BIOAVAILABILITY & BIOEQUIVALENCE

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DEFINITIONS

BIOAVAILABILITY: According to 2003 FDA guidance,

‘ Bioavailabilty is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For the products that are not intended to be absorbed into blood stream, bioavailability may be assessed by measurement intended to reflect the rate and extent to which the active ingredient or active ingredient or active moiety becomes available at the sit of action .'

In other words, it is the **fraction of administered dose that actually reaches the systemic circulation**

Route	Bioavailability(%)	Chracteristics
Intravenous	100(by definition)	Most rapid onset
Intramuscular	75 to 100 large volume often feasible;	may be painful
Subcutaneous	75 to 100 Smaller volumes than IM;	may be painful (SC)
Oral (PO)	5 to < 100 Most convenient;	first pass effects may be significant
Rectal (PR)	30 to < 100	Less first-pass effects than oral
Inhalation	5 to < 100	Often very rapid onset

OBJECTIVES OF BIOAVAILIBILITY STUDIES

- Primary stages of development of a suitable dosage for a new drug entity.
- Development of a new formulations of the existing drugs.
- Control of quality of a drug product during the early stages of marketing in order to determine the influence of processing factors, storage and stability on drug absorption.
- Useful in determining the safety and efficacy of the drug product.

BIOEQUIVALENT DRUG PRODUCTS:-

Two products are **bioequivalent** if

- they are **pharmaceutically equivalent**
- both **rate and extent** after administration in the **same molar dose** are similar to such a degree that their effects can be expected to be essentially the same.

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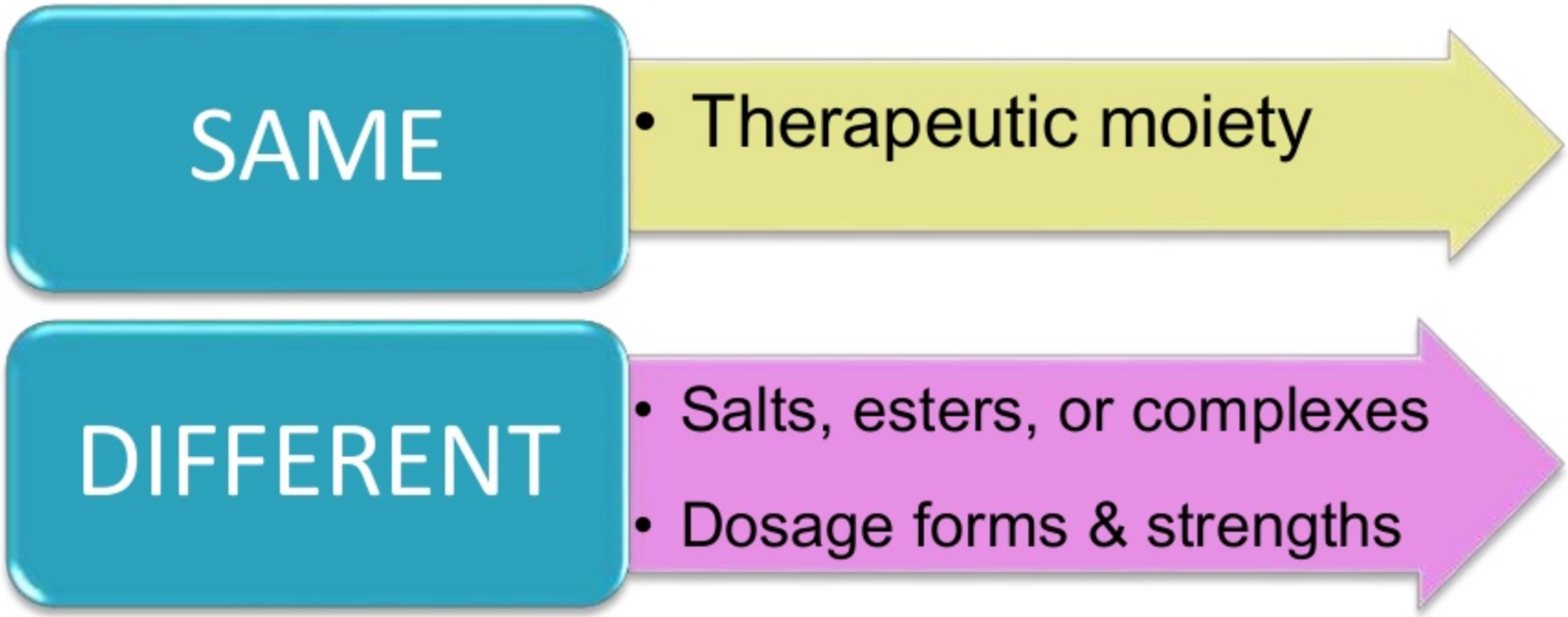
- For drugs products that are not intended to be absorbed into the bloodstream :

