Bioequivalence Studies

Module 3 Topic 5

Outline

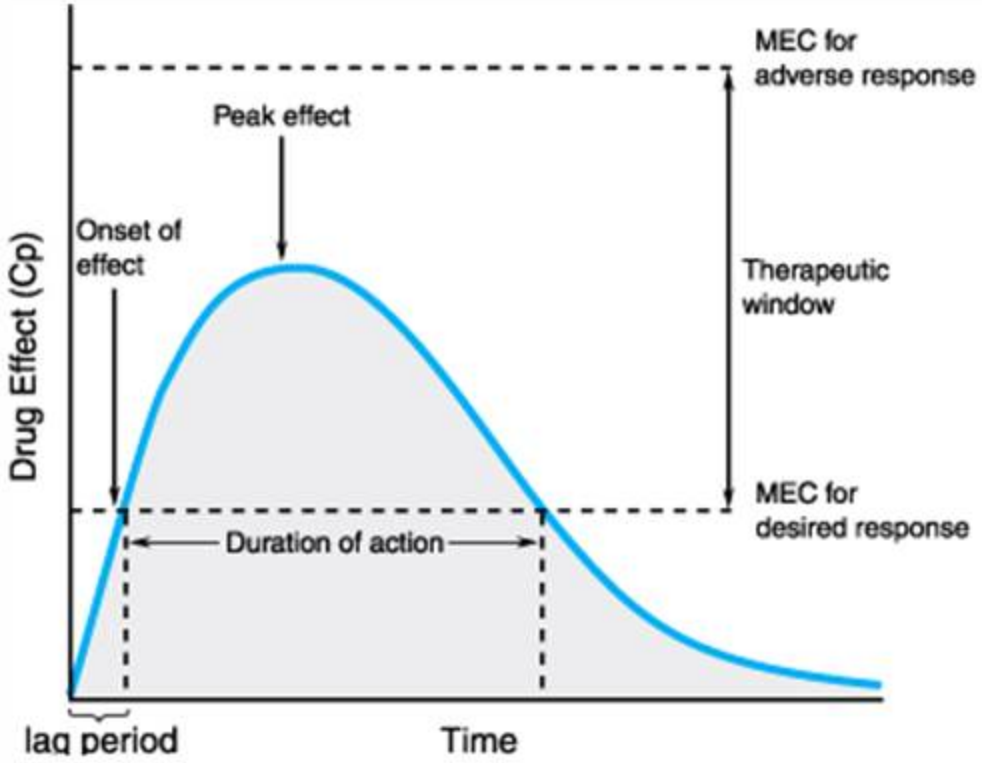
- Concept of bioavailability
- Historical cases of bio-inequivalence
- Bioequivalence testing : CDSCO, EMA and FDA guidelines
- Study designs
- Bioequivalence criteria
- Special issues

GUIDELINES FOR BIOAVAILABILITY & BIOEQUIVALENCE STUDIES

Central Drugs Standard Control Organization,
Directorate General of Health Services,
Ministry of Health & Family Welfare,
Government of India,
New Delhi.
(March 2005)

These guidelines should be read in conjunction with Schedule Y to the Drugs and Cosmetic Rules, GCP Guidelines issued by CDSCO, Ministry of Health and Family Welfare, GLP and the Ethical Guidelines for Biomedical research on human subjects issued by Indian Council of Medical Research. All provisions described in above documents shall appropriately apply to the conduct of bioavailability and bioequivalence studies.

Pharmacokinetics



Temporal characteristics of drug effect and relationship to the therapeutic window (e.g., single dose, oral administration).

