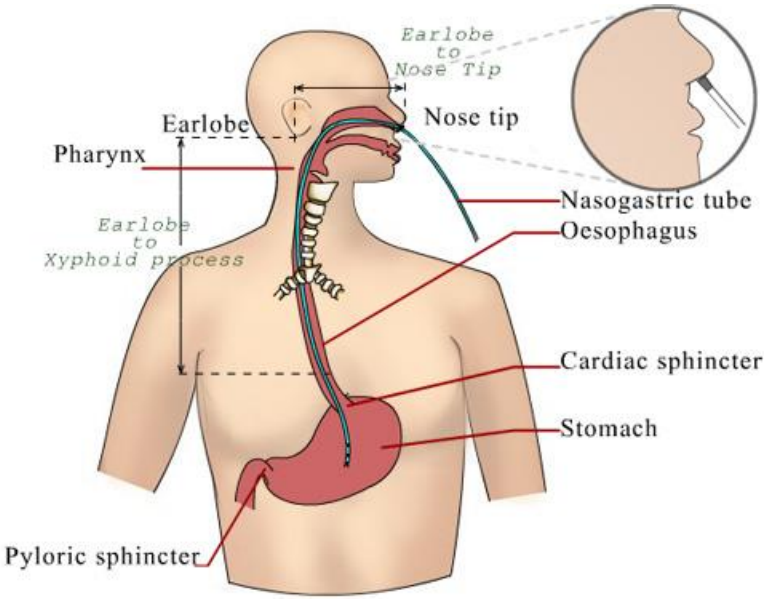


  - **Buccal**
    - placed in the oral cavity between the gum & cheek
    - **absorbed more slowly than sublingual route**
    - suitable for sustained-release drug delivery
      - e.g. nicotine chewing gum for smoking cessation



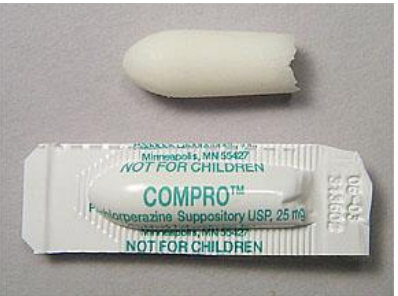
(ii) Routes of Drug administration

- **Enteral Administration**
  - **Nasogastric** (NG)
    - NG tube = nose → → → stomach
    - drugs are usually in liquid form



(ii) Routes of Drug administration

- **Topical Administration**
  - drugs applied locally to:
    - skin, eye, ear, nose, respiratory tract, rectum
  - **Formulations**
    - creams, lotions, gels, powders, sprays, drops, inhalers
  - **Effect can be**
    - **local - effect only at site of application, very small amounts absorbed into the general circulation**
    - **systemic - drug released and absorbed into general circulation**



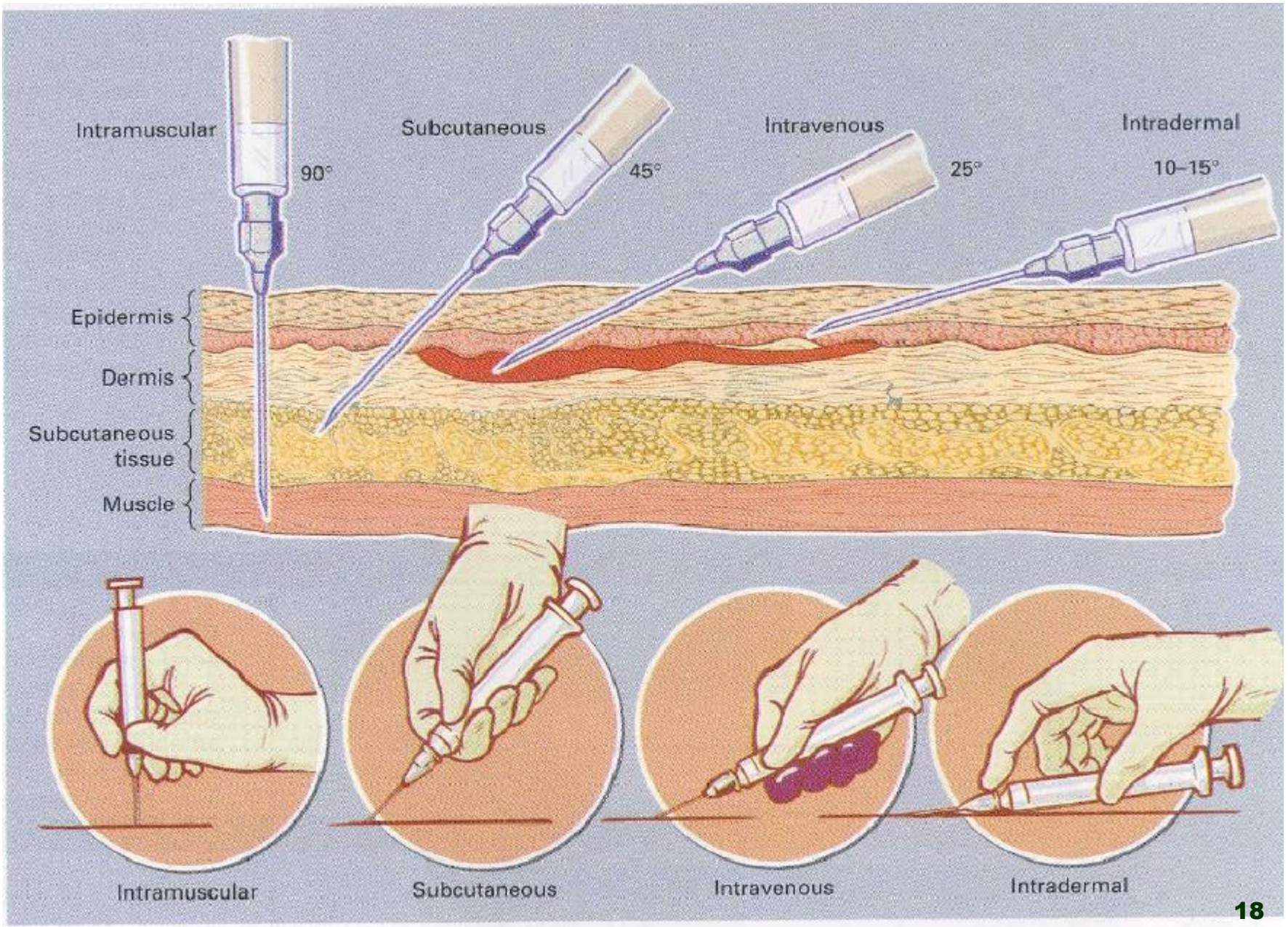
(ii) Routes of Drug administration

- **Topical Administration**
  - Local topical delivery of drugs produces fewer side effects compared with the same drugs given orally or parenterally because they are absorbed very slowly and only small amounts reach the general circulation.
  - Some drugs are given topically to ensure slow release and absorption of the drug into the general circulation to produce systemic effects.
  - Drugs applied topically should generally not be applied to abraded or broken skin, except for antiseptics.