1. other *in-vivo* or *in-vitro* test methods may be used to demonstrate bioequivalence,

2. *in- vitro* bioequivalence standard may be used, especially when such an *in-vitro* test has been correlated with human *in-vivo* bioavailability data,

3. in other cases B.E may be demonstrated through comparative clinical trials or pharmacodynamic studies.

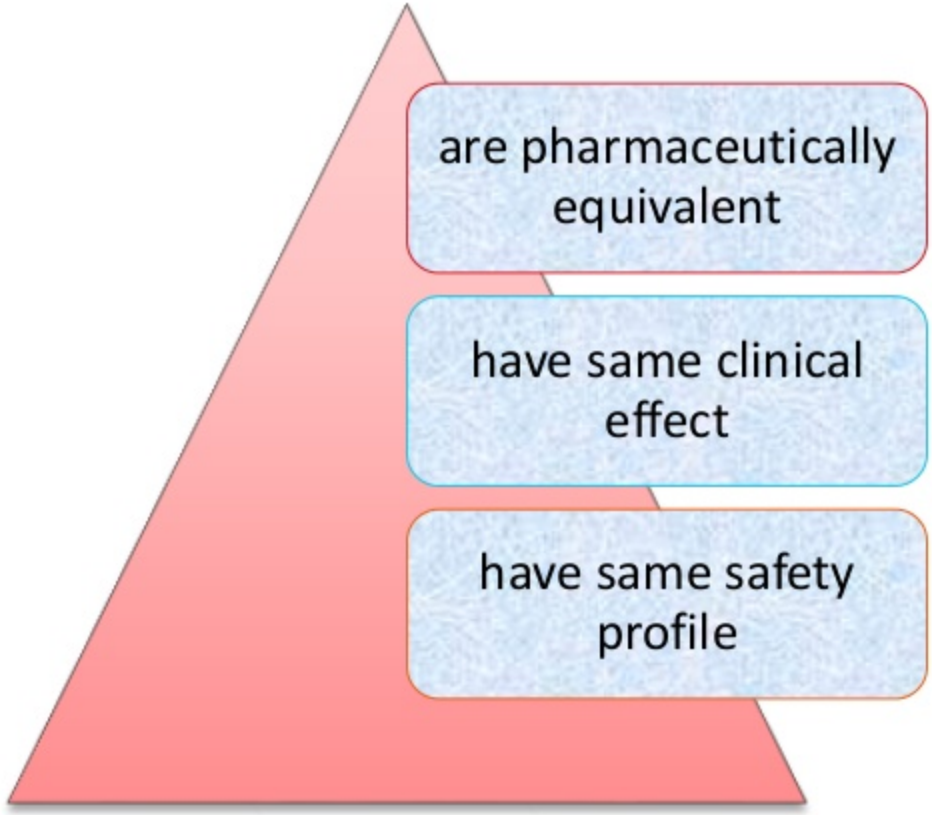
PHARMACEUTICAL ALTERNATIVES:-



EXAMPLE:-Tetracycline phosphate or Tetracycline hydrochloride equivalent to 250 mg Tetracycline base are considered Pharmaceutical alternative

THERAPEUTIC EQUIVALENCE

FDA classifies those products as therapeutically equivalent which :



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- EXAMPLE:-

- A 10 mg. tablet of Zocor (used to treat high cholesterol) is therapeutically equivalent to a 10 mg. tablet of **simvastatin.**

- A 50 mg. tablet of Zoloft (used to treat depression) is therapeutically equivalent to a 50 mg. tablet of **sertraline.**

THERAPEUTIC ALTERNATIVE

Drug products containing **different active ingredients** that are indicated for the **same therapeutic** or clinical objectives.

