BIOAVAILABILITY & BIOEQUIVALENCE

CONTENTS:-

- DEFINITIONS
- METHODS OF ASSESSMENT
- DESIGN OF STUDY
- EVALUATION OF DATA
- BIOWAIVERS
- BCS

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.

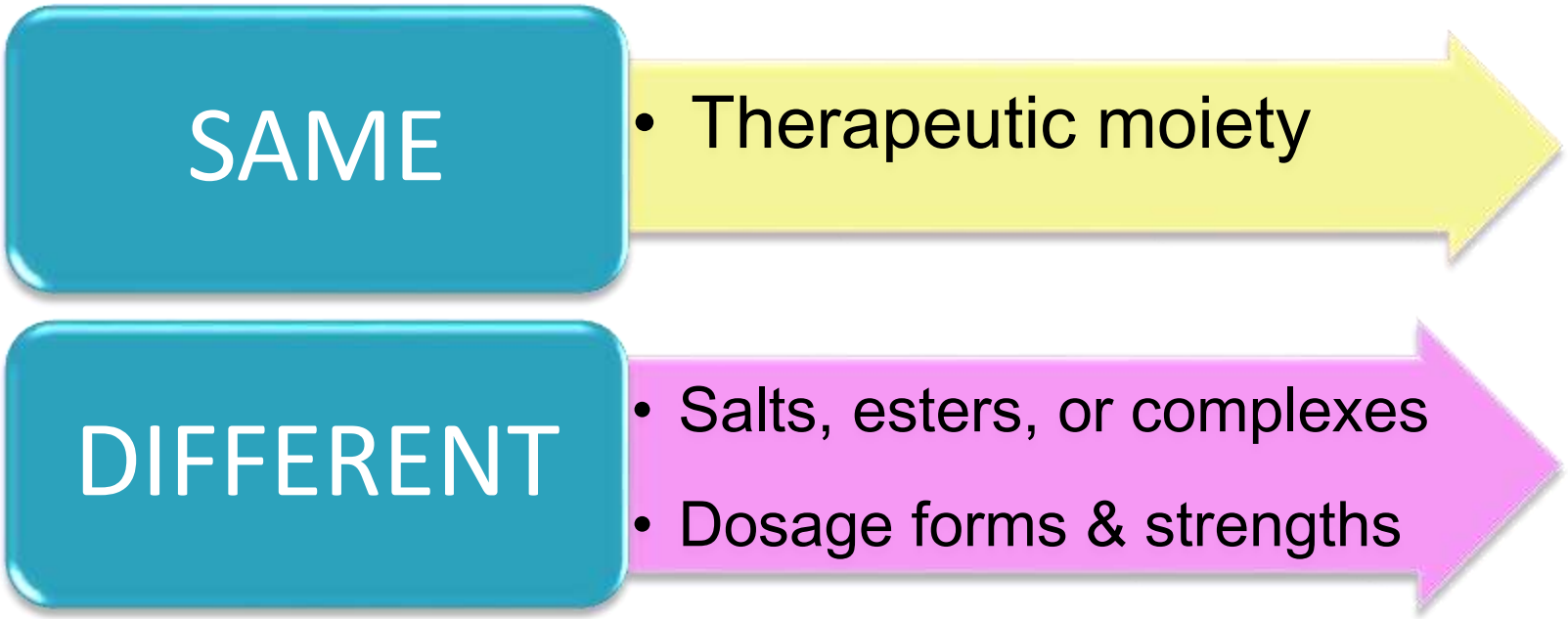
- For drugs products that are not intended to be absorbed into the bloodstream :

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.

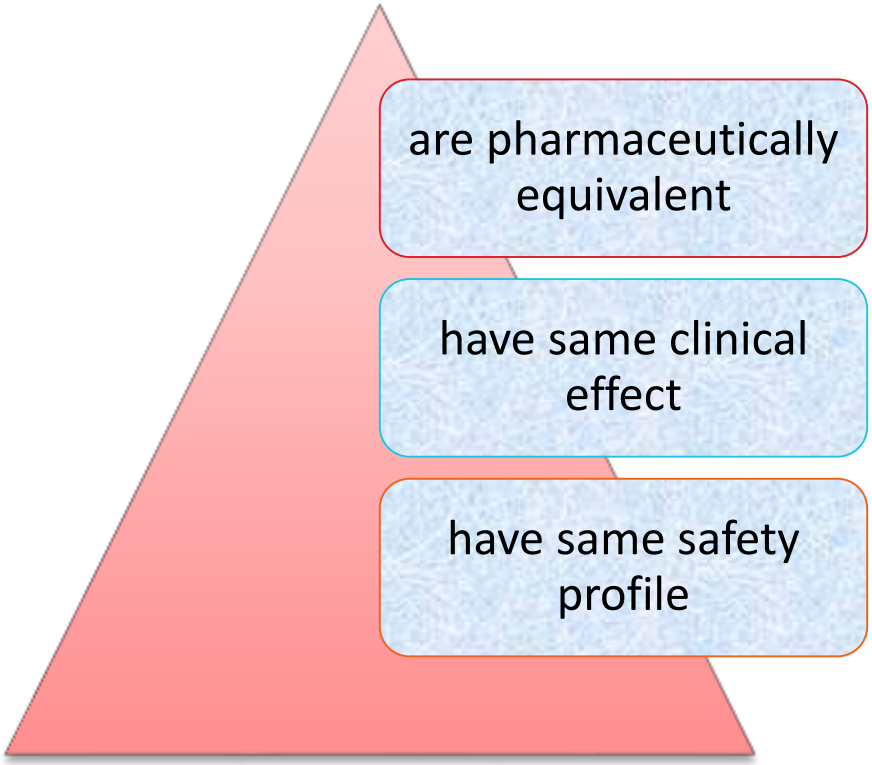
PHARMACEUTICAL ALTERNATIVES:-



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 :



- 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

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

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.

$$F_{rel} = \frac{AUC_{extravascular\,1}}{AUC_{extravascular\,2}} \times \frac{Dose_{extravascular\,2}}{Dose_{extravascular\,1}}$$

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

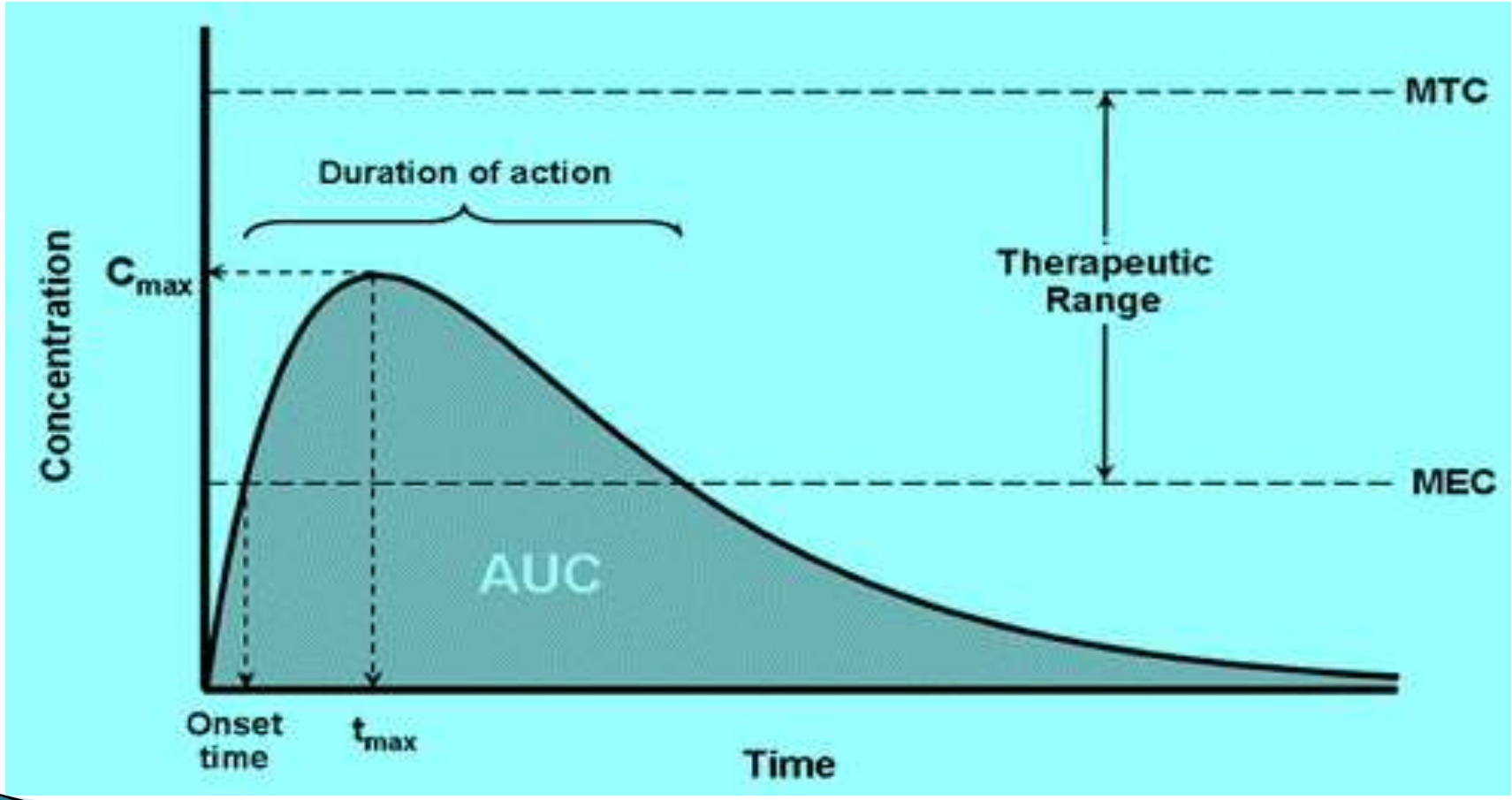
- Pharmacokinetic Methods :
  - a)Blood Level Studies
  - b)Urine Level Studies
- Non-pharmacokinetic Methods
  - a) Pharmacodynamic Studies
  - b) Comparative Clinical Study Methods

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

Plasma concentration time profile:-



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MINIMUM EFFECTIVE CONCENTRATION-

The minimum plasma concentration of the drug required to **achieve a given pharmacological or therapeutic response**. This value varies from drug to drug and from individual to individual as well as with the type and severity of the disease.

MAXIMUM SAFE CONCENTRATION-

The plasma concentration of the drug beyond which **adverse effects are likely to happen.**

THERAPEUTIC RANGE-

The range of plasma drug concentration in which the **desired response is achieved** yet avoiding adverse effect. The aim is clinical practice is to maintain plasma drug concentration within the therapeutic range.