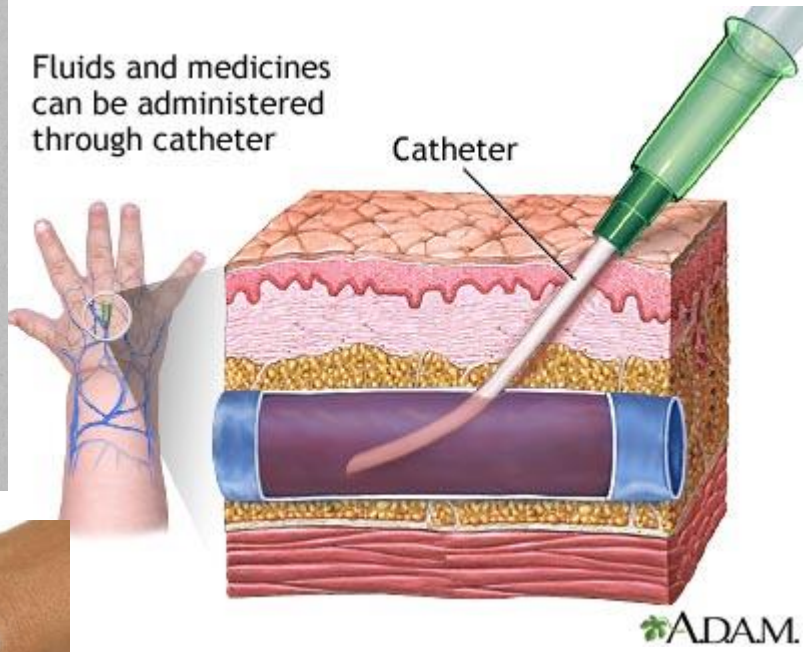
(ii) Routes of Drug administration

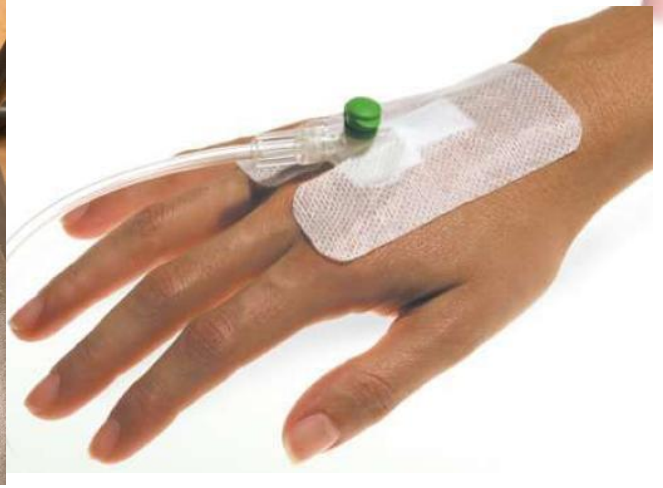
- **Parenteral Administration**
  - via a needle into the skin layers angled at different degrees
    - intradermal (ID), subcutaneous (SC), intramuscular (IM), intravenous (IV)
  - more invasive than topical or enteral administration
  - aseptic technique
    - prevent entry of microbes
  - Parenteral administration: **bypasses enzymes of digestive tract** & **first-pass effect of liver**
  - Rapid onset of action
    - IV > IM > ID or SC

IM SC IV ID


Intramuscular
90°
Subcutaneous
45°
Intravenous
25°
Intradermal
10–15°
Epidermis
Dermis
Subcutaneous tissue
Muscle
Intramuscular
Subcutaneous
Intravenous
Intradermal

Intravenous Cannula



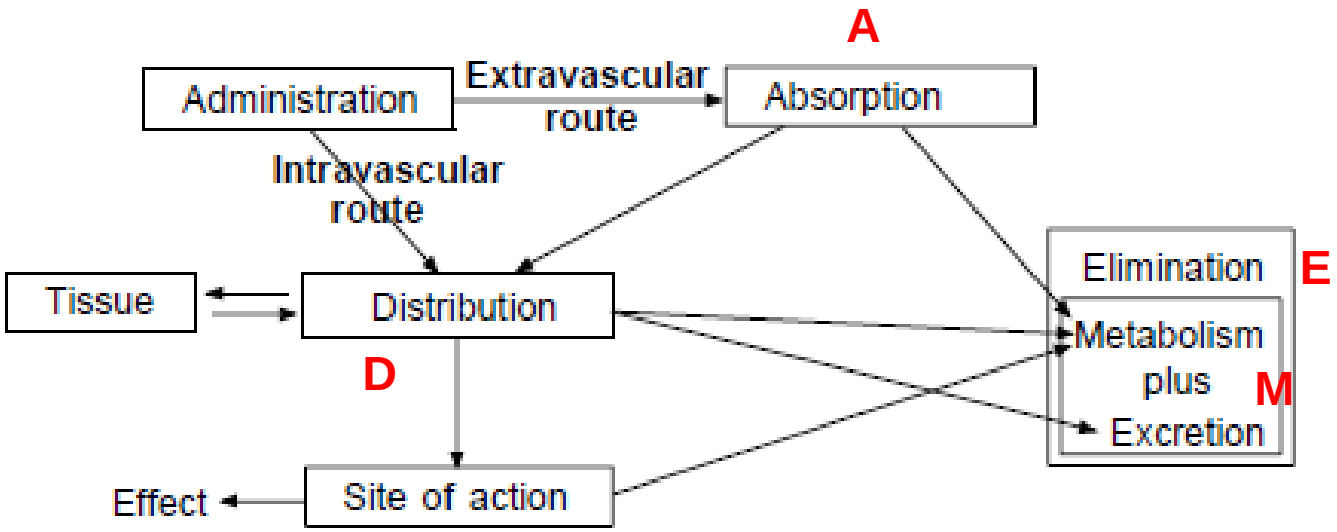


Intravenous injection – 1 shot
Intravenous infusion – drip by drip

Pharmacokinetic Phase
Action of Drugs in the Body

Pharmacokinetic phase

- The study of **how the body handles a drug**
- It attempts to quantify **ADME**
  - drug **absorption** (A)
  - drug **distribution** (D)
  - drug **metabolism** (M)
  - drug **elimination** (E)