Bioavailability

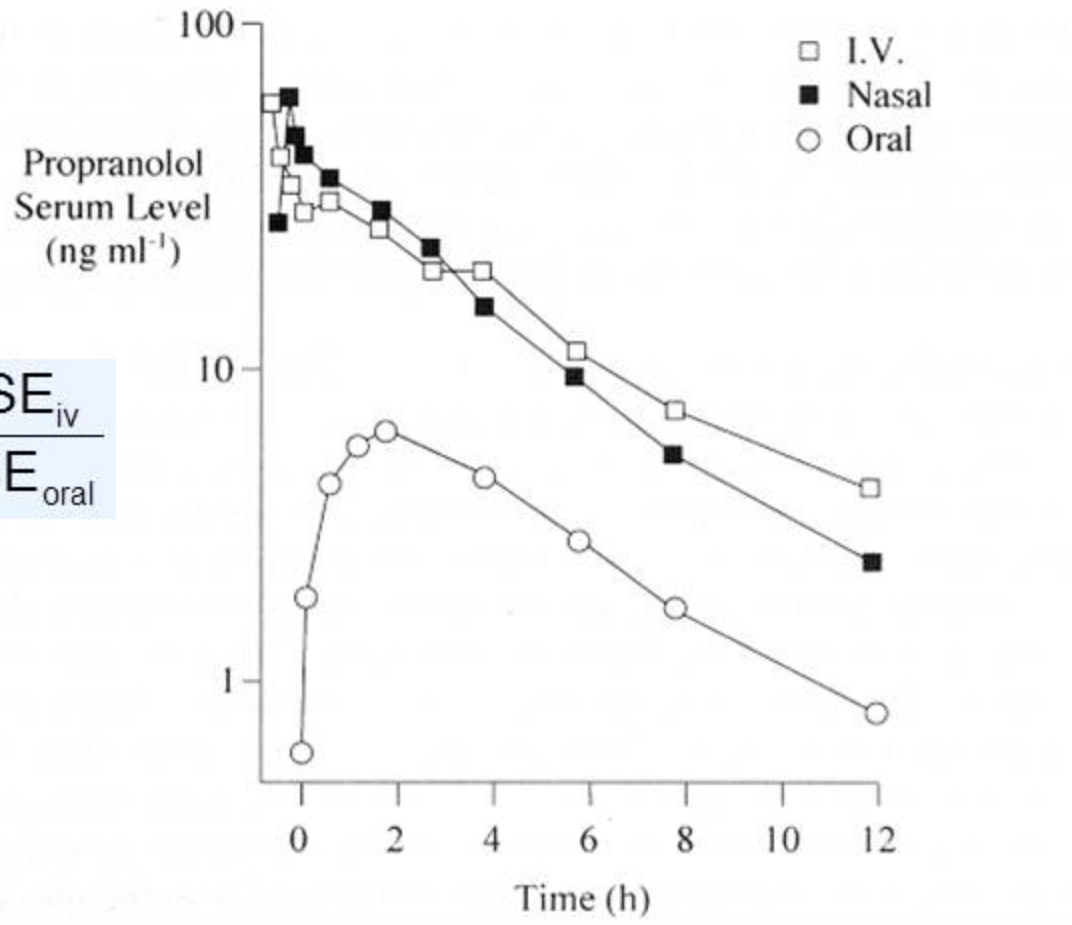
- The extent and the rate to which a drug substance or its therapeutic moiety is delivered from a pharmaceutical form into the general circulation
  - absolute bioavailability
  - relative bioavailability

Bioavailability refers to the relative amount of drug from an administered dosage form which enters the systemic circulation and the rate at which the drug appears in the systemic circulation.