ONSET OF ACTION-

The beginning of pharmacological response.

On set of action is the time required to achieve the minimum effective plasma concentration following administration of drug formulation.

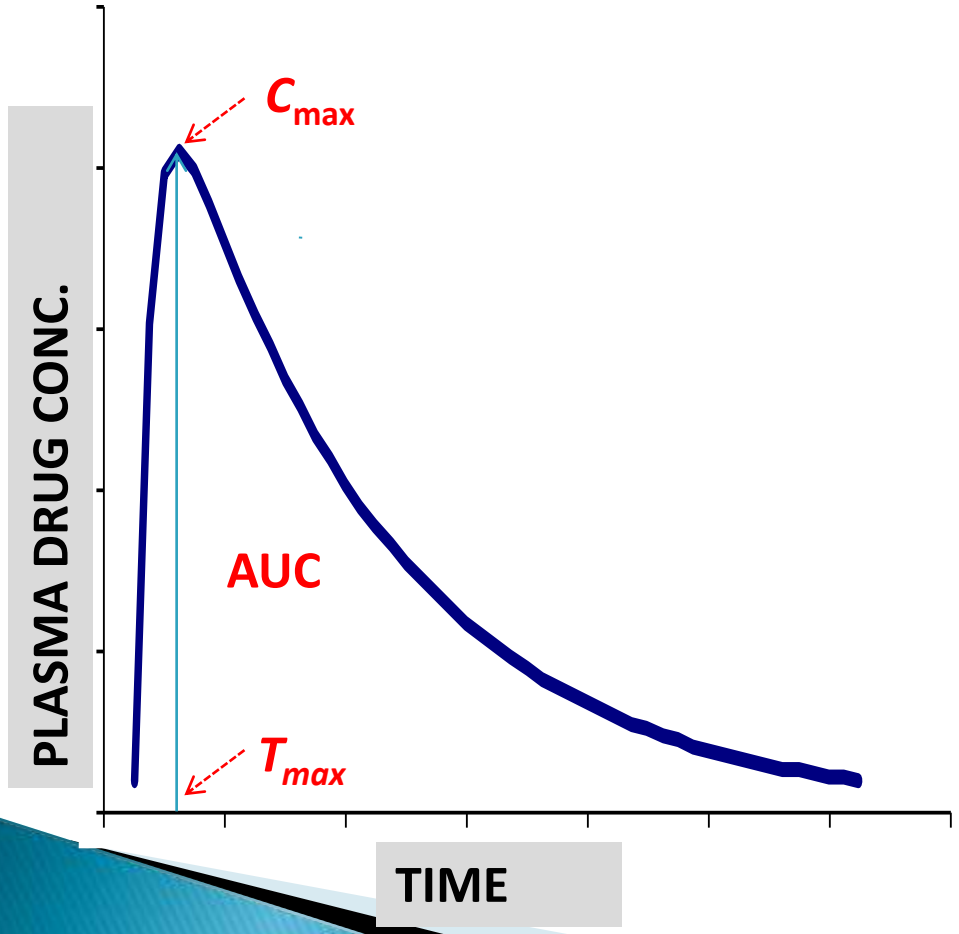
DURATION OF ACTION-

Duration of action of the therapeutic effect of the drug is defined as the time period during which the plasma concentration of the drug exceeds the minimum effective level.

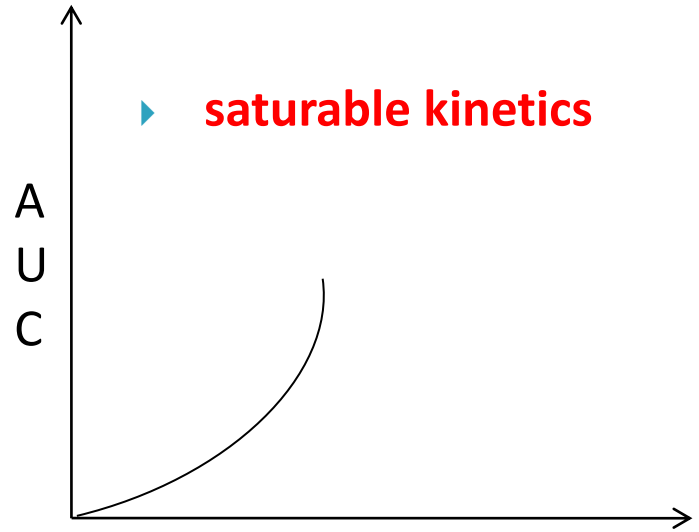
INTENSITY OF ACTION-

It is the maximum pharmacological response produced by the peak concentration of drug.

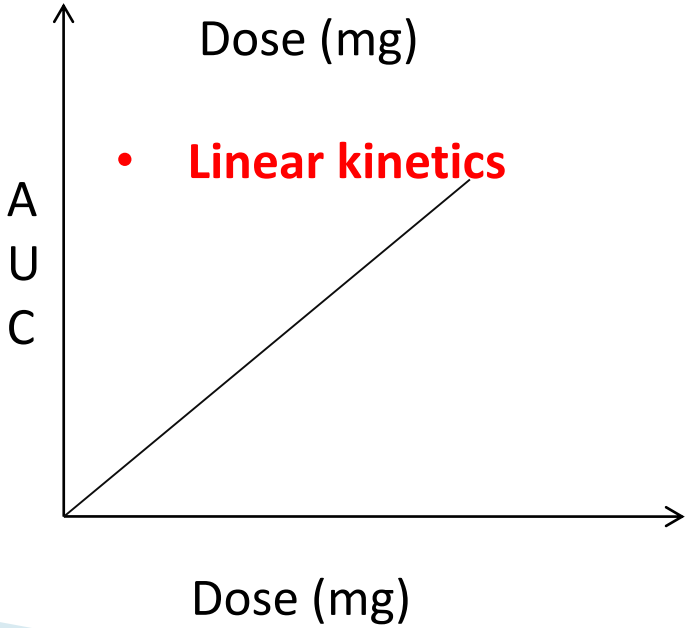
PLASMA DRUG CONC.-TIME STUDIES DATA



- saturable kinetics



- Linear kinetics



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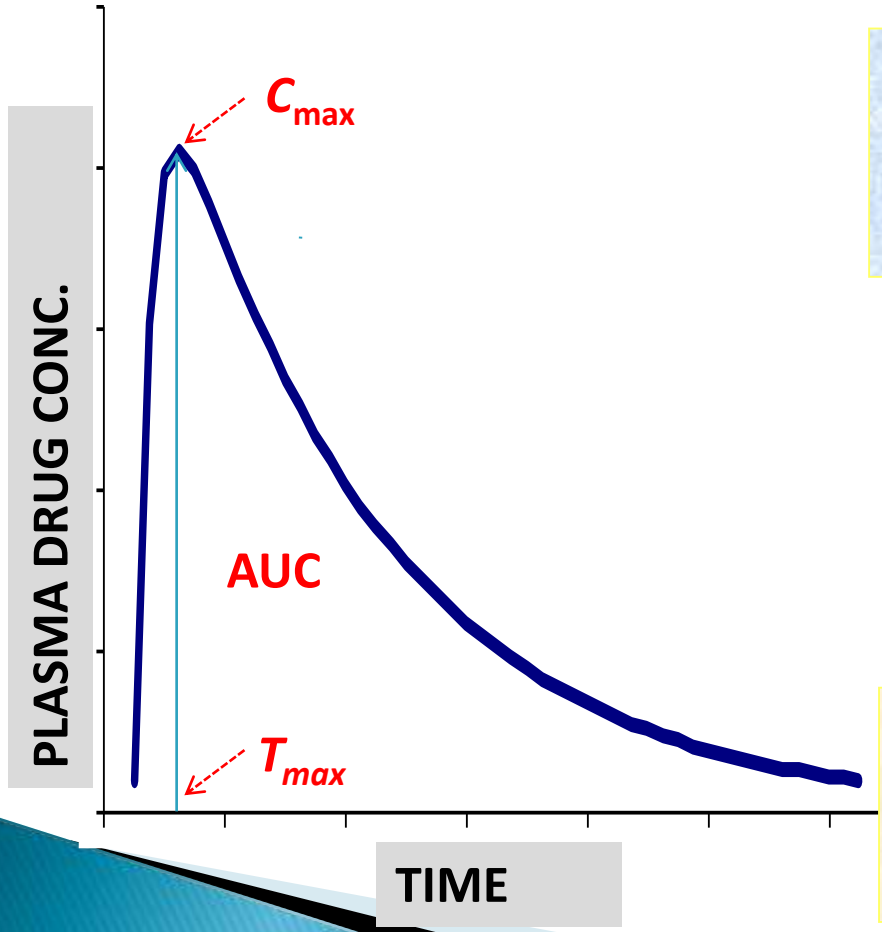