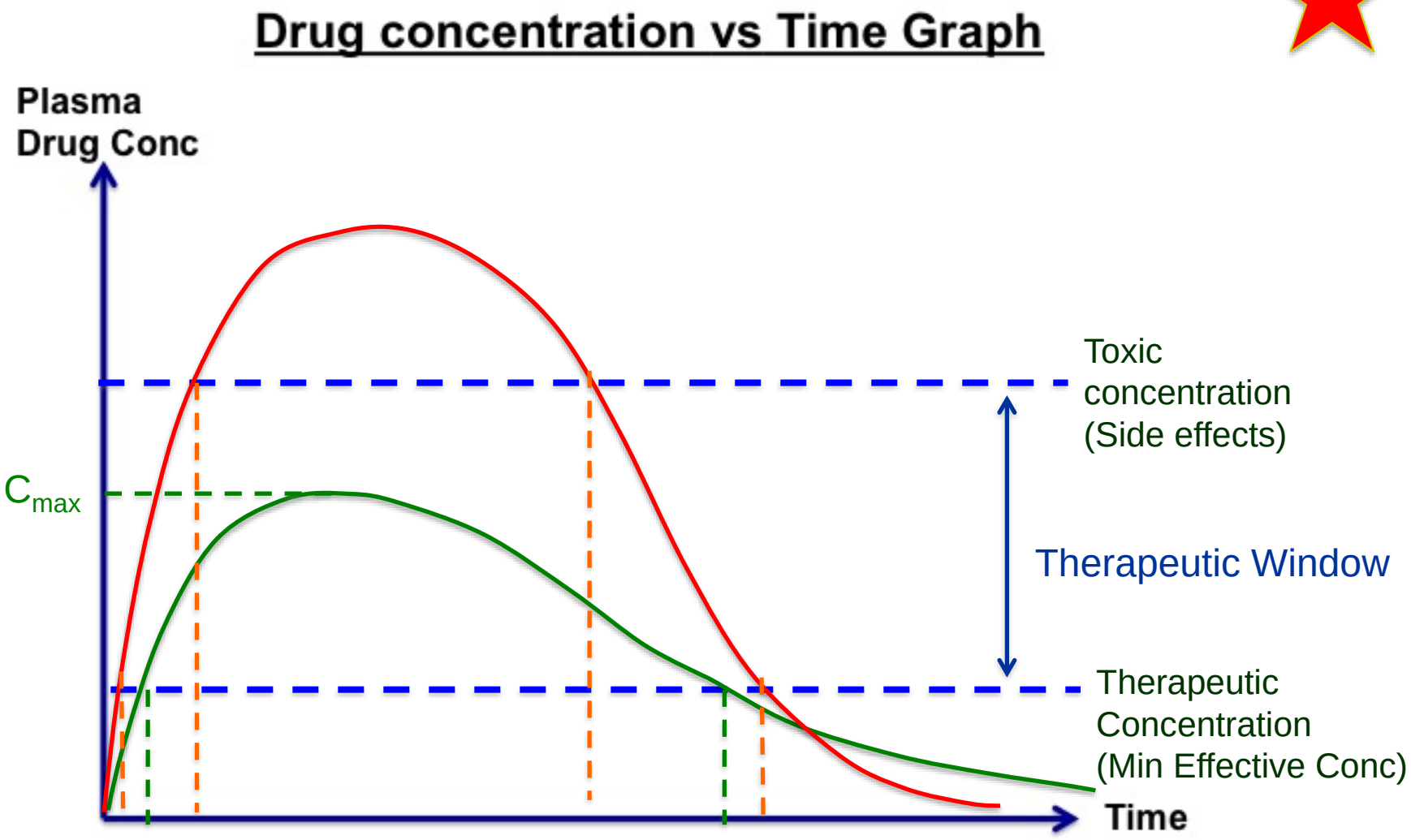


Therapeutic Window/Range

- range of plasma concentration over which a drug is therapeutically effective

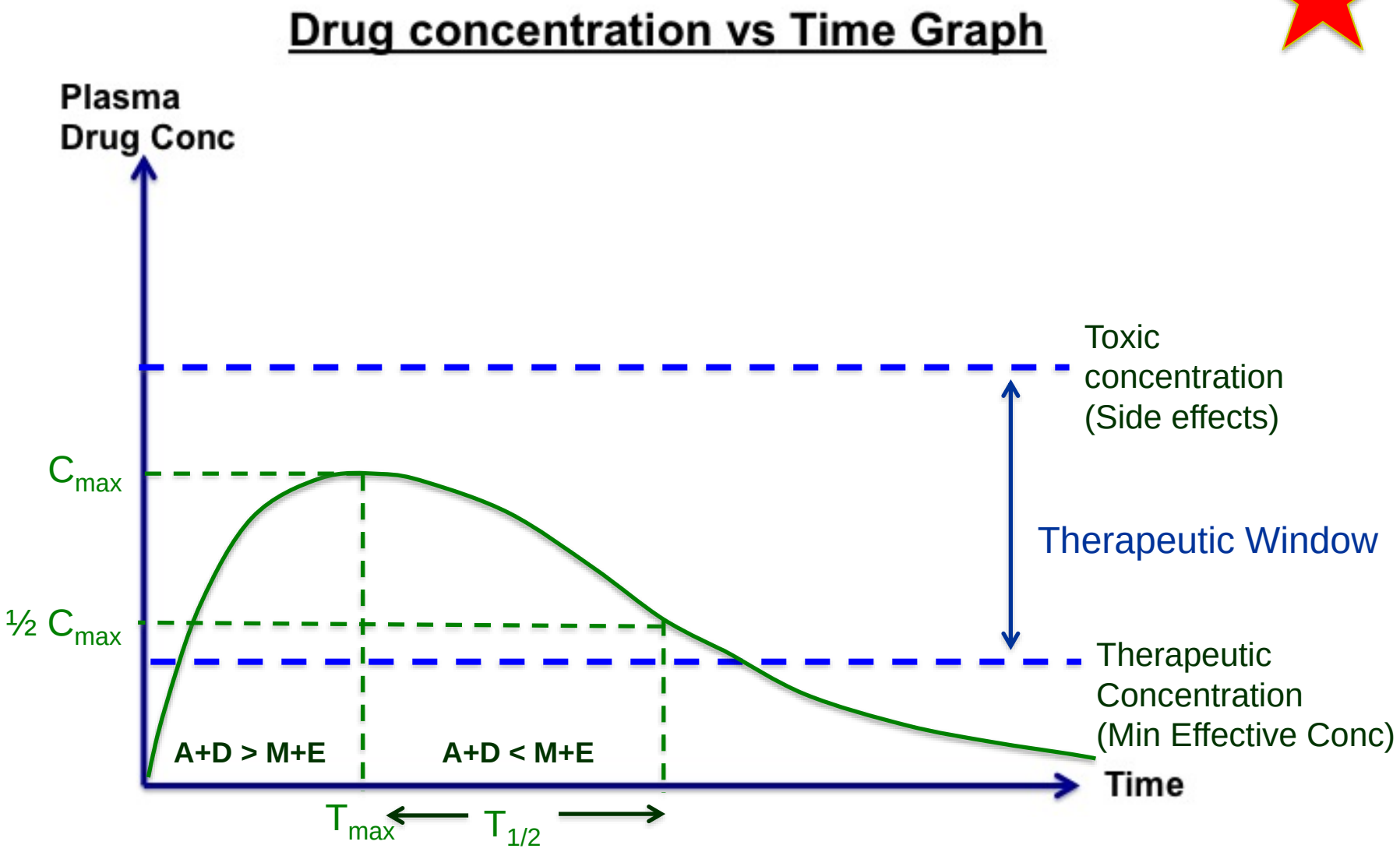
- Between therapeutic concentration and toxic concentration.

Fig 9.5



Question: So how long is the duration of drug action from the graph? When will the patient experience side effects / toxic effects?