CDSCO Guidance Document 2005

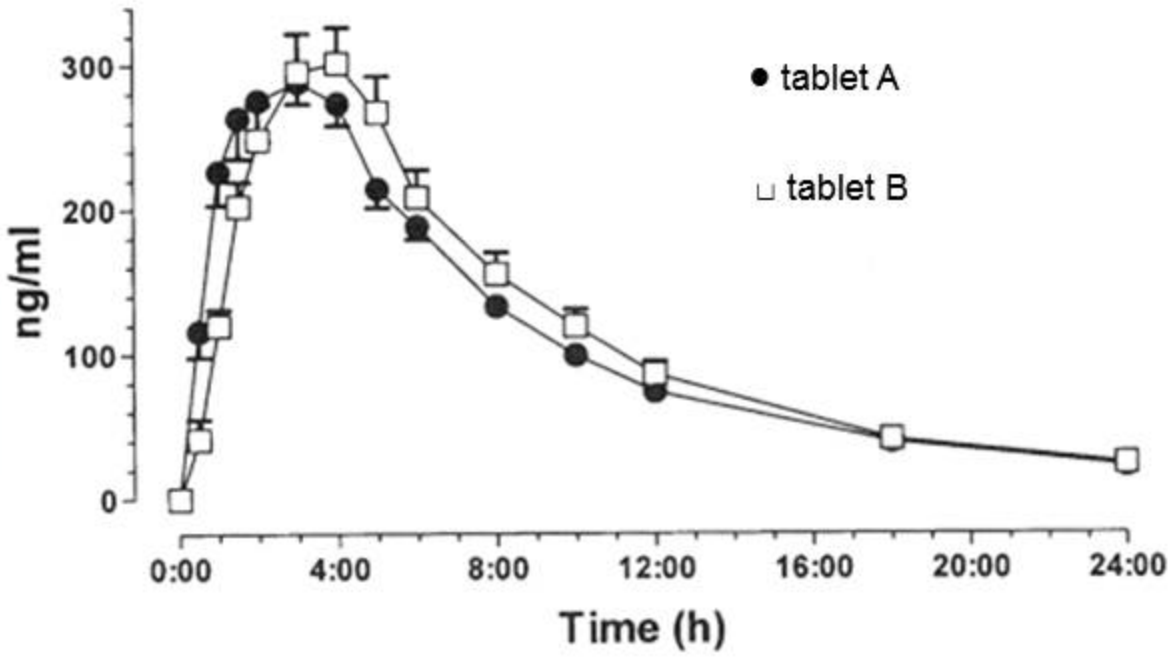
Absolute Bioavailability

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

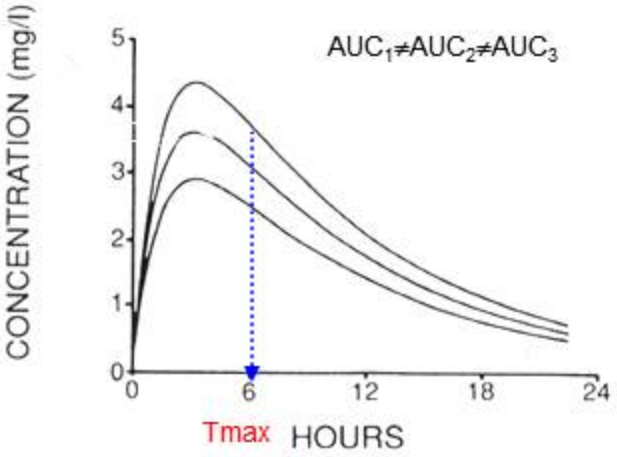


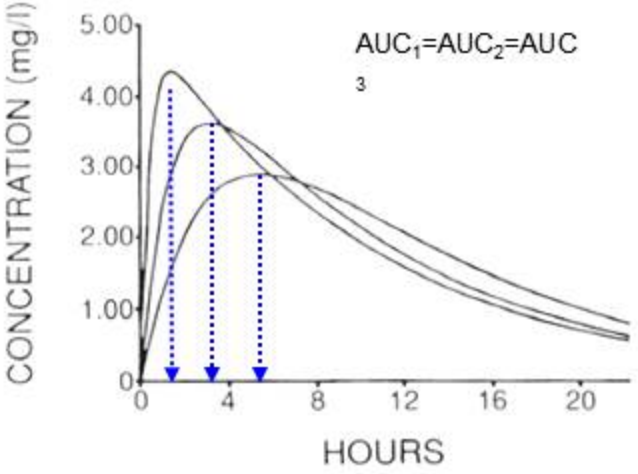
Relative Bioavailability

$$F_{rel} = \frac{AUC_{formA}}{AUC_{formB}}$$



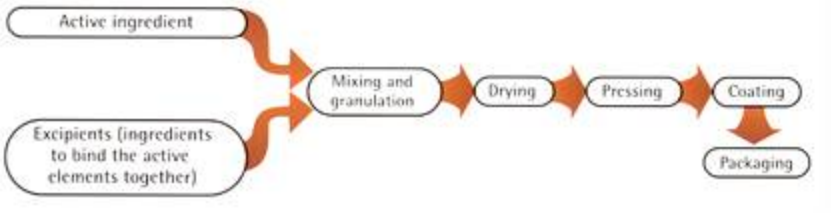
Bioavailability





Changes in extent and/or rate of absorption influence the drug plasma concentration-time profile and may therefore affect the therapeutic efficacy

Bioavailability



formulation and physicochemical factors influencing drug absorption and bioavailability

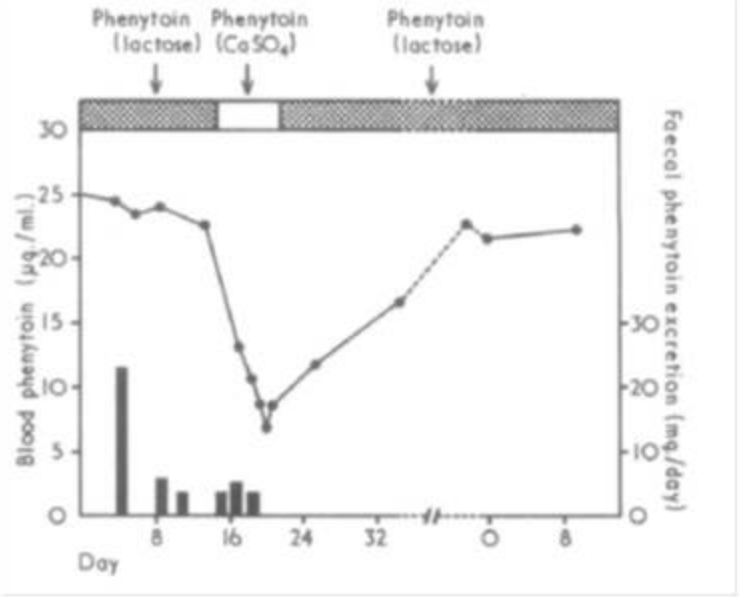
Bioavailability

- The practical importance of BA/BE testing has been demonstrated by a number of clinical reports in the 60's and the 70's documenting medical problems due to bio-inequivalence
- To allow prediction of the therapeutic effect the performance of the pharmaceutical dosage form containing the active substance should be known and reproducible
- Bioavailability and Bioequivalence is all the more important in India where the same drug is available from different companies in 100s of pharmaceutical forms.