Single dose studies

$$F = \frac{AUC_{oral}}{AUC_{iv}} \times \frac{Dose_{iv}}{Dose_{oral}}$$

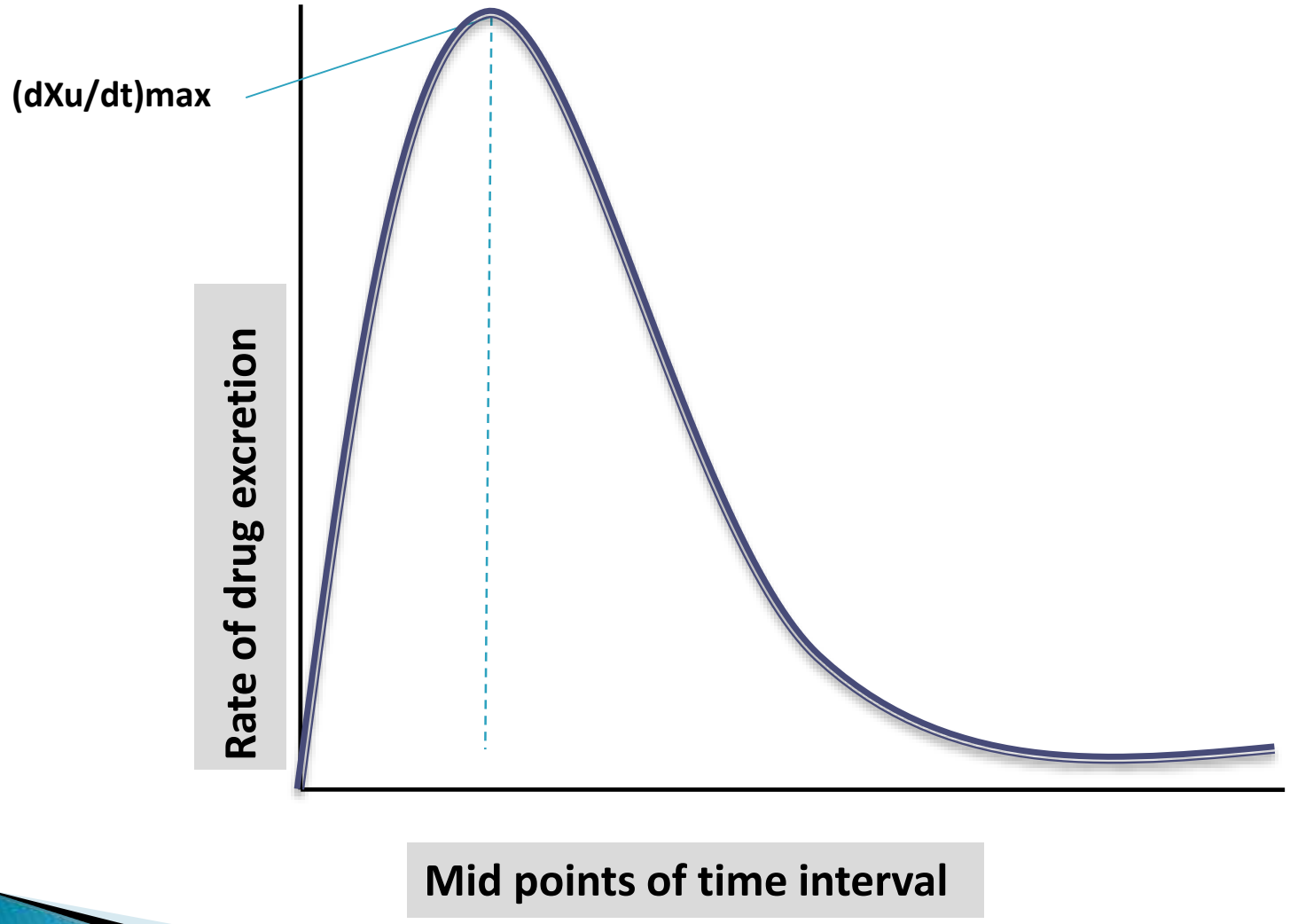
Multiple dose studies

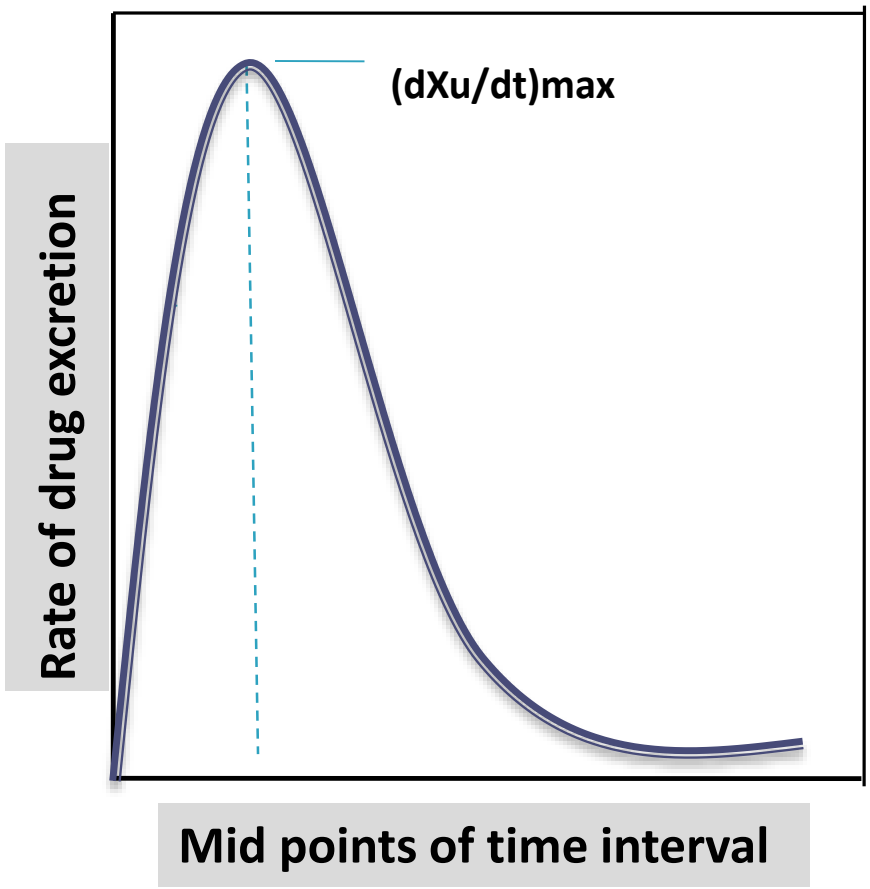
$$F = \frac{[AUC]_{test}}{[AUC]_{std}} \times \frac{D_{std} \times \tau_{test}}{D_{test} \times \tau_{std}}$$

PARAMETERS OBTAINED FROM URINARY DRUG EXCRETION STUDIES

1. $(dX_u/dt)_{max}$ (maximum urinary excretion rate)	• value increases as the rate and/or extent of absorption increases. • **Analogous to C_{max} derived from plasma studies.**
2. $(t_u)_{max}$ (time for maximum excretion rate)	• value decreases as the absorption rate increases. • **Analogous to t max derived from plasma studies**.
3. X_u: (cumulative amount of drug excreted in urine)	• value increases as the extent of absorption increases. • **Related to AUC of plasma level data**

URINARY DRUG EXCRETION PROFILE





Total qty of unchanged drug excreted in urine is the reflection of qty of drug absorbed from GIT

$$F = \frac{(X_u)_{oral}}{(X_{u\infty})_{iv}} \times \frac{D_{i.v}}{D_{oral}}$$

$$F = \frac{(X_{u,\,ss})_{test}}{(X_{u,\,ss})_{std}} \times \frac{D_{std} \times \tau_{test}}{D_{test} \times \tau_{std}}$$

CRITERIA FOR URINARY EXCRETION STUDIES

- Significant amount of drug must be excreted unchanged in the urine(40%).
- Not appropriate where urinary excretion is not a significant mechanism of elimination.
- **Analytical method must be specific for the unchanged drug; metabolites should not interfere.**
- Volunteers must instructed to completely empty their bladder while collecting urine samples .

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- Frequent sampling should be done in order to obtain a good curve.
- During sampling the exact time and volume of urine excreted should be noted.
- Urine sample must be collected for at least 7-10 biological half lives.
- Changes in urine pH and urine volume may alter the urinary excretion rate.

ADVANTAGES OF URINARY EXCRETION STUDIES

- ✓ Method is useful when there is lack of sufficiently sensitive analytical techniques to measure concentration of drug in plasma with accuracy.
- ✓ Method is non-invasive.
- ✓ Convenience of collecting urine samples.
- ✓ Less sensitive analytical method is required for determining urine drug concentration as compared to plasma concentration.

CHARACTERISTICS INVESTIGATED DURING BA/BE STUDIES

- Active drug substance in biological matrix.
- Active or inactive metabolite in cases where:
  - concentrations of drug(s) –too low to be measured in biological matrix
  - limitations of analytical method
  - unstable drug(s)
  - drugs with very short half-life or
  - in the case of prodrugs

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- Racemates should be measured using an achiral assay method.

- Individual enantiomers must be measured in case:
  - exhibit different pharmacodynamic characteristics
  - exhibit different pharmacokinetic characteristics
  - primary activity/safety resides with the minor enantiomer
  - non-linear absorption of at least one of the enantiomers

Parameters assessed :

SINGLE DOSE STUDY

- C_{max}
- T_{max}
- AUC_{0-t}
- $AUC_{0-\infty}$

STEADY STATE STUDY

- C_{max}
- C_{min}
- $AUC_{0-\tau}$
- Degree of fluctuation

There are many other metrics that have been suggested for assessing the rate of absorption of the drug, such as: $C_{max}/AUC_{0-\infty}$, AUC_i (upto T_{max}), $AUC_i/AUC_{0-\infty}$, AUC_e (AUC upto T_{max} of reference or test, whichever occurs first), AUC_r (AUC upto T_{max} of reference), $AUC_e/AUC_{0-\infty}$, $AUC_r/AUC_{0-\infty}$, C_{max}/T_{max}, and C_{max}/AUC_i

DESIGN OF BIOEQUIVALENCE STUDIES

BASIC DESIGN IS DETERMINED BY :

- Scientific questions to be answered
- Nature of the reference material and the dosage form to be tested
- Availability of analytical methods
- Benefit-risk considerations in regard to testing in humans

STUDY DESIGN

- Basic Design Considerations
  - Minimize variability not attributable to formulations
  - Minimize bias
  - REMEMBER: goal is to compare performance of the two products
- "Gold Standard" Study Design
  - Single-dose, two-period crossover
  - Healthy volunteers
  - Subjects receive each formulation once
  - Adequate washout

1. Selection Criteria for Subjects

- ✓ Studies should be conducted in individuals **representative of the general population**, taking into account age, sex, and race.
- ✓ Healthy subjects, above **18** years of age.
- ✓ Choice of gender based on usage & safety criteria

Selection Criteria for Subjects(Contd…)

- ✓ If drug product is to be used predominantly in elders, then test should include as many subjects of 60 years of age or older as possible.
- ✓ **Pregnant** women or those taking **contraceptives** should **not** be included in the test.
- ✓ For drugs hazardous for one group of users, choice of subjects may be narrowed down, e.g., studies on **teratogenic drugs** should be conducted only on **males**.
- ✓ For drugs primarily intended for use in only males or only females- volunteers of only respective gender should be included in the studies.
- ✓ For drugs where risk of toxicity or side effects is significant, studies may be carried out **in patients**, but whose **disease** state is **stable.**

2. Selection of the Number of Subjects

Number of Subjects should be statistically significant & is determined by following considerations :

- Error variance associated with primary characteristic to be studied.
- Significance level desired :usually 0.05.
- Expected deviation from the reference product compatible with bioequivalence.
- The required (discriminatory) power, normally 80% to detect maximum allowable difference (usually +20%) in primary characteristics to be studied.
- Should be sufficient to allow for possible withdrawals or removals (dropouts) from the study
- Minimum number should not be less than 12

Minimum information required to calculate sample size

- It is the ability to detect a true difference b/w standard & intervention arm
- Detects “false-negative results”
- Usually set at 80%

POWER

- Generally established based on previous studies
- Determined for both standard & treatment group

UNDERLYING POPULATION EVENT RATE

- The chosen level of significance sets likelihood of detecting a treatment effect when no effect exists
- Defines threshold “p values”
- Detect “false-positive results”
- Usually set at 5% (p=0.05)

LEVEL OF SIGNIFICANCE

GENERIC EXPRESSION FOR CALCULATING SAMPLE SIZE

$$\text{SAMPLE SIZE } \alpha \frac{(\text{POWER, INVERSE FUNCTION OF SIGNIFICAN CE LEVEL})}{(\text{ABSOLUTE DIFFERENCE})^2}$$

BASED ON LOG TRANSFORMED DATA

$$N = 2 \times \left[t_{(\alpha, N-2)} - t_{(\beta, N-2)} \right]^2 \left[\frac{CV}{\ln \nabla - \ln \theta} \right]^2$$

$$CV = \sqrt{e^{MSE^2} - 1}$$

$$\theta = \frac{\mu_{test}}{\mu_{ref}}$$

CV = Coefficient of variation
MSE = Mean square of error from ANOVA
t-value from Student t- distribution for N-2 degree of freedom
∇= Equivalence limit
θ = Ratio of means of 2 formulations

Highly Variable Drugs

- Drugs in which the within subject variability (WSV) in pharmacokinetics estimated from the ANOVA equals or exceeds 30%.