Fig 9.5



A, D, M & E happens all the time. Which one is more determines (+) or (-) gradient

Same drug, different dosage forms

Fig 9.6

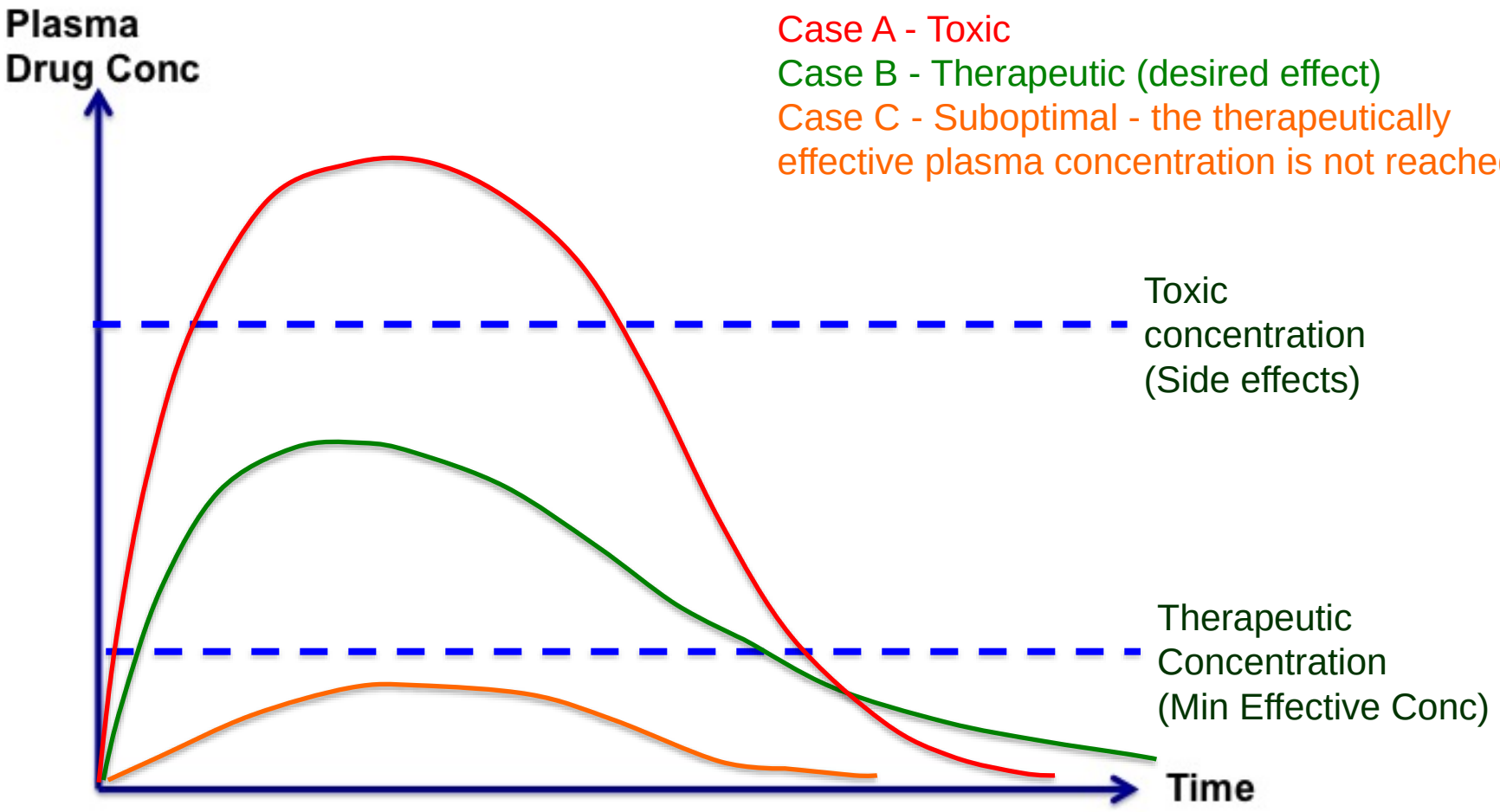
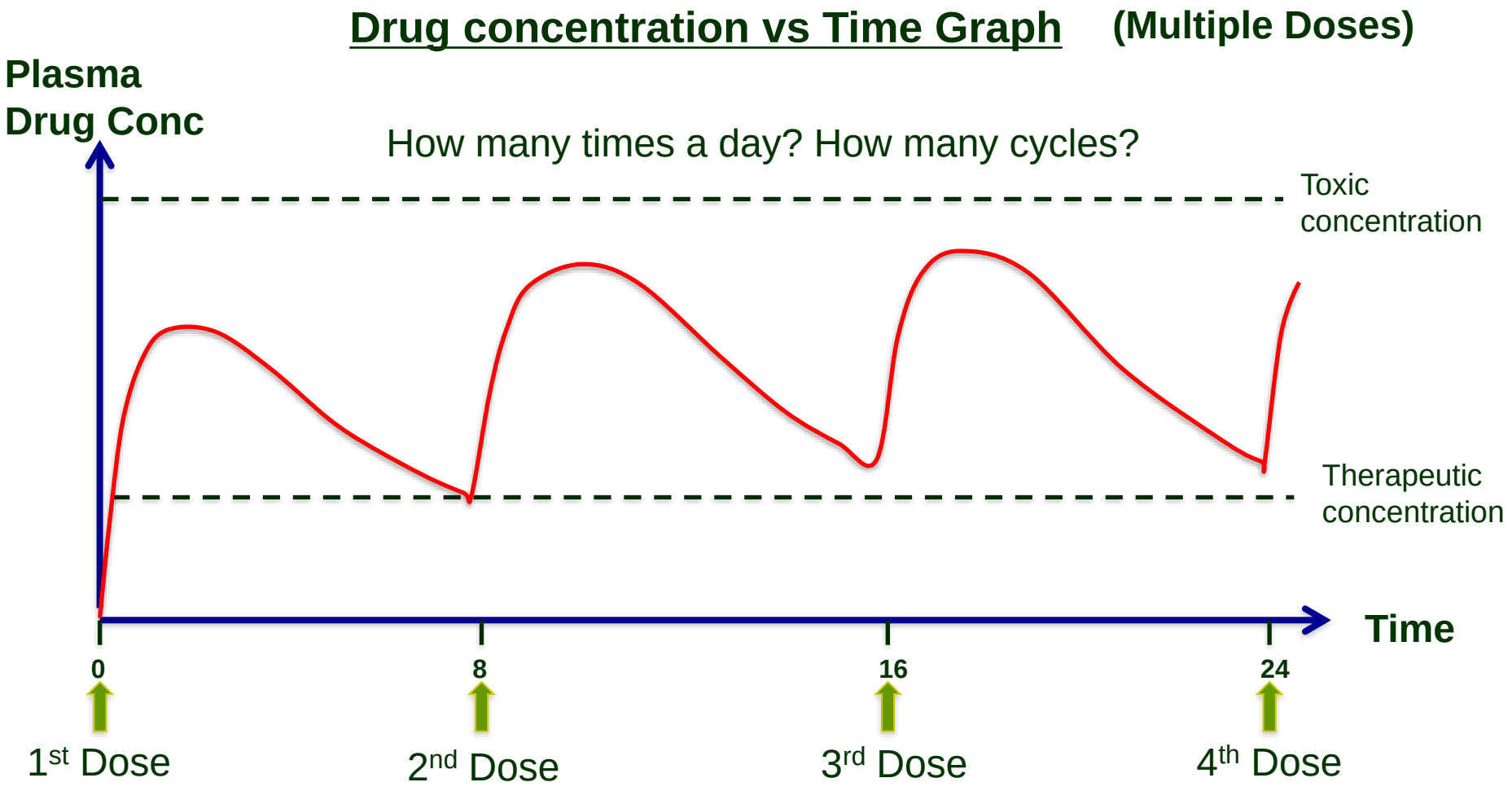