For example:-

Cimetidine may be given instead of **Rantidine**

PHARMACEUTICAL EQUIVALENTS:-

FDA considers drug products to be pharmaceutical equivalents if they meet these criterion:

SAME

- Active ingredients
- Dosage form
- Route of administration
- Strength/ Concentration

DIFFERENT

- Shape
- Labeling
- Release mechanism
- Scoring configuration
- Excipient

ABSOLUTE & RELATIVE BIOAVAILABILITY

ABSOLUTE BIOAVAILABILITY

The absolute bioavailability of drug is the systemic availability of a drug after extra vascular administration compared to intravenous dosing

$$F = \frac{AUC_{extravascular}}{AUC_{\text{int}ravenous}} \times \frac{Dose_{\text{int}ravenous}}{Dose_{extravascular}}$$

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RELATIVE BIOAVAILABILITY

It is the systemic availability of the drug from a dosage form as compared to the reference standard given by the same route of administration.

$$F_{rel} = \frac{AUC_{extravascular1}}{AUC_{extravascular2}} \times \frac{Dose_{extravascular2}}{Dose_{extravascular1}}$$

TYPES OF BIOEQUIVALENCE

AVERAGE BE

- Focuses on comparison of population averages of BA.

POPULATION BE

- Assess total variability in the population.

INDIVIDUAL BE

- Assess , within subject variability as well as subject-by-formulation interaction.

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- **AVERAGE BIOEQUIVALENCE.**
  - Population means (μ_T , μ_R)

- **POPULATION BIOEQUIVALENCE.**
  - Population means (μ_T , μ_R)
  - Total variances (σ_{TT}^2, σ_{TR}^2)

- **INDIVIDUAL BIOEQUIVALENCE.**
  - Population means (μ_T , μ_R)
  - Within-subject variances (σ_{WT}^2 , σ_{WR}^2)
  - Subject-by-formulation interaction (σ_D^2)

BIOEQUIVALENCE CRITERIA

[Criterion] $\leq$ BE Limit

- **Average BE:** $(\mu_T - \mu_R)^2 \leq \theta_A^2$

- **Individual BE:** $$\frac{(\mu_T - \mu_R)^2 + \sigma_D^2 + (\sigma_{WT}^2 - \sigma_{WR}^2)}{\sigma_{WR}^2} \leq \theta_I$$

- **Population BE:** $$\frac{(\mu_T - \mu_R)^2 + (\sigma_{TT}^2 - \sigma_{TR}^2)}{\sigma_{TR}^2} \leq \theta_P$$

IN-VIVO STUDIES REQUIRED FOR:-

- Oral immediate release drug formulations with systemic action.
- Non-oral & Non- parenteral formulations for systemic action (suppositories, transdermal patches, etc.).
- Fixed dose combination products with systemic action
- Sustained or modified release formulations designed to act by systemic absorption.
- Non-solution pharmaceutical products which are for non-systemic use(oral, nasal, ocular, dermal, vaginal, rectal, etc. application) & are intended to act without systemic absorption