- Within-subject variability is contained in the Residual Variance (also called the 'Error Mean Square or Error Term')

- The Residual Variance is made up of several components:
  (i) WSV in absorption, distribution, metabolism and excretion combined with a component of analytical variability,
  (ii) within-formulation variability (WFV),
  *(iii) the subject by formulation interaction (S*F) and*
  (iv) unexplained, random variability

- highly variable drug substances, e.g. statins
- highly variable drug products, e.g. enteric coated

3. Genetic Phenotyping

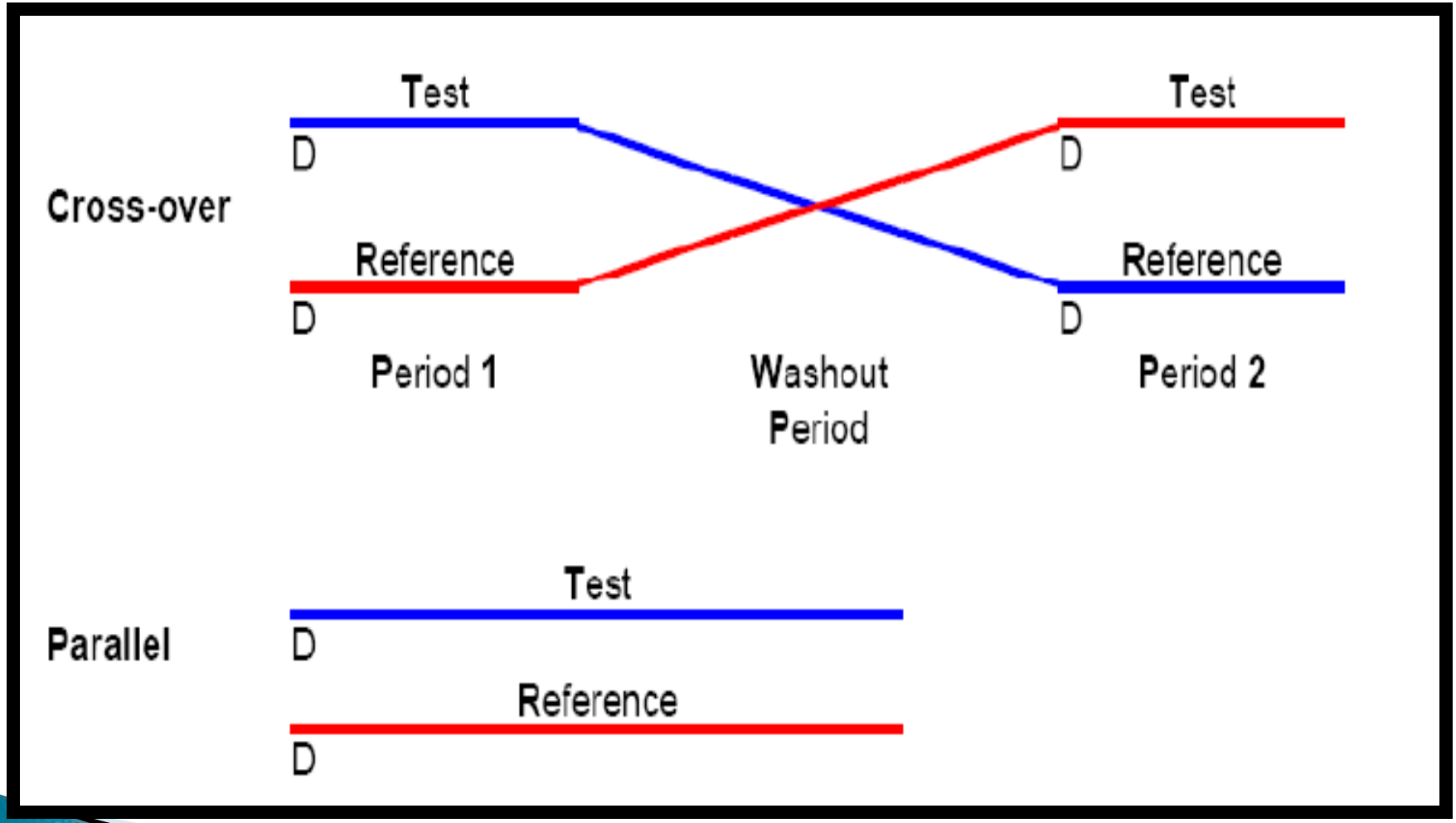
- Phenotyping and/or genotyping should be considered:
  - For exploratory BA studies and all studies using *parallel design.*
  - For safety or pharmacokinetic reasons in *crossover studies.*

- With drugs under genetic polymorphic metabolism :

  different half-life values in poor metabolizers (PMs), extensive metabolizers (EMs), and ultra-rapid metabolizers (UM) are produced.

  In case of drugs with known genetic polymorphism, studies should be done on subjects of known phenotype or genotype.

Cross-over and parallel design

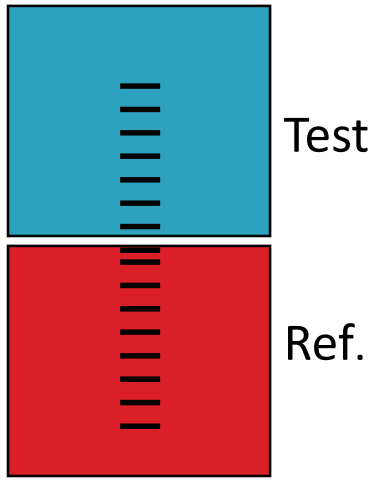


a) PARALLEL DESIGN

A parallel design is a completely randomised design in which each subject receives one & only one formulation of a drug in a random fashion.

The simplest parallel design is the two- group parallel design, which compares 2 formulations of a drug.

Each group contains equal number of subjects



Parallel

b) CROSS-OVER EXPERIMENTAL DESIGNS

1. Completely randomized designs (CRD)

2. Randomized complete block design (RCBD)

3. Latin square design (LSD)

4. Balanced incomplete block design (BIBD)

5. Partially incomplete block design (PIBD)

Randomized Complete Block Design of 6 subjects receiving four treatments

SUBJECT	WEEK 1	WEEK 2	WEEK 3	WEEK 4
1	B	C	A	D
2	D	C	A	B
3	B	C	D	A
4	D	C	B	A
5	C	D	A	B
6	D	C	B	A

Latin Square Design for four subjects each receiving four treatments

SUBJECT	WEEK 1	WEEK 2	WEEK 3	WEEK 4
1	A	B	C	D
2	D	C	A	B
3	C	D	B	A
4	B	A	D	C

Balanced Incomplete Block Design for 6 subjects receiving two treatments

SUBJECT	WEEK 1	WEEK 2
1	A	B
2	B	C
3	C	D
4	D	A
5	B	D
6	A	C

Partially Balanced Incomplete Block Design of 4 subjects and 4 treatments

SUBJECT	WEEK 1	WEEK 2	WEEK 3	WEEK 4
1	A	B	C	D
2	B	C	A	D
3	C	D	B	A
4	D	A	C	B

Replicate Cross-Over Design

SUBJECT	WEEK 1	WEEK 2	WEEK 3	WEEK 4
1	A	B	A	B
2	B	A	B	A

ADVANTAGES

- Allows comparisons of within-subject variances for the test and reference products.
- Provides more information about the intrinsic factors underlying formulation performance
- Reduces the number of subjects participating in the BE study

Wash-out period

- An adequate washout period (e.g., more than 5 half lives of the moieties to be measured) should separate each treatment.
- If more highly complex kinetic models are anticipated or for drugs with the potential for physiologic carryover effects, the washout time should be adjusted accordingly.
- The washout period should be sufficiently long to allow the second period of the cross-over study to be applicable in the statistical analysis.

Parallel *vs* Cross-over design

PARALLEL DESIGN

Advantages

- ✓ Easy to organise
- ✓ Easy to analyse
- ✓ Easy to interpret

Disadvantages

- ✓ Comparison is carried-out between subjects: Not very powerful

CROSS-OVER DESIGN

Advantages

- ✓ Comparison is carried out within & between subjects: Much Powerful
- ✓ Each cross-over patient serves as his or her own control

Disadvantages

- ✓ Unsuitable for long half-life drugs
- ✓ carry-over effect due to inappropriate wash-out
- ✓ Order effects the results
- ✓ Difficult to analyse
- ✓ Takes long time to complete
- ✓ Not optimal for study in patients

Crossover vs. Parallel Designs

- Intra-subject comparison
- Lower variability
- Generally fewer subjects required

Crossover design preferred

- Drug with very long half-life
- Crossover design not practical

Parallel design may be useful

Parallel design may be considered as an alternative to a crossover design if :

- Inter-subject variability is relatively small compared with the intra-subject variability.
- Drug is potentially toxic or has a very long elimination half-life.
- Population of interest consists of very ill patients and
- Cost for increasing the number of subjects is much less than that of adding an additional treatment period

2. Fasting or fed conditions

- Fasted conditions
  - Study conducted under fasted conditions normally
  - Comparator product labeling (SPC)
    - Specifies fasted conditions
    - Does not specify fasted/fed for administration
    - States that either fasted or fed administration
- Fed conditions
  - If specified in comparator product labeling (SPC)
- Type of meal to be consumed
  - high-fat, high-calorie meal
  - “standard” or typical breakfast”

Fasting or fed conditions(contd…)

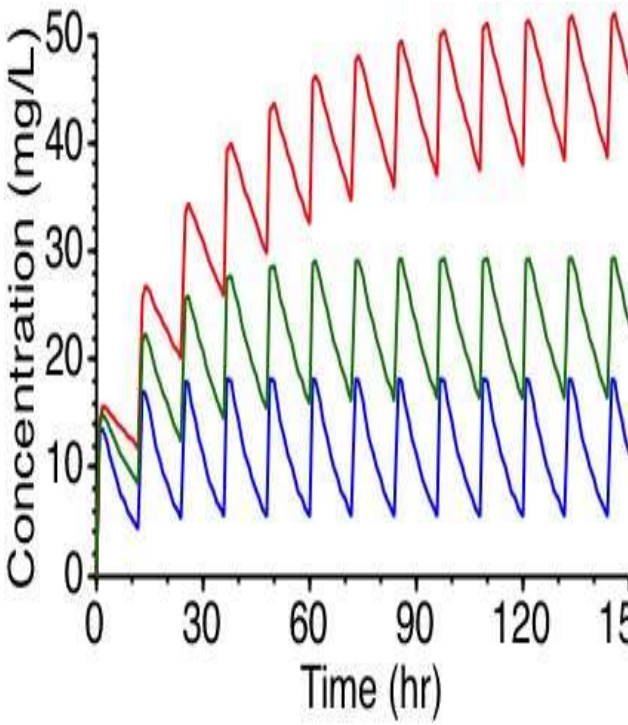
- For products with enhanced release characteristics differing from conventional immediate release formulations (e.g. microemulsions or solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required.