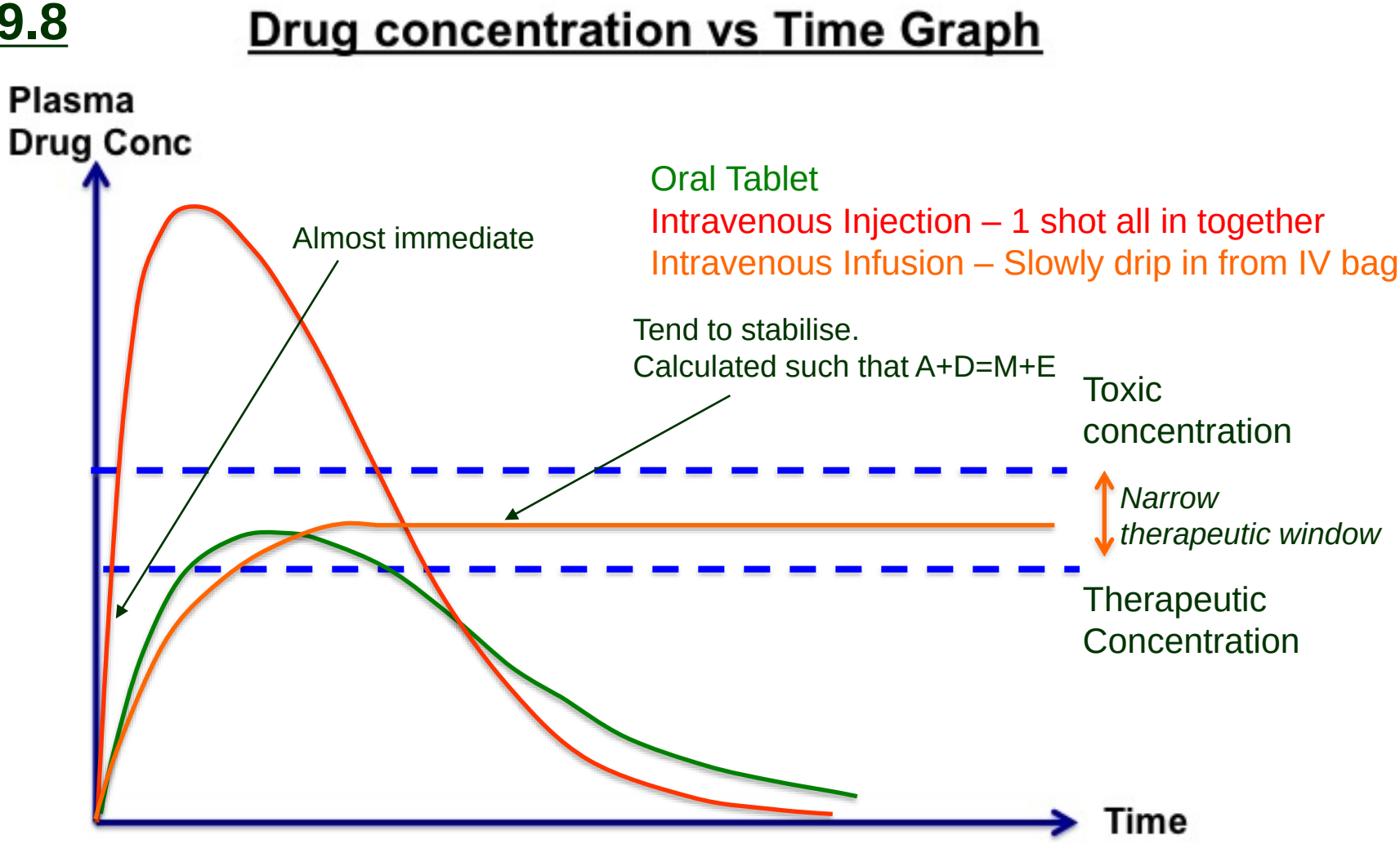
Fig 9.7



When drugs are administered in multiple doses, the drug concentration should stay within the therapeutic window during the drug regimen.

Intravenous Injection *vs* Intravenous infusion

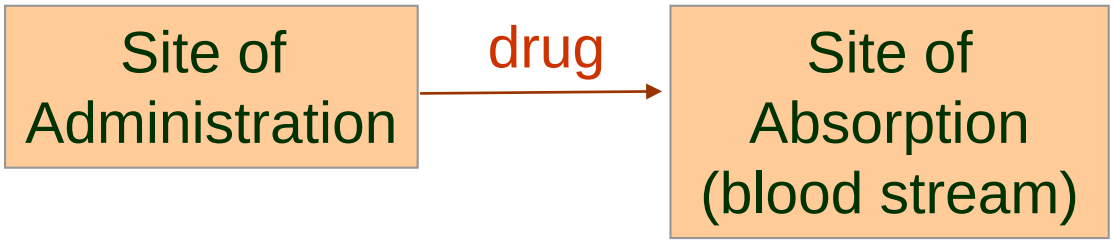
Fig 9.8



Hospital draw blood periodically to plot the graph

Pharmacokinetic phase

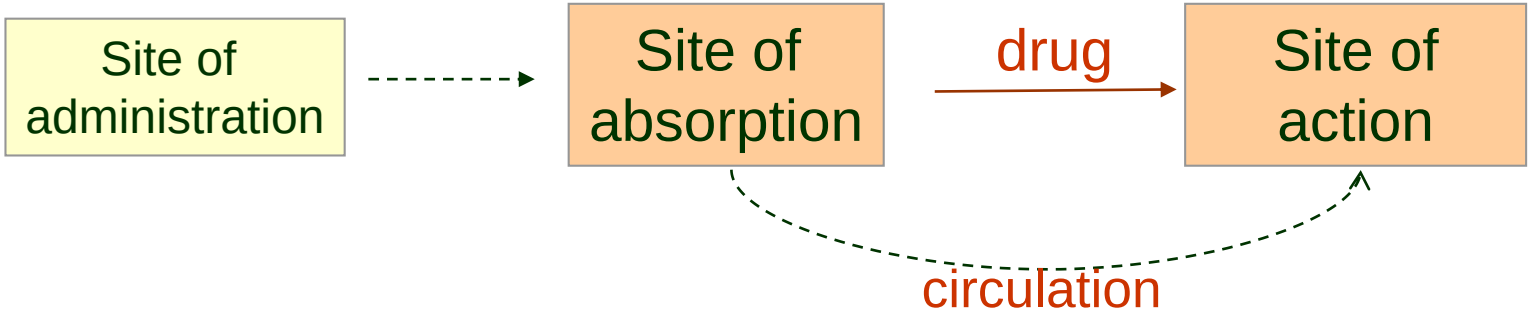
- Drug **Absorption**
  - Refers to the **passage of drug** from **site of administration** into the **blood stream** (site of absorption)



  - **not applicable to intravenous (IV) administration**
    - **absorption =100%**

Pharmacokinetic phase

- Drug **Distribution**
  - Refers to the **transport of drug** from its **absorption** to **site of action**



  - **blood circulation**
    - **main route of distribution**
    - important factor that **slows down drug distribution**
      - ⇒ **binding of drug to plasma proteins**
  - other distribution routes
    - lymphatic system

Pharmacokinetic phase

- Drug **Metabolism**
  - Refers to the **biotransformation** of drug into metabolites
  - Occurs mainly in liver
  - others: blood, brain, lungs, kidneys
  - **Effects:**
    - lowering of drug effects
    - complete suppression of drug effects *(degradative metabolism)*
    - produces active form of drug for **prodrugs** (drug that is administered in an inactive form)

Prodrug $\xrightarrow{\text{metabolism}}$ Active Drug

E.g. *Prednisone* (a synthetic corticosteroid drug), is converted by the liver into the active drug *prednisolone*, which is also a steroid.