Bioavailability

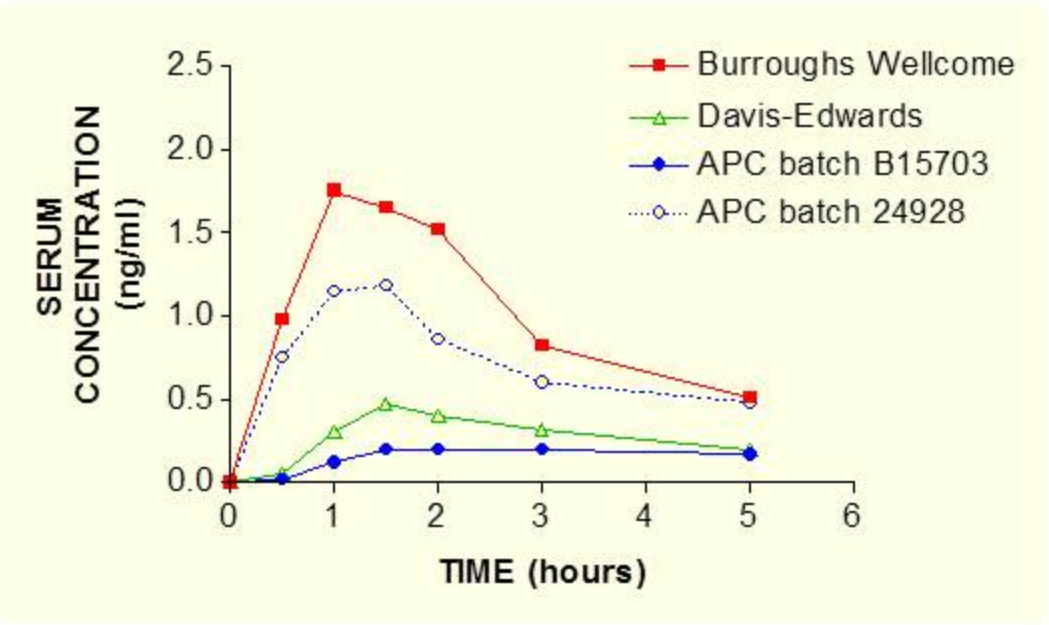
Outbreak of phenytoin intoxication around 1970 in Queensland, Australia

Calcium sulphate dihydrate in the phenytoin capsules had been replaced by lactose



Tyrer et al.: Outbreak of anticonvulsant intoxication in an Australian city. *Brit. Med. J.* 4: 271-273, 1970.

Bioavailability



Lindenbaum et al.: Variation in the biologic availability of digoxin from four preparations. *New Engl. J. Med.* 1344-1347, 1971.

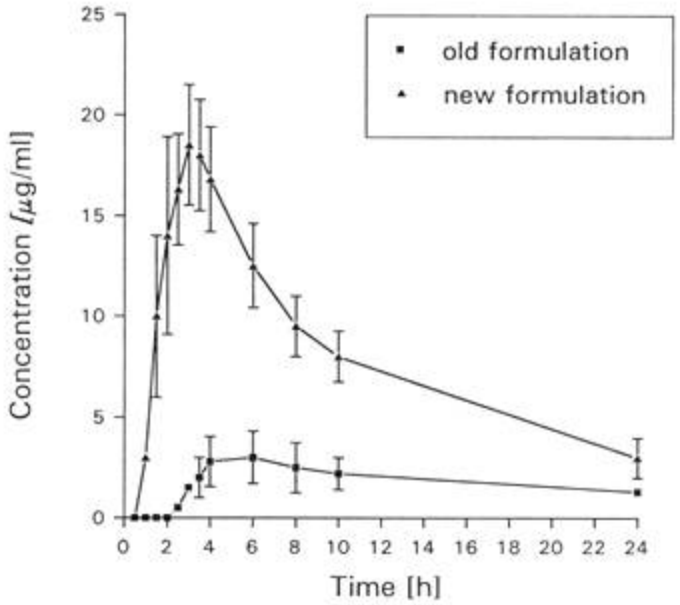
Bioequivalence

- "Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent of absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy."
- Bioequivalence of a drug product is achieved if its extent and rate of absorption are not statistically significantly different from those of the reference product when administered at the same molar dose.

CDSCO Guidance document 2005

Bioequivalence Testing

BE tests are not only required for the registration of generic drugs but are also carried out during the development of new drugs: e.g. during scale-up and for post-approval changes (SUPAC).