EXAMPLES

With food	• Ritonavir • Artemether
Without food	• Isoniazid • Rifampicin
Both Fasted and fed	• Didanosine (enteric-coated)

3. Single dose vs multiple dose studies

- **Multiple-dose Studies may be employed when:**
  - Non-linear pharmacokinetics at steady-state (e.g., saturable metabolism)
  - Assay not sufficiently sensitive for single-dose study
  - Drug is too potent/toxic for administration in healthy volunteers
    - Patients / no interruption of therapy
  - Extended/modified release products
    - Accumulation using recommended dosing interval
    - In addition to single-dose studies



4. Replicate Designs

- Typically four-period design
  - Each product administered twice
- Intra-subject variability
- Subject X formulation interaction
- Different approaches possible
  - Average bioequivalence
  - Individual bioequivalence
- Advantages
  - More information available
  - Different approaches to assessment possible
- Disadvantages
  - Bigger commitment for volunteers
  - More administrations to healthy volunteers
  - More expensive to conduct

Study conduct

- 1. STANDARDISATION

  To minimise the variability of all factors involved except that of the products being tested. It is recommended to standardise diet, fluid intake and exercise.

  - The time of day for ingestion should be specified.
  - **FLUID INTAKE WITH DRUG** As fluid intake may influence gastric passage for oral administration forms, the test and reference products should be administered with a standardised volume of fluid (at least 150 ml).
  - **POSTURE AND PHYSICAL ACTIVITY** As the bioavailability of an active moiety from a dosage form could be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardised.

Standardisation contd…

- **FOOD AND FLUID INTAKE** may interact with circulatory, gastrointestinal, hepatic or renal function (e.g. alcoholic or xanthine-containing beverages or grapefruit juice).

- **CONCOMINANT MEDICATION** Subjects should not take any other concomitant medication (including herbal remedies) for an appropriate interval before as well as during the study. In case concomitant medication is unavoidable and a subject is administered other drugs, the use must be reported (dose and time of administration) and possible effects on the study outcome must be addressed.

2. Sampling

- **Blood sampling**
  - Should be extended to at least 3 elimination half lives
  - At least 3 sampling points during absorption phase, 3–4 at the projected Tmax, and 4 points during elimination phase
  - Sampling should be continued for a sufficient period to ensure that AUC_{0-t} to $AUC_{0-\infty}$ is only a small percentage (normally ,20%) of the total AUC.

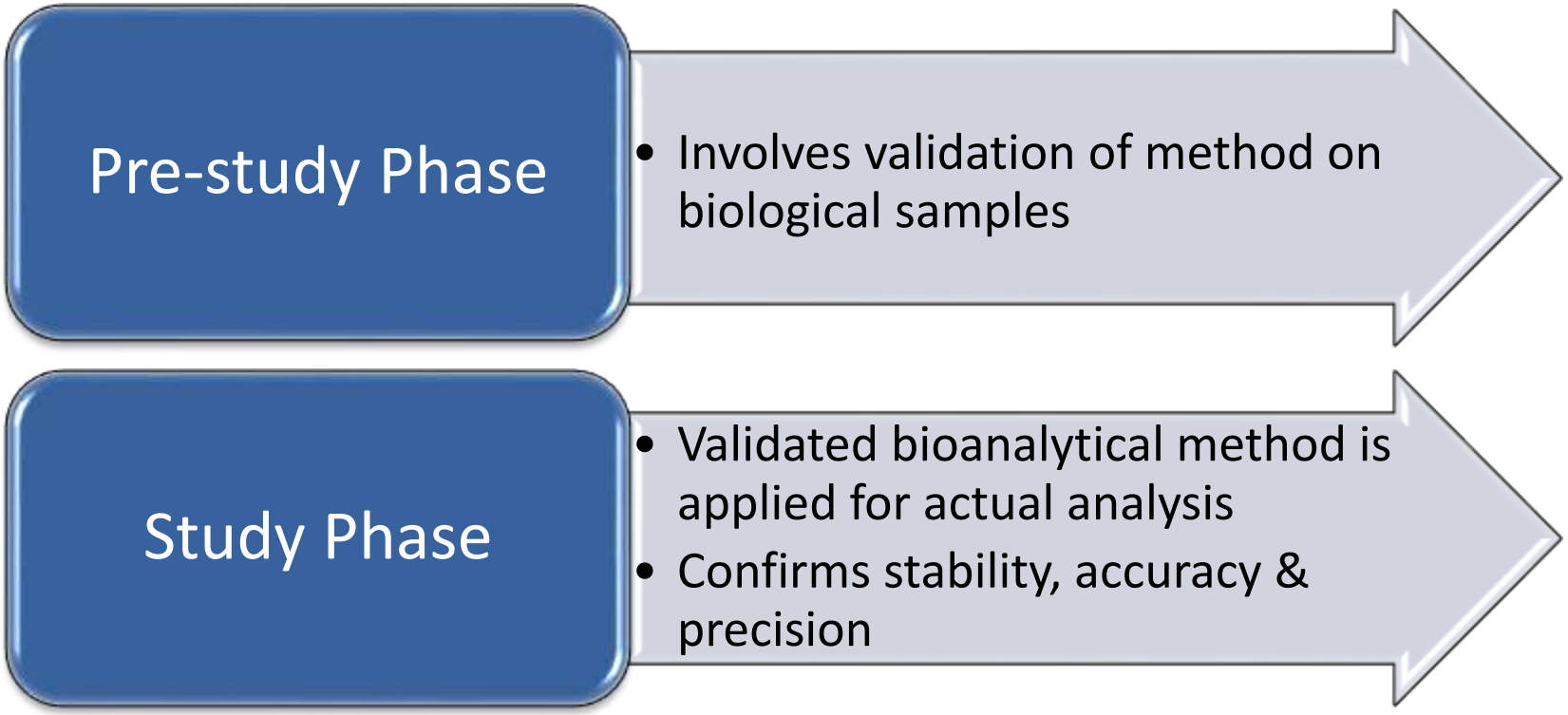
- **Urinary sampling**
  - Collect urine samples for 7 or more half-lives

3.Bioanalysis

- Should address the following characteristics of the assay:
  - a) Stability of stock solutions.
  - b) Stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.
  - c) Specificity.
  - d) Accuracy.
  - e) Precision.
  - f) Limits of detection and quantification.
  - g) Response function.
  - i) Robustness and ruggedness

Validation of analytical method

- Consists of two phases :



Pre-Study Phase

- Bioanalytical Method must be evaluated for:

STABILITY	• Of drug &/or metabolite in biological matrix under experimental conditions
SELECTIVITY/ SPECIFICITY	• Data to show – assay is free from interference by endogenous / degradation products, other drugs/metabolites
PRECISION & ACCURACY	• Should be documented at low, intermediate & high concentrations • Intra-assay precision (within days) –in terms of coefficient of variation N.M.T 15% • Inter-assay precision (between days) –N.M.T 20%

SENSIVITY

- Capacity to detect even small concentration
- Limit of Detection < Limit of Quantification

RANGE & LINEARITY

- Entire range should be covered
- For Linear relationships- Standard curve at 5 points should be defined
- For Non-Linear relationships-additional points taken

RECOVERY

- Documentation of extraction at high, medium, low concentrations
- Method with low recovery- more error prone
- Recovery of any internal standard should also be assessed

ANALYTICAL SYSTEM STABILITY

- Reproducibility of standard curve should be monitored during the assay
- Run analytical standard at beginning and at end of analytical run

Post Study Phase

- Analysis of sample done by single determination, with acceptable variability as defined by validation data without the need for a duplicate or replicate analysis

- A standard curve should be
  - ✓ generated for each analytical run for each analyte
  - ✓ used to calculate concentration of the analyte in the unknown samples assayed with that run
  - ✓ Able to cover entire range of concentrations in the unknown samples

- Extrapolation of Standard Curve below the lowest or above the highest standard concentration not recommended

4. STATISTICAL EVALUATION OF THE DATA

Analysis of Variance (ANOVA)

- Is a statistical procedure used to determine difference between TREATMENT and CONTROL groups
- May evaluate variability in:
  - **S**ubjects
  - **T**reatment groups
  - **S**tudy period
  - **F**ormulation
- Parameters tested include:

  C_{max} , AUC_{0-t}, $AUC_{0-\infty}$, t_{max}

  obtained for each treatment or dosage form

(t_{max} in case it is clinically relevant; analysed by non-parametric method)

DECISION RULES

Decision rules were proposed by FDA for testing the BE in terms of average bioavailability

- **75/75 RULE**

  BE is claimed if at least 75% of individuals being tested had ratios (relative individual bioavailability of the test formulation to the reference formulation) within (75%,125%) limits.