Pharmacokinetic phase

- Drug **Elimination**
  - **irreversible** removal of the active form of drug from the body
  - **methods:**
    - degradative metabolism
    - all forms of excretion
  - **main excretion routes:**
    - kidneys - in solution in urine
    - bowel - faeces
  - other excretion routes:
    - exhalation, sweating, breast feeding

Pharmacokinetic phase
Bioavailability

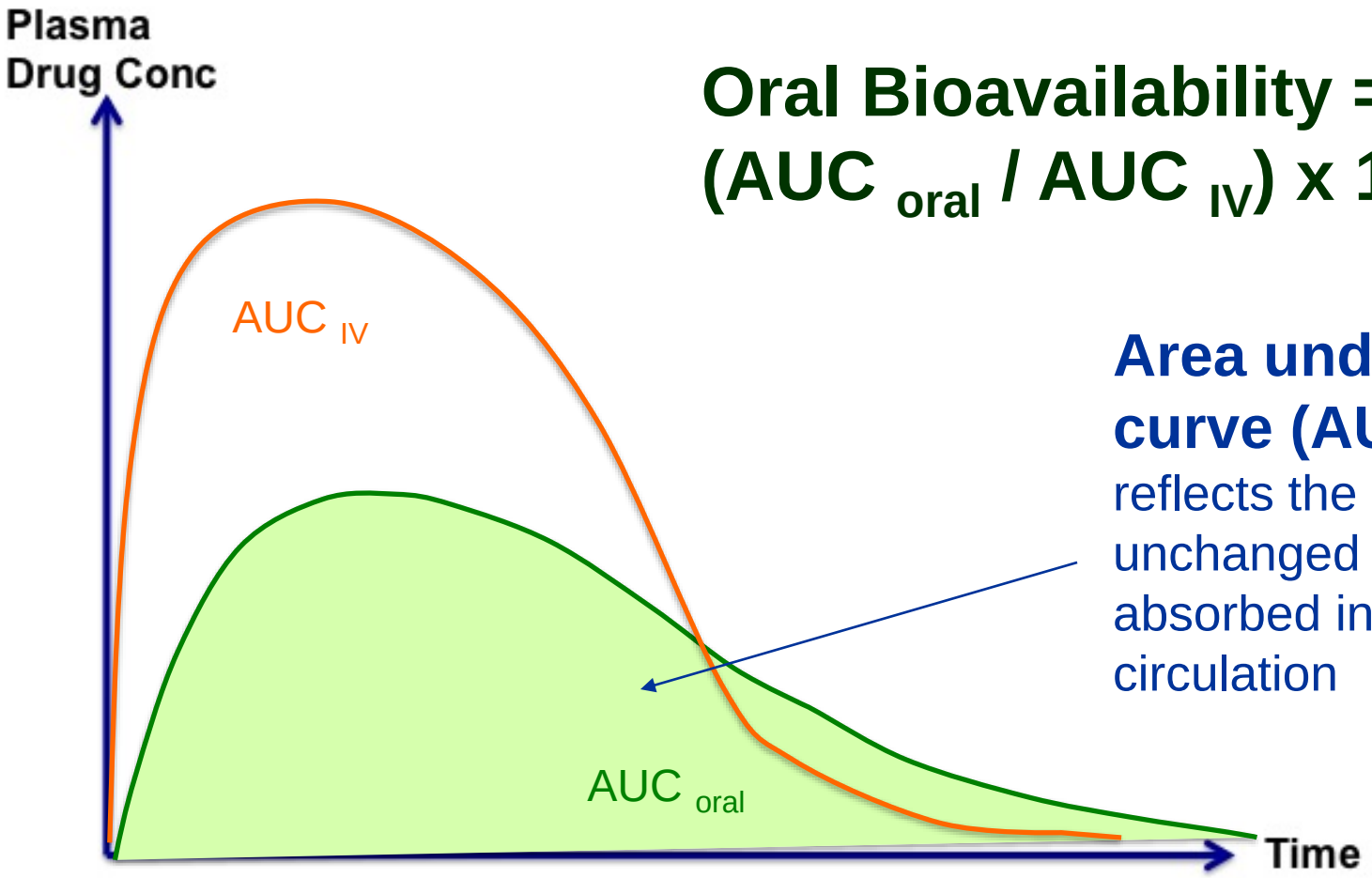
- Bioavailability is the fraction of the administered dose of unchanged drug that reaches the systemic blood circulation.
- **Intravenous administration**
  - immediate absorption
- **Other routes of administration**
  - Usually a small **time lapse** before drug reaches the blood (= This is the time taken for a drug to reach the site of absorption)

Pharmacokinetic phase
Bioavailability

- Amount of drug absorbed
  - calculated from the total area under the concentration-time curve
  - **100% for drugs administered intravenously**

Fig 9.10

Drug concentration vs Time Graph



Oral Bioavailability = (AUC $_{oral}$ / AUC $_{IV}$) x 100%

Area under the curve (AUC)
reflects the amount of unchanged drug absorbed into systemic circulation

The rate at which a drug reaches the systemic circulation is reflected as the time taken to reach maximum plasma concentration.

Pharmacokinetic phase
Bioavailability

Factors Affecting Bioavailability of Oral Drugs :

1. Drug factors
2. Patient factors
3. Drug Interactions *(in GIT)*
4. First Pass Effect – drug stability in the hepatic portal circulation and liver

1. Drug Factors

- **Aqueous and lipid solubilities of drug**

determines dissolution rate

determines ease of membrane permeation

- **Type of dosage form**
  - determines **rate and extent of release** of active drug
    - Bioavailability: liquid preparations > liquid suspension > solids
- **Nature of excipients**
  - affects **release** of drug from dosage form
- **Manufacturing process**
  - e.g. tablet compression force ⇒ hard / soft tablets
  - affect **drug release and dissolution**
- **Particle size & crystalline forms of drug**
  - influence **drug dissolution**

2.Patient Factors

- pH of gastrointestinal fluids
- Gastric-emptying rate
- Gastrointestinal motility rate
- Disease states

2. Patient Factors

- **pH of gastrointestinal fluids**
  - affects drug **solubility**
  - affects **degree of ionization** of drug
  - e.g. basic drug - more soluble in acidic than alkaline pH
  - non-ionised fraction $\Rightarrow$ more lipid soluble $\Rightarrow$ easier movement across cell membranes & vice versa
- **Gastric-emptying rate**
  - **rate** at which **drug is discharged** from the **stomach**
  - **determines the rate of absorption** in the **small intestine**