FDA Guidance for Industry

Bioequivalence Recommendations for Specific Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2010

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072872.pdf

EMA Guideline on the Investigation of Bioequivalence, 2010

- STUDY DESIGN

  - standard design: ***randomized, two-period, two-sequence, single dose cross-over design***

  - alternative designs: ***parallel design*** (substances with very long half-lives) and ***replicate designs*** (in case of highly variable drugs or drug products)

Study Design

The basic design of an in-vivo bioavailability study is determined by the following:

i What is the scientific question(s) to be answered.

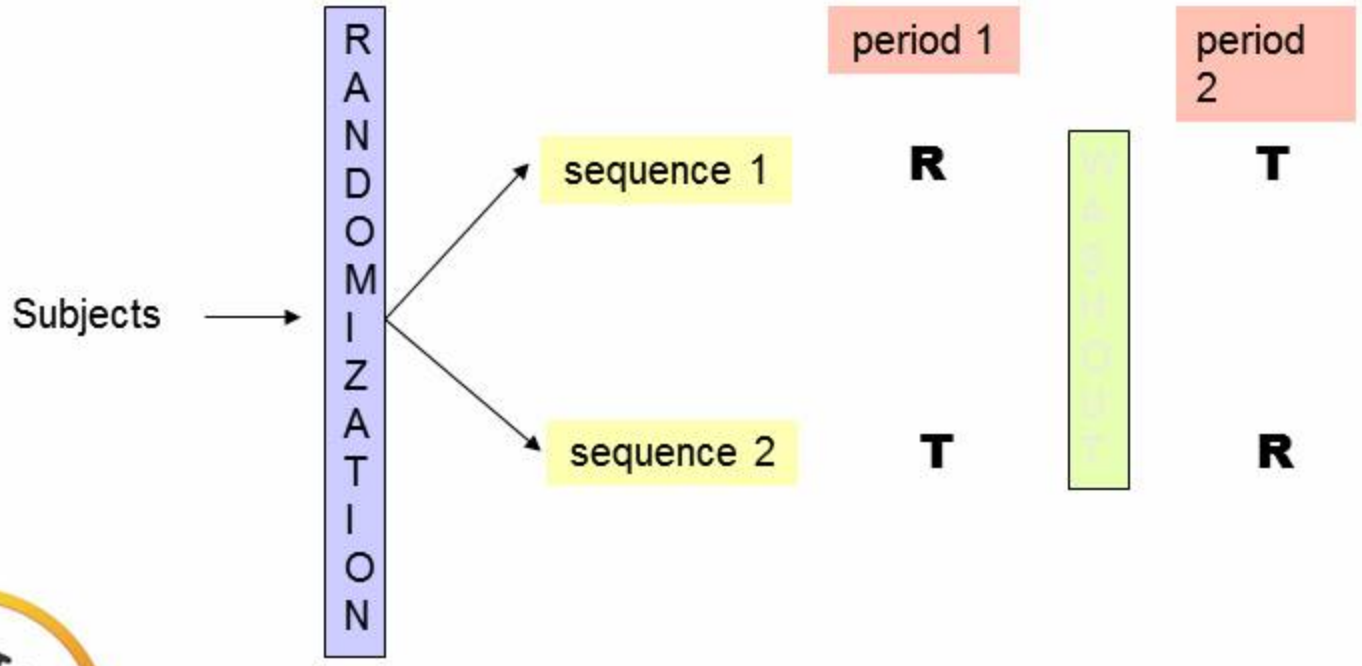
ii The nature of the reference material and the dosage form to be tested.

iii The availability of analytical methods.

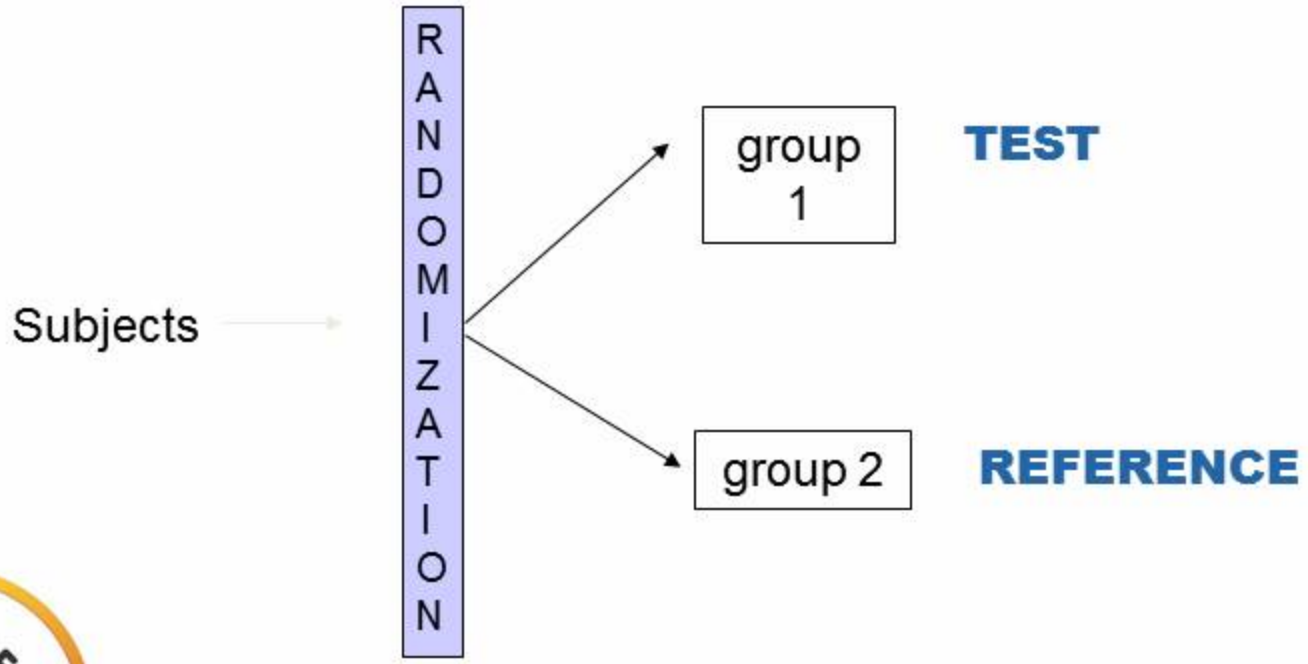
iv Benefit-risk ratio considerations in regard to testing in humans.