- **80/20 RULE**

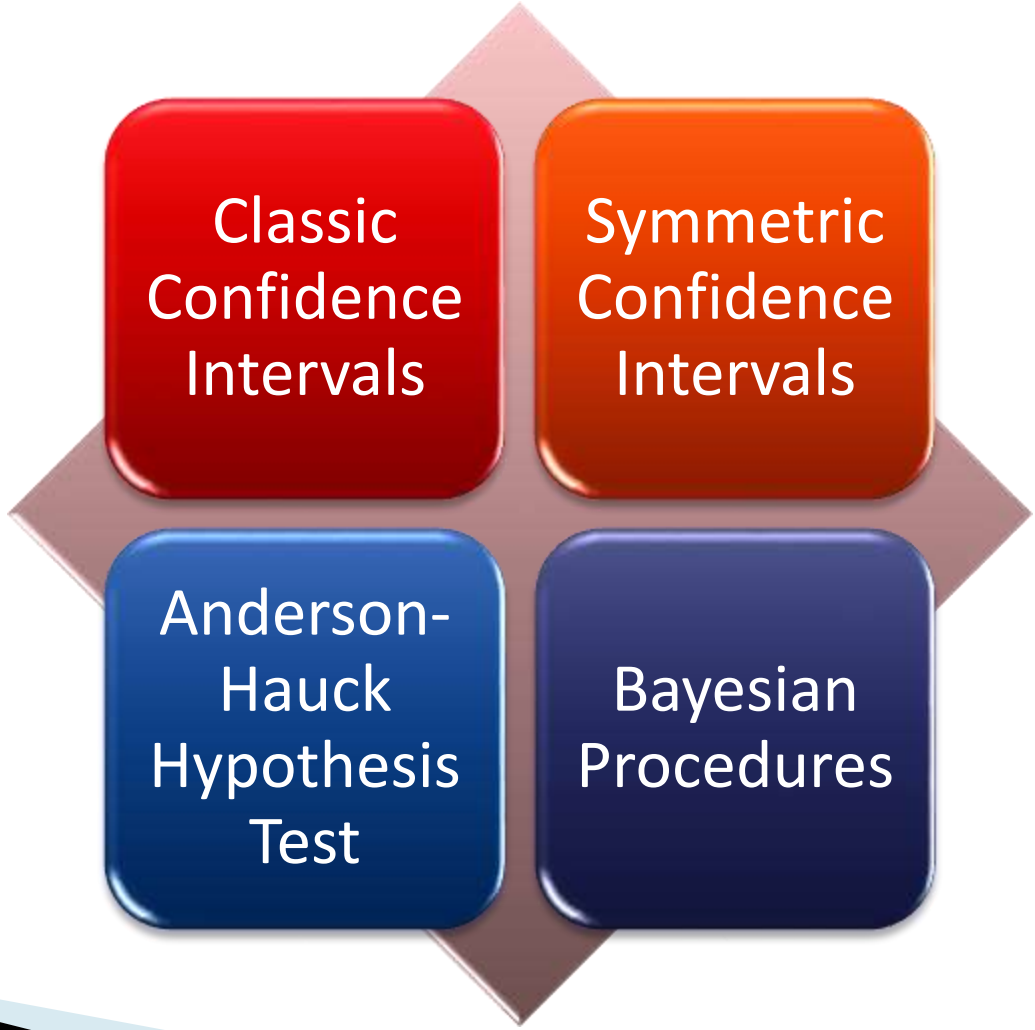
  If the test average is not statistically significantly different from the reference average & if there is at least 80% power for detection of a 20% difference of the reference average, then bioequivalence is concluded

DECISION RULES (contd...)

- **±20 RULE**

  BE is concluded if the average bioavailability of the test formulation is within ±20% of that of the reference formulation, with a certain assurance.

Decision Procedures



CONFIDENCE INTERVAL APPROACH (Schuirmann, 1987)

- Confidence interval is estimated based on Student's *t*-distribution.
- When log-transformed data are used, the 90% confidence interval is set at 80-125%.

90% Confidence interval is a function of:

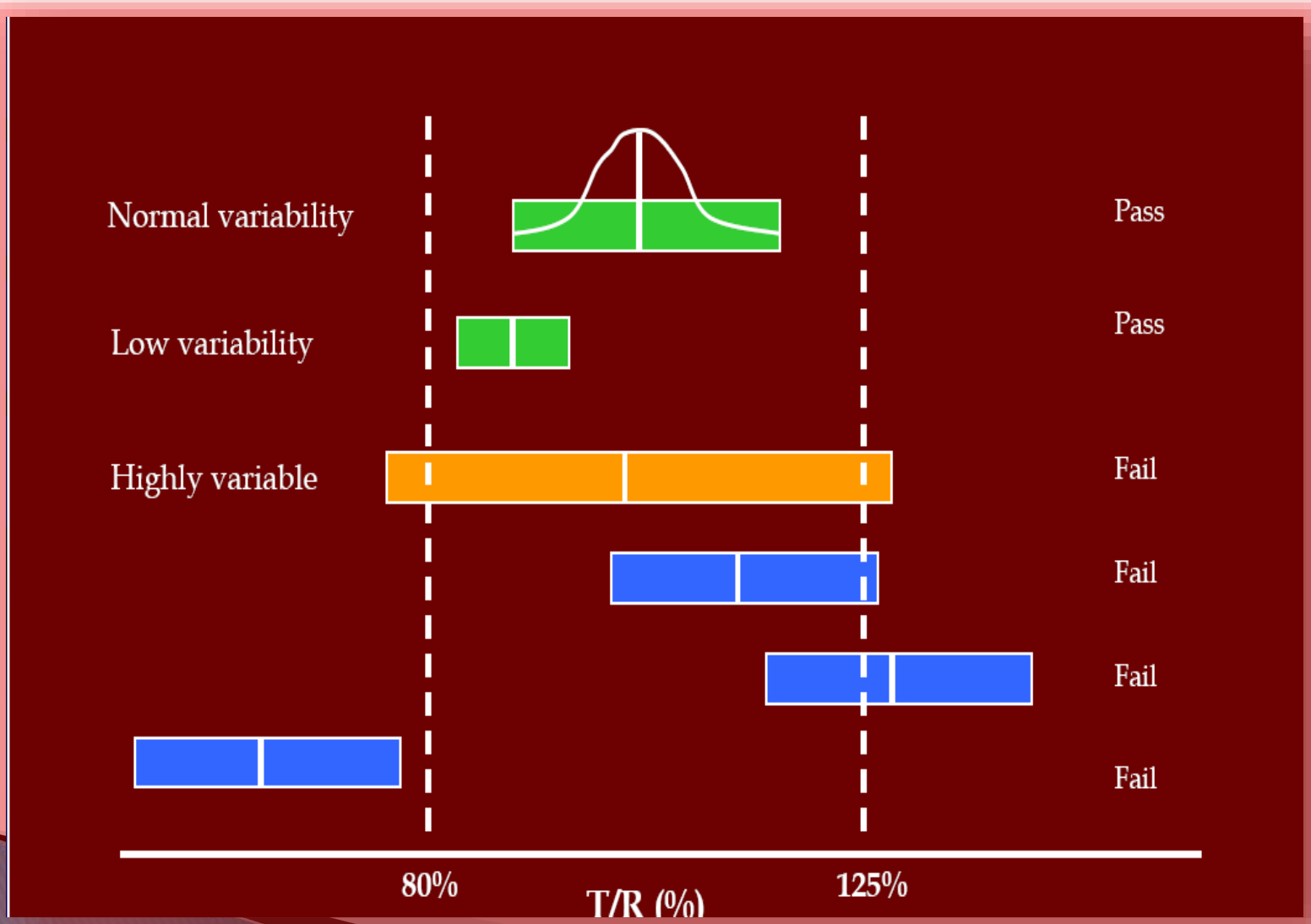
- Sample size
- Study variability

- Logarithmic transformation of parameters should be done before performing statistical analysis to meet assumption of normality.

Two One-Sided Tests Procedure

±

Possible BE Results(90%CI)



DECISION RULES

REALITY

DECISION	BIOEQUIVALENT	BIOINEQUIVALENT
BIOEQUIVALENT	CORRECT DECISION EVERYBODY GAINS	INCORRECT DECISION CONSUMER LOSES
BIOINEQUIVALENT	INCORRECT DECISION MANUFACTURER LOSES	CORRECT DECISION CONSUMER GAINS

Biowaivers

IN VITRO STUDIES

Only *in vitro* studies sufficient as surrogate

IN VIVO STUDIES

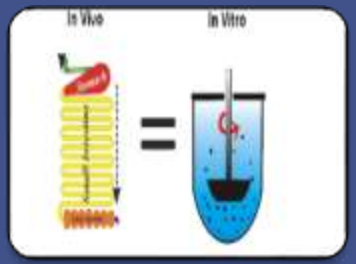
Exemption to *in vivo studies is* BIOWAIVER

Contd…

Applications for biowaivers are granted on the basis of:

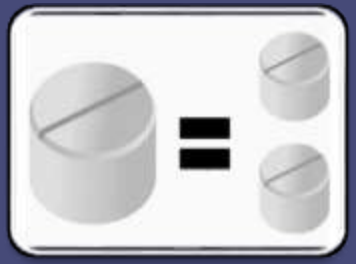
BCS

- Considers the dose:solubility ratio, permeability and dissolution behaviour.



IVIVC

- Based on correlation between *in vitro* data and *in vivo* profile.



Composition Proportionality

- New product is qualitatively same and quantitatively proportional to bio-batch.

Biowaivers

A

- Aqueous parenteral solutions
- Solutions for oral use (syrups, elixirs, tinctures & other soluble forms but not suspensions)
- Powders for reconstitution as a solution
- Otic or ophthalmic aqueous solutions
- Topical aqueous solutions
- Aqueous nebulizing inhalations or nasal sprays

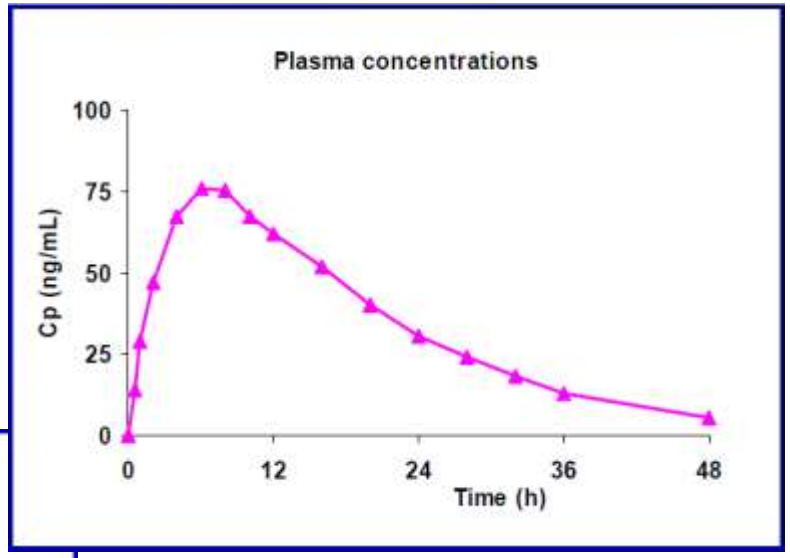
Composition Proportionality

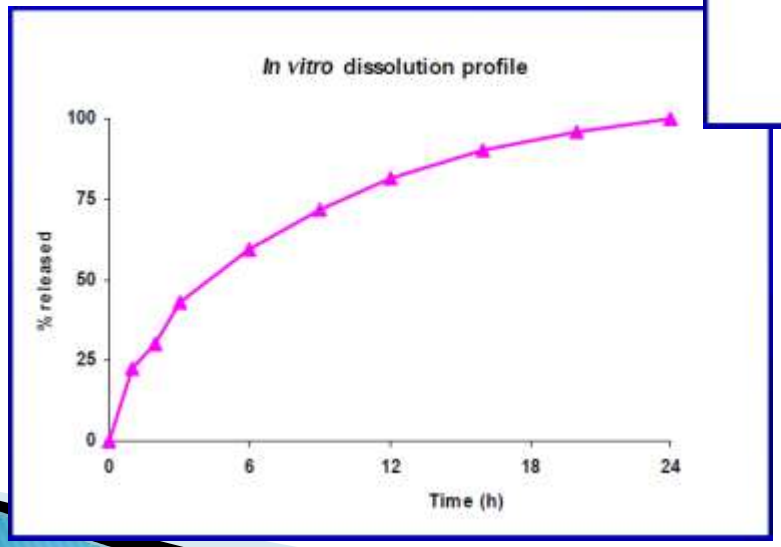
- Basis of biowaivers for additional strength
- Criterion: API and excipients must be-
  - ❖ Qualitatively same
  - ❖ Quantitatively *proportional*
- Manufactured by same manufacturing process

in vitro - in vivo Correlation

Used for biowaiver grants of :