2. Patient Factors

- **Gastrointestinal motility rate**
  - determines **transit rate** through **small intestine**
  - determines the **time available for drug dissolution** and **absorption**
- **Disease states**
  - alter drug absorption characteristics
  - e.g. changes in gastro-emptying rate, GI motility, etc

3. Drug Interactions

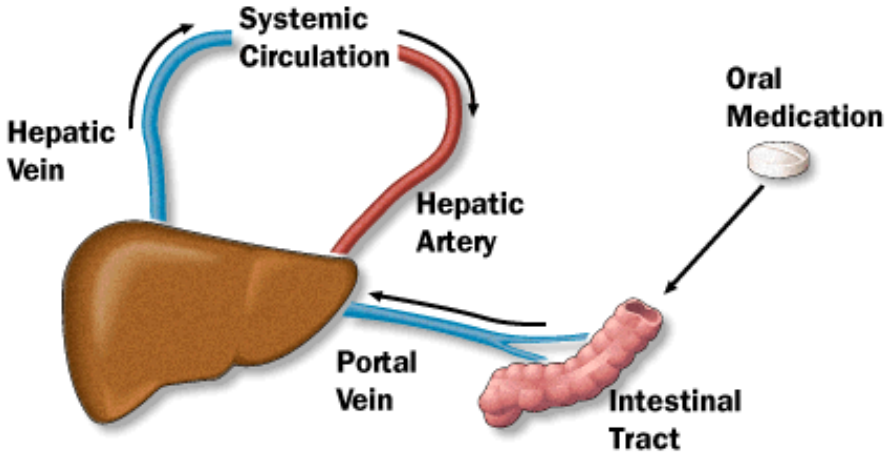
- Generally
- Empty stomach favours GI absorption
- 2 or more drugs, including food, administered in close sequence
  - one drug may interfere with absorption of another
  - some may form insoluble complexes or other effects

    e.g. tetracycline (antibacterial) + antacids (gastric)

  Impact: tetracycline complexes with divalent cations forming an insoluble complex

4. First Pass Effect

- only affects **orally** administered drugs
- drugs are absorbed into the **hepatic portal circulation** which **carries blood directly to the liver** from the upper digestive tract
- the drugs can be **rendered inactive** by the **metabolic processes in the liver** before they reach the general circulation



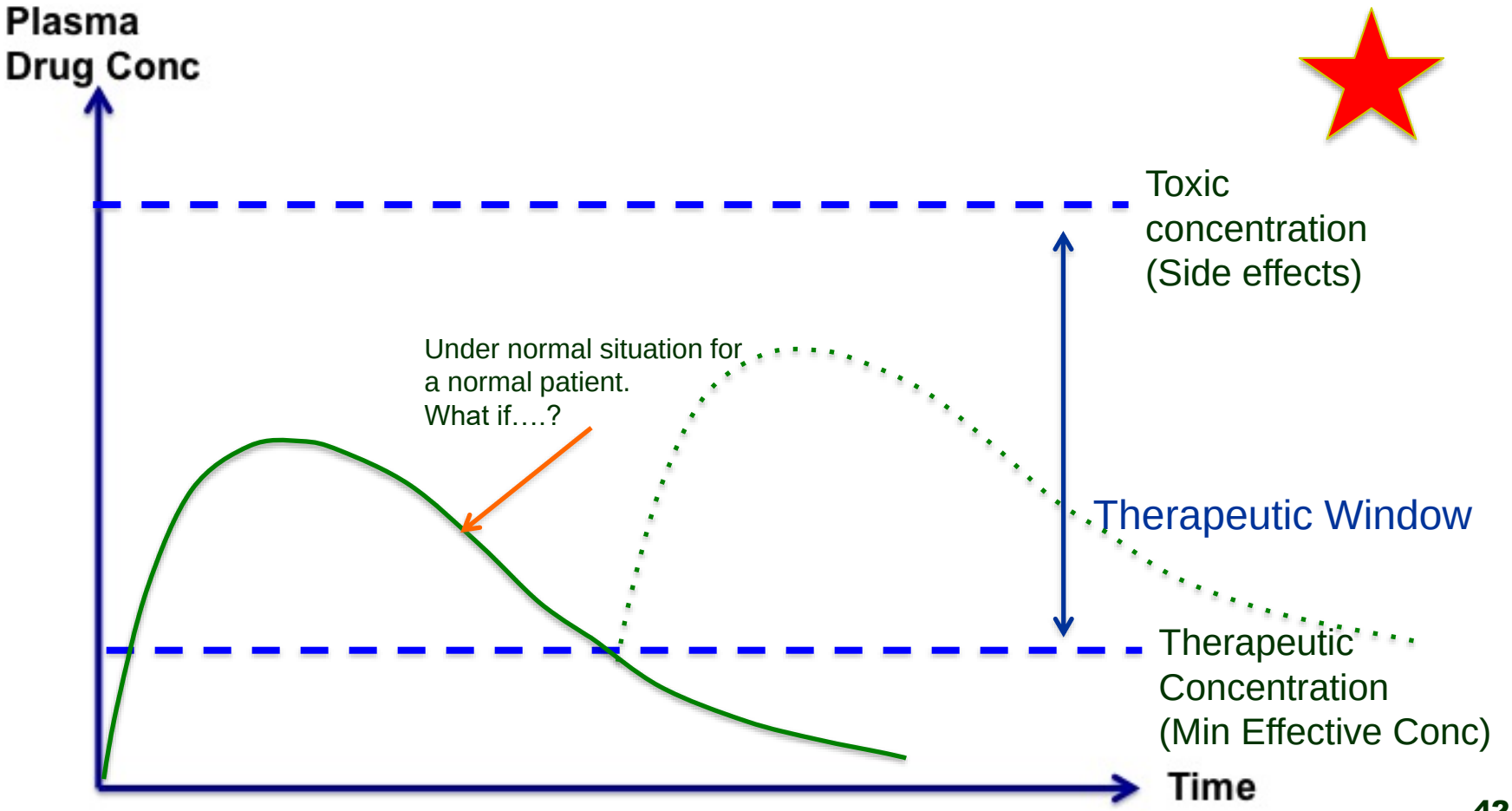
Discussion: What happens to the curve when the ADME is not typical?