Typically, if two formulations are to be compared, a two-period, two-sequence crossover design is the design of choice with the two phases of treatment separated by an adequate washout period which should ideally be equal to or more than five half life's of the moieties to be measured.

2 x 2 Cross over design

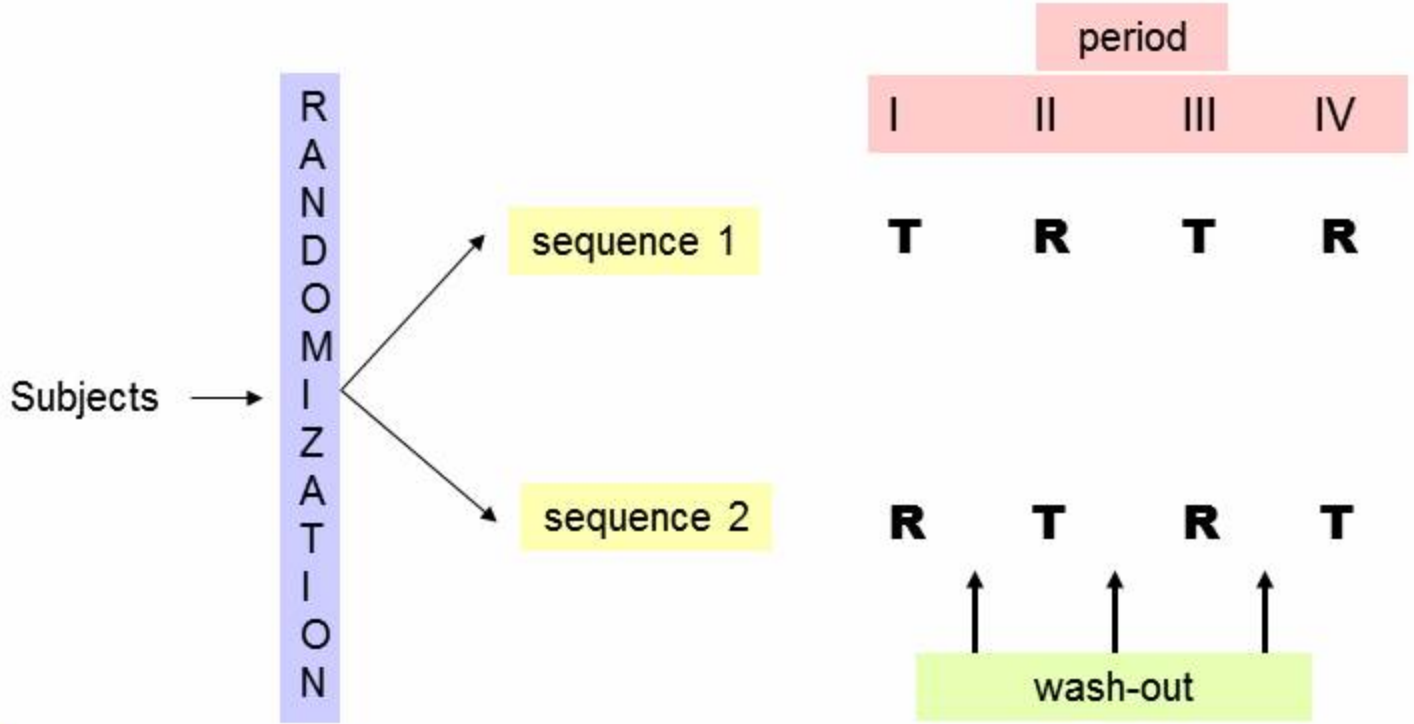


Two Group Parallel Design



Replicate Design

4-period, 2-sequence, 2-formulation design



Sample Size

The number of subjects required for a study should be statistically significant and is determined by the following considerations:

i. The error variance associated with the primary characteristic to be studied as estimated from a pilot experiment, from previous studies or from published data.