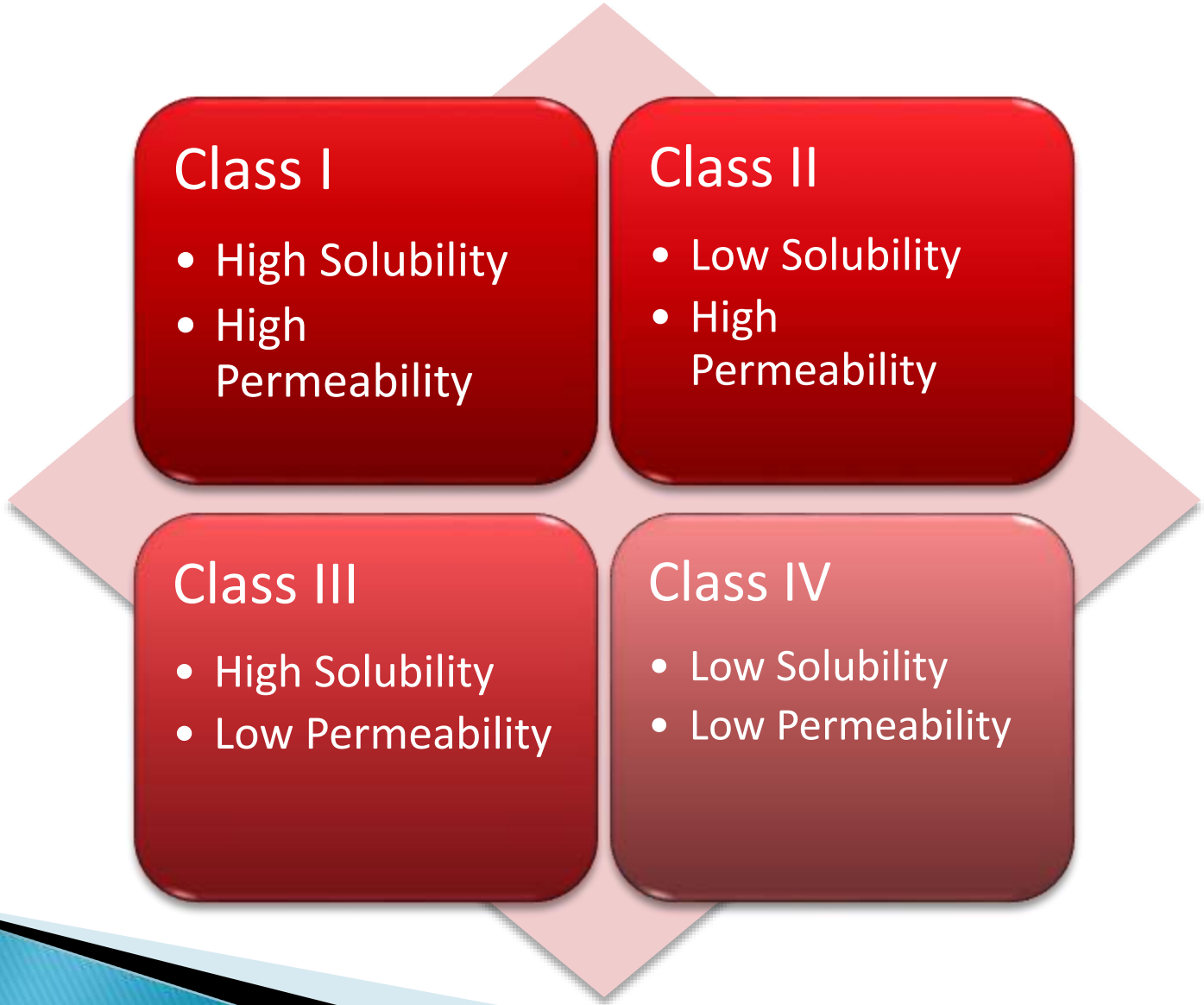
- *modified release* products or
- products subject to change in manufacturing procedure.





Waiver of Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (B.C.S)

BCS based biowaivers



Biopharmaceutics Classification System (BCS)

Goals of the BCS Guidance:

- To recommend methods for classification according to dosage form dissolution, along with the solubility and permeability characteristics of the drug substance
- Predict in vivo performance of drug products from in vitro measurements of permeability and solubility
- To recommend a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on in vitro dissolution tests
- To improve the efficiency of drug development and the review process by recommending a strategy for identifying expandable clinical bioequivalence tests

	High Solubility	Low Solubility
High Permeability	**Class 1** Abacavir Acetaminophen *Acyclovir*[b] *Amiloride*[S,I] Amitryptyline[S,I] Antipyrine *Atropine* **Buspirone**[c] Caffeine *Captopril* Chloroquine[S,I] **Chlorpheniramine** Cyclophosphamide Desipramine **Diazepam** **Diltiazem**[S,I] **Diphenhydramine** Disopyramide **Doxepin** Doxycycline Enalapril Ephedrine Ergonovine Ethambutol Ethinyl Estradiol Fluoxetine[I] Glucose Imipramine[I] **Ketorolac** Ketoprofen Labetolol Levodopa[S] Levofloxacin[S] **Lidocaine**[I] Lomefloxacin **Meperidine** Metoprolol Metronidazole **Midazolam**[S,I] **Minocycline** Misoprostol **Nifedipine**[S] Phenobarbital Phenylalanine Prednisolone **Primaquine**[S] Promazine Propranolol[I] **Quinidine**[S,I] Rosiglitazone Salicylic acid Theophylline Valproic acid **Verapamil**[I] Zidovudine	**Class 2** **Amiodarone**[I] **Atorvastatin**[S, I] **Azithromycin**[S ,I] **Carbamazepine**[S,I] **Carvedilol** Chlorpromazine[I] **Cisapride**[S] *Ciprofloxacin*[S] **Cyclosporine**[S, I] **Danazol** **Dapsone** Diclofenac Diflunisal Digoxin[S] *Erythromycin*[S,I] Flurbiprofen **Glipizide** **Glyburide**[S,I] Griseofulvin Ibuprofen **Indinavir**[S] Indomethacin **Itraconazole**[S,I] **Ketoconazole**[I] **Lansoprazole**[I] **Lovastatin**[S,I] *Mebendazole* Naproxen Nelfinavir[S,I] Ofloxacin Oxaprozin Phenazopyridine Phenytoin[S] Piroxicam Raloxifene[S] **Ritonavir**[S,I] **Saquinavir**[S,I] **Sirolimus**[S] Spironolactone[I] **Tacrolimus**[S,I] Talinolol[S] **Tamoxifen**[I] **Terfenadine**[I] Warfarin

	High Solubility	Low Solubility
Low Permeability	**Class 3** *Acyclovir* *Amiloride* [S,I] Amoxicillin [S,I] Atenolol *Atropine* Bisphosphonates Bidisomide *Captopril* Cefazolin Cetirizine Cimetidine [S] *Ciprofloxacin* [S] Cloxacillin Dicloxacillin [S] *Erythromycin* [S,I] Famotidine Fexofenadine [S] Folinic acid *Furosemide* Ganciclovir *Hydrochlorothiazide* Lisinopril Metformin *Methotrexate* Nadolol Pravastatin [S] Penicillins Ranitidine [S] Tetracycline Trimethoprim [S] Valsartan Zalcitabine	**Class 4** Amphotericin B Chlorthalidone Chlorothiazide Colistin *Ciprofloxacin* [S] *Furosemide* *Hydrochlorothiazide* *Mebendazole* *Methotrexate* Neomycin

Conditions for BCS Bio-waivers

Firms can request waivers of in vivo testing for Class 1 drug substances

Drug products must meet these criteria:

- Immediate-release solid oral dosage forms
- Highly soluble, highly permeable drug substance
- Rapid in vitro dissolution

Note: Waivers not applicable for narrow therapeutic range therapeutic range (Digoxin, Lithium, phenytoin, warfarin) drugs

BCS Class I: Dissolution

- **USP Apparatus I (100 rpm) or II (50 rpm)**
- **Three media**
  - 0.1 N HCl or SGF USP without enzymes 0.1 N HCl or SGF USP without enzymes
  - pH 4.5 buffer pH 4.5 buffer
  - pH 6.8 buffer or SIF USP without enzymes
- **NLT 85% dissolves within 30 minutes**
- **Similarity factor (f_2) for test (T) v. reference (R) profile comparisons should > 50**

HHS-Food and Drug Administration

Dosage Forms

- Parenterals, solutions, IR solid oral dosage forms

Drug Efficacy Study Implementation (DESI)

- No past *bioINequivalence* case
- Example: Hydroxyzine Hydrochloride Tablets

Fed-BE Study

- If taken on empty stomach
- No effect of food

HHS-Food and Drug Administration

BCS Based Biowaivers

- Only IR products with class 1 APIs
- Post-change products *(for minor changes)*

Proportional Similarity based biowaivers

- Else additive change must be NMT 10% *or*
- Change of API compensated by excipients in different strengths

IVIVC based biowaivers

- For MR products
- Post-change products (SUPAC Level 3)

COMPARISON


CDSCO


TGA
Health Safety
Regulation


World Health Organization


FDA


emea

Biopharmaceutics Classification System

HHS-FDA

WHO

High Aqueous Solubility:

- Ratio of highest orally administered dose (in mg) to the solubility (mg/ml) is **250 ml or lower** over pH range **1-7.5** at 37°C

pH range 1-6.8

INDIAN:
Same as FDA

High Permeability:

- **90% or more** of orally administered dose is absorbed in small intestine

85% or more

HHS-FDA

CLASS I *Highly permeable* *Highly soluble* *Eligible*	**CLASS II** *Highly permeable* *Poorly soluble* *Not eligible*
CLASS III *Poorly permeable* *Highly soluble* *Not eligible*	**CLASS IV** *Poorly permeable* *Poorly soluble* *Not eligible*

FOR BIOWAIVER

D:S 250 ml

85% abs

CLASS I *Highly permeable* *Highly soluble* *Eligible*	**CLASS II** *Highly permeable* *Poorly soluble* *Eligible only if the D:S is 250 ml or lower at pH 6.8*
CLASS III *Poorly permeable* *Highly soluble* *Eligible if very rapidly dissolving*	**CLASS IV** *Poorly permeable* *Poorly soluble* *Not eligible*

WHO

CRITERIA FOR BIOWAIVER

	HHS-FDA	WHO		INDIAN
Category	Rapidly dissolving	Very rapidly dissolving	Rapidly dissolving	Rapidly dissolving
Release	at least 85% of its content in 30 min.	>85% of labeled amount of drug in 15 min.	>85% of labeled amount of drug in 30 min.	>80% dissolution within 15 min.
Dissolution media of pH	1.2, 4.5, 6.8	1.2, 4.5, 6.8		1.2, 4.5, 6.8
Temperature (°C)	37±1	37±1		37±0.5
Apparatus	Paddle: 50 rpm Basket: 100 rpm	Paddle: 75 rpm Basket: 100 rpm		Paddle: 50 rpm Basket: 100 rpm
APIs of BCS	Class I	Class III	Class I &/or Class II	Class I
Similarity Factor	>50	>50		

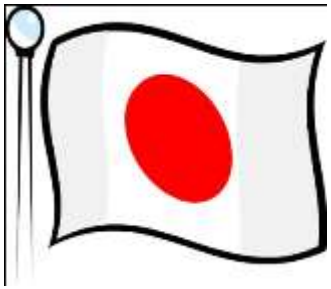
EMEA

	EMEA 2010
Volume of Dissolution media	900 ml
Temperature (°C)	37±1
Agitation Speed	Paddle: 50 rpm Basket: 100 rpm
Buffer	pH 1.0-1.2 pH 4.5 pH 6.8
Other conditions	No surfactant, in case of gelatin capsules or tablets with gelatin coatings use of enzymes acceptable
Similarity factor f_2	50-100

500 ml

EMEA 2008

pH 1.2, 4.5, 6.8



Oral Conventional Dosage Forms

Apparatus	JP paddle (50, 100 rpm)
Volume of dissolution media	900 ml
Temperature (°C)	37±0.5

% DISSOLVED	TIME	SIMILARITY FACTOR
85%	15 min.	Not required
85%	Between 15 & 30 min.	NLT 42
Not reaches 85%	Within 30 min.	
-- reaches 85%	Specified	NLT 42
-- 50 to 85%	Specified	NLT 46
-- not reaches 50%	Specified	NLT 53

Oral Controlled Release Products

Apparatus	Agitation	Test fruid	Other conditions
Paddle	50rpm	(1) pH1.2	
		(2) pH3.0-5.0[a)]	
		(3) pH6.8-7.5[a)]	
		(4) Water	
		(3) pH6.8-7.5[a)] + Polysorbate(1.0*W/V*%)	
	100rpm	(3) pH6.8-7.5[a)]	
	200rpm	(3) pH6.8-7.5[a)]	
Basket	100rpm	(3) pH6.8-7.5[a)]	
	200rpm	(3) pH6.8-7.5[a)]	
Disintegration	30 cpm	(3) pH6.8-7.5[a)]	without disk
	30 cpm	(3) pH6.8-7.5[a)]	with disks

a) The test solution should be selected which provides the slowest dissolution from the reference product and gives average 85% dissolution or more within the testing time specified, 2 hr at pH1.2 and 6 hr at other pHs. If the dissolution from reference product does not reach 85 % at the specified time in any test fluids, the test solution providing the fastest dissolution should be used.

Modified Release Products

FDA

- Delayed release
- Extended (controlled) release

WHO

- Delayed Release
- Extended release (controlled, prolonged, sustained)

INDIAN

- Delayed release
- Sustained release
- Mixed immediate & SR
- Mixed delayed & SR
- Mixed immediate & delayed release

Standard design (FDA)

- A single-dose, fasting study on all strengths of tablets and capsules and highest strength of beaded capsules
- A single-dose, food-effect study on the highest strength
- A steady-state study on the highest strength

Submitted as NDA

- A single-dose, fasting non replicate study comparing the highest strength of the test and reference
- A food-effect, non replicate study comparing the highest strength of the test and reference

Submitted as ANDA

Standard design (WHO)

- Single- dose
- Non-replicate cross-over
- Fasting study comparing highest strength of test & reference
- Multiple-dose (in addition of single-dose) for Extended release products
- Fed state study to ensure absence of dose-dumping

Standard design (INDIAN)

IF EFFECT OF FOOD ON REFERENCE NOT KNOWN	• 2-way cross-over study • One in fasted & other in fed state
IF IT IS KNOWN WITH CERTAINITY THAT REFERENCE IS NOT EFFECTED BY FOOD	• 3-way cross-over study – reference in fasted state – test in fasted state – test in fed state

Fasting and Fed State Considerations

	FDA	WHO	INDIAN	EMEA	JAPAN
Fast pre-dose	10 h	10 h	10 h	8 h	10 h
Fast post-dose	4 h	4 h	4 h	4 h	4 h
Volume of water administered with dose	240 ml (8 ounces)	150-250 ml		At least 150 ml	100-200ml (150 ml)
Meal should be eaten within	30 min.	20 min.	15 min.	30 min.	20 min.
Test meal	High fat diet: 800-1000 kcal- 50% from fats	High fat diet: 800-1000 kcal- 50% from fats	High fat diet: 950-1000 kcal- 50% from fats	High fat diet: 800-1000 kcal- 50% from fats	Low fat diet: 700 kcal or less- NMT 20% from lipids

Water can be allowed as desired except for **1 hour before and after** drug administration.

FDA

Water is permitted *ad libitum* **2 hours after** drug administration

WHO

Blood Sampling

INDIAN

3 during absorption phase
3-4 at projected T_{max}
4 during Elimination phase

WHO

Pre-dose sample
1-2 before C_{max}
2 around C_{max}
3-4 during Elimination phase

Sampling is continued until AUC_{0-t} covers at least 80% of $AUC_{0-\infty}$ (at least 3 times terminal half-life)

FDA

12-18 samples
Pre-dose sample
Sufficient samples for C_{max}
3-4 around Elimination phase

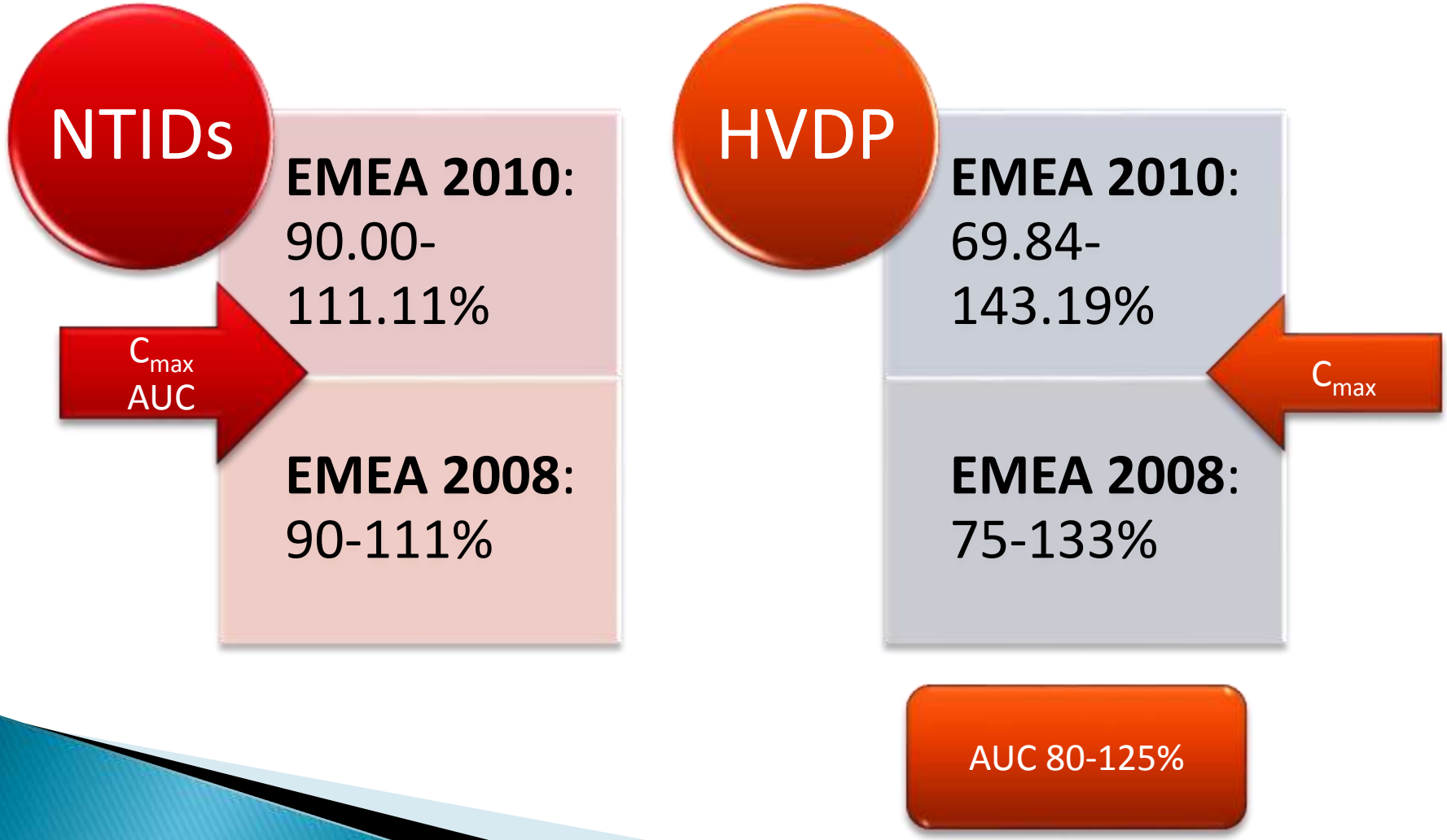
JAPAN

Zero time
1 before C_{max}
2 around C_{max}
3 during Elimination phase

Number of Subjects

FDA, EMEA, WHO, Australia, Canada	Indian
• Minimum 12	• Not less than 16

Acceptance Criteria




Thank You!