(Eg: Liver failure patient, kidney failure, diarrhea)

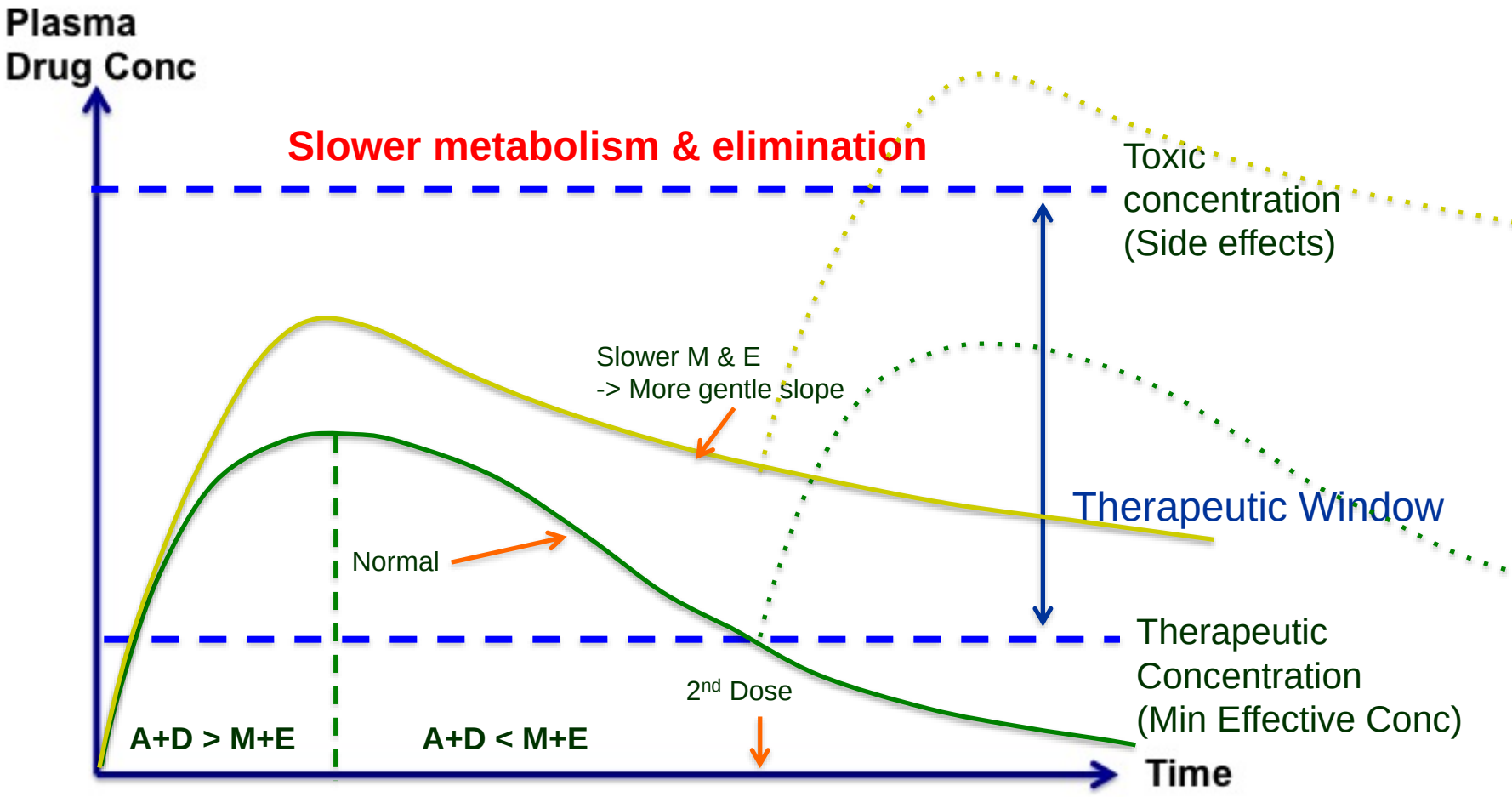
What impact on dosage regiment?

What can the pharmacist do to ensure safety?

Draw on Pg 104 **Drug concentration vs Time Graph**

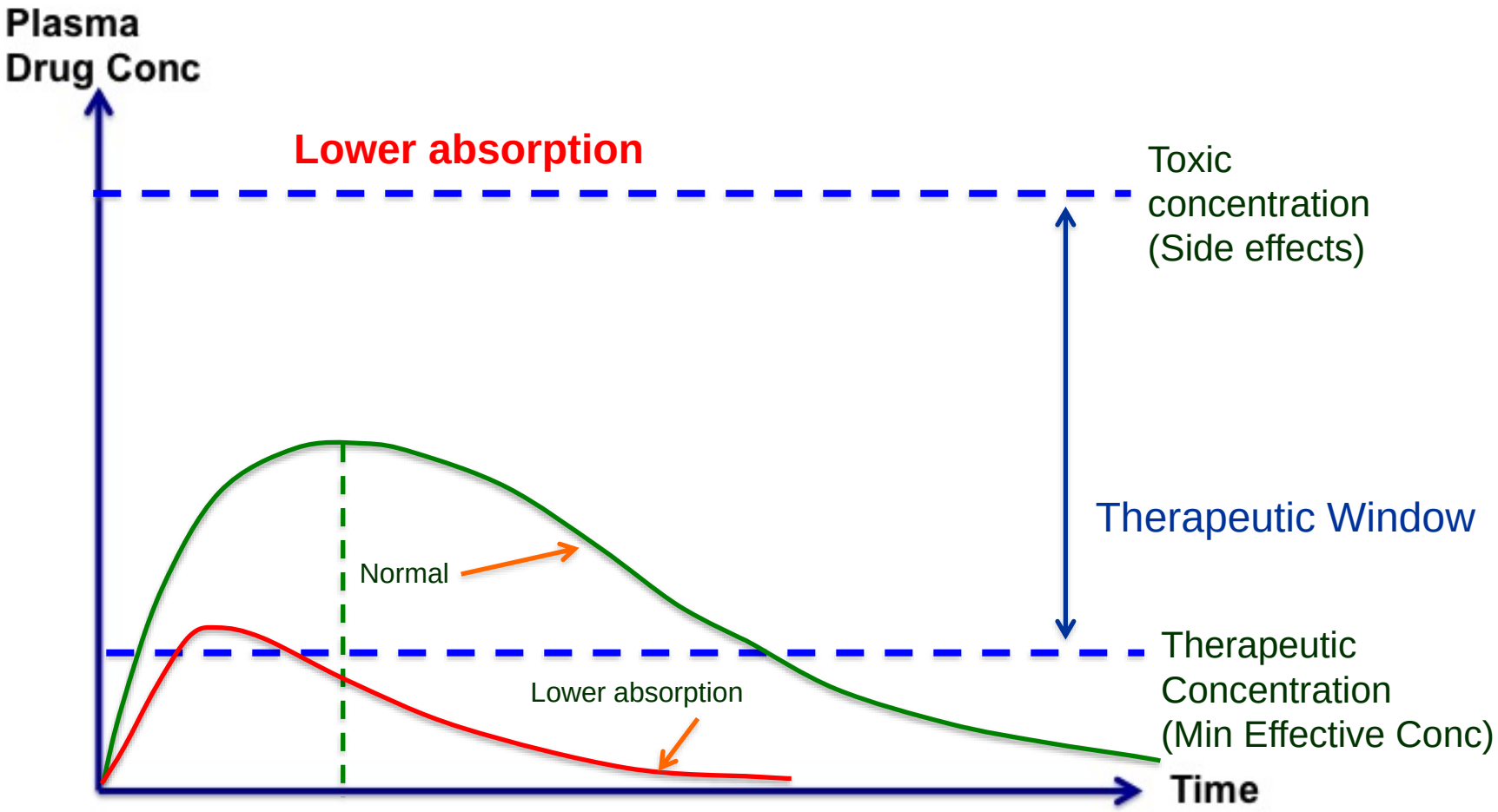


Drug concentration vs Time Graph



- Longer duration of drug action
- Take less frequently, take lower dose

Drug concentration vs Time Graph



- Lower bioavailability.
- Higher dose or change route of absorption.