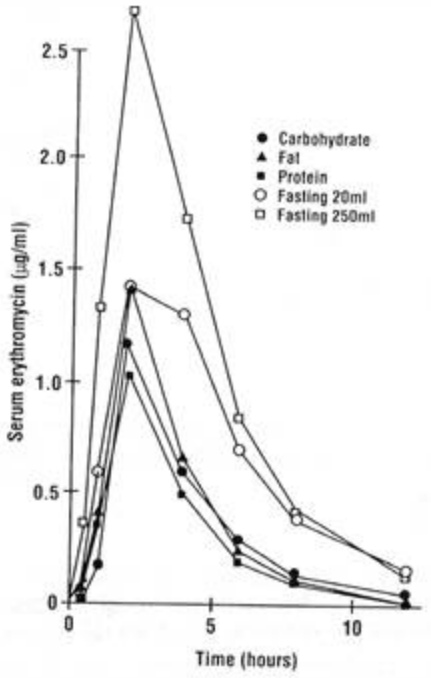
ii. The significance level desired: usually 0.05

iii. The expected deviation from the reference product compatible with bioequivalence.

CDSCO "Guidelines for Bioavailability and Bioequivalence Studies 2005"

CDSCO Guidelines 2005

The sampling period in single-dose trials of an immediate release product should extend to at least three-elimination half-lives. Sampling should be continued for a sufficient period to ensure that the area extrapolated from the time of the last measured concentration to infinite time is only a small percentage (normally less than 20%) of the total AUC.



CDSCO "Guidelines for Bioavailability and Bioequivalence Studies 2005"

Characteristics for Study

Characteristics to be Studied

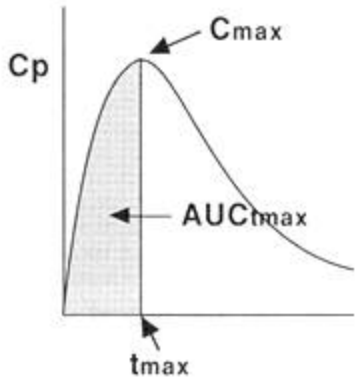
- The plasma-time concentration curve is mostly used to assess the rate and extent of absorption of the study drug. These include pharmacokinetic parameters such as the Cmax, Tmax, AUC0-tand AUC0-∞.
- For studies in the steady state AUC0-τ, Cmax, Cmin and degree of fluctuation should be calculated.

CDSCO "Guidelines for Bioavailability and Bioequivalence Studies 2005"

Rate of Absorption

- For drug products where rapid absorption is of importance, partial AUCs can be used as a measure of early exposure (FDA Guidance for Industry, 2003).

- The partial area can in most cases be truncated at the population median of Tmax values for the reference formulation: AUC_{tmax}



Analytical Method

- The bioanalytical methods used to determine the drug and/or its metabolites in body fluids must be well characterised, standardised, fully validated. The validation of the analytical method can be envisaged to consist of two distinct phases:

1. The pre-study phase involves the validation of the method on body fluids spiked with drug.
2. The study phase to confirm the stability, accuracy and precision.

CDSCO "Guidelines for Bioavailability and Bioequivalence Studies 2005"

Bioequivalence Criteria

Bioequivalence criteria are based on the calculation of a 90% confidence interval according to the two one-sided tests procedure of Schuirmann

D.J. Schuirmann: A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokinet. Biopharm.* 15: 657-680, 1987.

Pharmacokinetic Parameters

The pharmacokinetic parameters under consideration (e.g. AUC_{0-t}, C_{max} in case of a single dose BE study) should be analysed using ANOVA.

The data should be transformed prior to analysis using a logarithmic transformation.

The terms to be used in the ANOVA model are usually sequence, subject within sequence, period and formulation.

CDSCO "Guidelines for Bioavailability and Bioequivalence Studies 2005"

Pharmacokinetic Parameters

A statistical evaluation of t_{max} is not required. However, if rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events, there should be no apparent difference in median t_{max} and its variability between test and reference product.