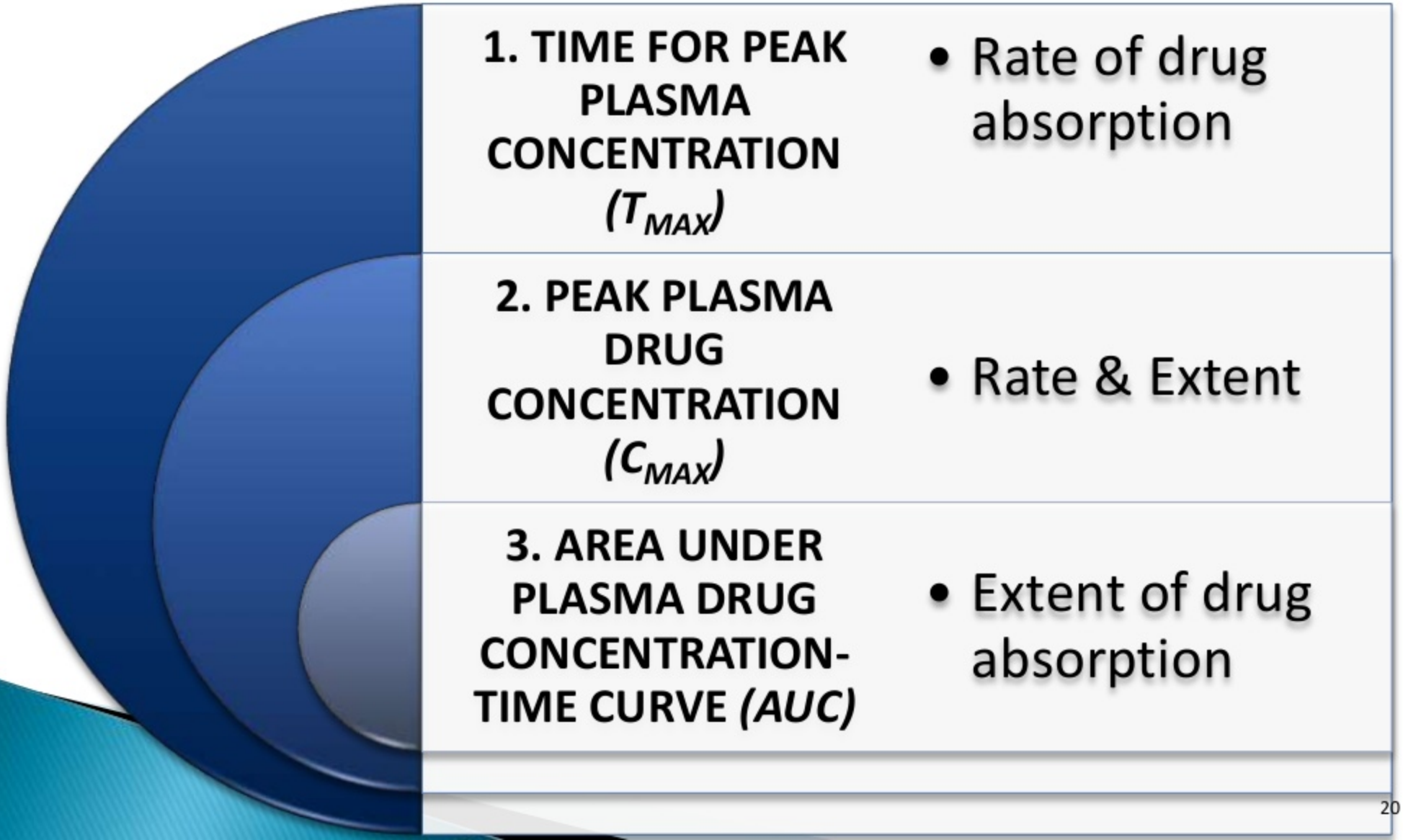
ASSESSMENT OF BIOAVAILABILITY

1. IN-VIVO STUDIES

- Pharmacokinetic Methods :
  - a)Blood Level Studies
  - b)Urine Level Studies
- Non-pharmacokinetic Methods
  - a) Pharmacodynamic Studies
  - b) Comparative Clinical Study Methods

2. IN-VITRO STUDIES

PARAMETERS OBTAINED FROM PLASMA LEVEL DATA



1. TIME FOR PEAK PLASMA CONCENTRATION *(T_{MAX})*	• Rate of drug absorption
2. PEAK PLASMA DRUG CONCENTRATION *(C_{MAX})*	• Rate & Extent
3. AREA UNDER PLASMA DRUG CONCENTRATION-TIME CURVE *(AUC)*	• Extent of drug absorption