CDSCO "Guidelines for Bioavailability and Bioequivalence Studies 2005"

Confidence Interval

- a ***90% confidence interval*** has to be calculated around the ratio of geometric means obtained for AUC (and C_{max}) following administration of test and reference preparation
- this ratio of geometric means is called the ***point estimate***

CDSCO "Guidelines for Bioavailability and Bioequivalence Studies 2005"

Confidence Interval

- For C_{max} and AUC_{0-t} the 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of **80.00-125.00%.**

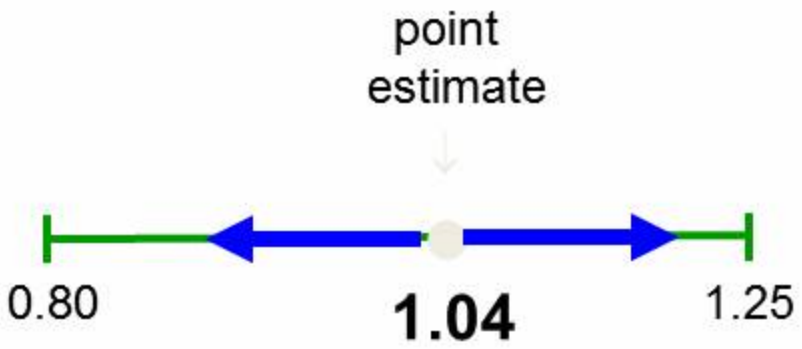
- In specific cases of products with a ***narrow therapeutic range***, the acceptance interval may need to be tightened. Moreover, for ***highly variable drug products*** the acceptance interval for C_{max} may in certain cases be widened (by using the reference scaled average bioequivalence approach).

CDSCO "Guidelines for Bioavailability and Bioequivalence Studies 2005"

Confidence Interval

90% CONFIDENCE INTERVAL

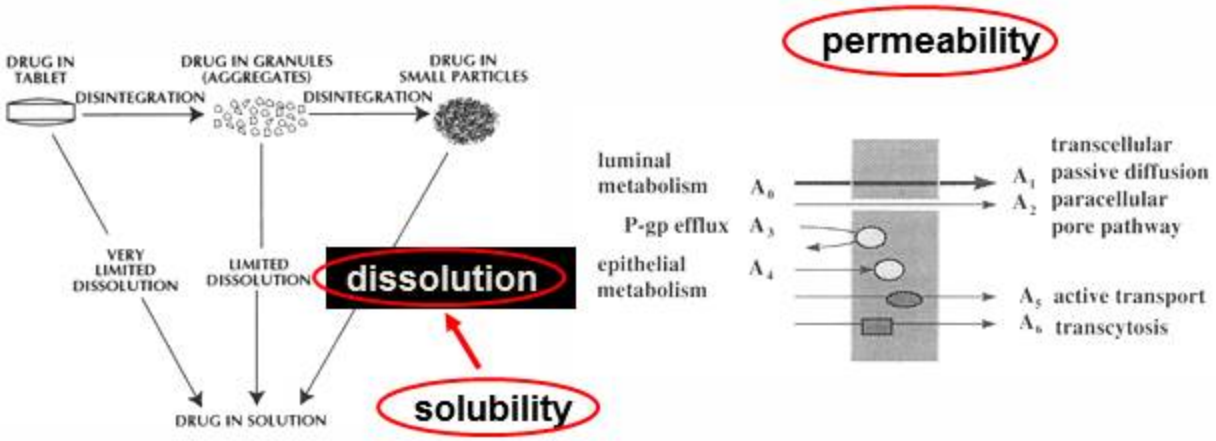
90% CI → 1.04 (0.91 – 1.20)



Narrow TI

- In specific cases of products with a narrow therapeutic index (NTI), the acceptance interval for AUC should be tightened to 90.00-111.11%.
- Where C_{max} is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter.
- It is not possible to define a set of criteria to categorise drugs as NTI drugs and it must be decided ***case by case*** if an active substance is and NTI drug based on clinical considerations.

Biopharmaceutic Classification



- **solubility**, **dissolution** and **permeability** are the 3 major factors controlling the oral absorption of drug substances from IR oral medicinal products

Biopharmaceutic Classification

Class I High solubility High permeability	**Class II** Low solubility High permeability
Class III High solubility Low permeability	**Class IV** Low solubility Low permeability

Amidon et al.: A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm. Res.* 12: 413-420, 1995.

Biopharmaceutic Classification

- The Biopharmaceutic Classification System (BCS) was developed for regulatory applications: to provide a basis for replacing, in certain cases, in vivo BE studies by equally or more accurate in vitro tests

- **biowaiver**: an acceptance for replacing an in vivo BE study with in vitro dissolution testing

Modified Release

Modified release products include:

i delayed release

ii sustained release

iii mixed immediate and sustained release

iv mixed delayed and sustained release

v mixed immediate and delayed release

Requirements

Modified Release Products must:

i act as modified-release formulations and meet the label claim

ii preclude the possibility of any dose dumping effect

iii there must be a significant difference between the modified release product and the conventional release product

iv provide a therapeutic performance comparable to the reference immediate-release formulation

v produce consistent pharmacokinetic performance between individual dosage units;

vi produce plasma levels which lie within the therapeutic range