Special topics in BA and BE

CPMP/EWP/QWP/1401/98 Rev. 1/ Corr

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DEFINITIONS

- **Pharmaceutical equivalence**
- Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.
- Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and/or absorption.
- **Pharmaceutical alternatives**
- Pharmaceutical alternatives are medicinal products with different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active moiety, or which differ in dosage form or strength.

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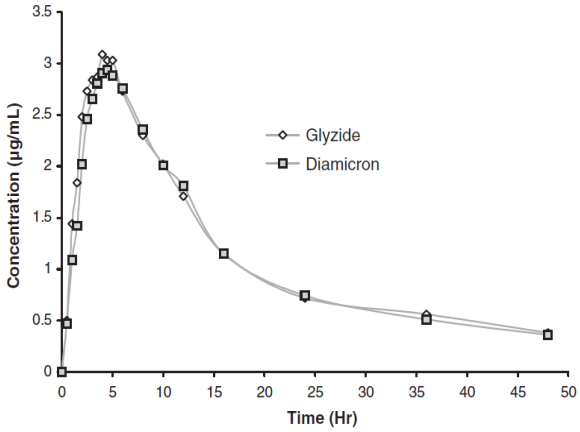
- This guideline specifies the requirements for the design, conduct, and evaluation of bioequivalence studies for immediate-release dosage forms with systemic action.
- In bioequivalence studies, the plasma(and/ or urine) concentration time curve is generally used to assess the rate and extent of absorption.



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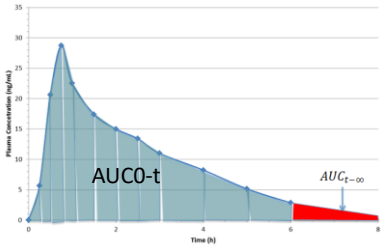
Pharmacokinetic parameters

$Ae_{(0\text{-}t)}$	Cumulative urinary excretion of unchanged drug from administration until time t;
$AUC_{(0\text{-}t)}$:	Area under the plasma concentration curve from administration to last observed concentration at time t;
$AUC_{(0\text{-}\infty)}$:	Area under the plasma concentration curve extrapolated to infinite time;
$AUC_{(0\text{-}\tau)}$):	AUC during a dosage interval at steady state;
$AUC_{(0\text{-}72h)}$	Area under the plasma concentration curve from administration to 72h;
C_{max}:	Maximum plasma concentration;
$C_{max,ss}$:	Maximum plasma concentration at steady state;
residual area	Extrapolated area ($AUC_{(0\text{-}\infty)}$ - $AUC_{(0\text{-}t)}$)/ $AUC_{(0\text{-}\infty)}$;
R_{max}	Maximal rate of urinary excretion;
t_{max}:	Time until C_{max} is reached;
$t_{max,ss}$:	Time until $C_{max,ss}$ is reached;
$t1/2$:	Plasma concentration half-life;
λ_z:	Terminal rate constant;
SmPC	Summary of Product Characteristics



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INTRODUCTION

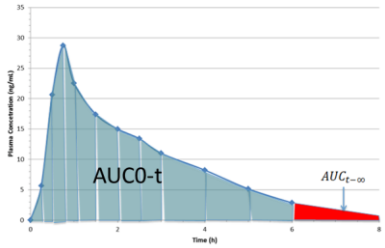
Selected pharmacokinetic parameters and preset acceptance limits allow the final decision on bioequivalence of the tested products.

AUC, the area under the concentration time curve, reflects the extent of exposure.

Cmax, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration,

tmax, are parameters that are influenced by absorption rate.

The possibility of using *in vitro* instead of *in vivo* studies is also addressed!



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Generic medicinal products

- The current definition for generic medicinal products is found in Directive 2001/83/EC, Article 10(2)(b), which states that a generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

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Generic medicinal products

- The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.
- Furthermore, the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form.
- The recommendations on design and conduct given for bioequivalence studies may also be applied to comparative bioavailability studies evaluating different formulations used during the development of a new medicinal product containing a new chemical entity and to comparative bioavailability studies included in extension or hybrid applications that are not based exclusively on bioequivalence data.

Hybrid medicines are medicines whose authorisation depends partly on the results of tests on the reference medicine and partly on new data from clinical trials.

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Introduction

- This guideline focuses on recommendations for bioequivalence studies for immediate release formulations with systemic action.
- It also sets the relevant criteria under which bioavailability studies need not be required (either waiver for additional strength, a specific type of formulation, see Appendix II or BCS based Biowaiver, see Appendix III).
- Specific recommendations regarding bioequivalence studies for modified release products, transdermal products and orally inhaled products are given in other guidelines.
- The scope is limited to chemical entities.
- Recommendation for the comparison of biologicals to reference medicinal products can be found in guidelines on similar biological medicinal products.

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- In case bioequivalence cannot be demonstrated using drug concentrations, in exceptional circumstances pharmacodynamic or clinical endpoints may be needed.
- This situation is outside the scope of this guideline and the reader is referred to therapeutic area specific guidelines.
- Although the concept of bioequivalence possibly could be considered applicable for herbal medicinal products, the general principles outlined in this guideline are not applicable to herbal medicinal products, for which active constituents are less well defined than for chemical entities.
- Furthermore, this guideline does not cover aspects related to generic substitution as this is subject to national regulation.

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LEGAL BASIS

- This guideline applies to Marketing Authorisation Applications for human medicinal products submitted in accordance with the Directive 2001/83/EC as amended, under Art. 10 (1) (generic applications).
- It may also be applicable to Marketing Authorisation Applications for human medicinal products submitted under Art. 8(3) (full applications), Art. 10b (fixed combination), Art. 10(3) (hybrid applications) of the same Directive, and for extension and variation applications in accordance with
- Commission Regulations (EC) No 1084/2003 and 1085/2003 as well.

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This guideline should be read in conjunction with the Annex I of Directive 2001/83/EC as amended, as well as European and ICH guidelines for conducting clinical trials, including those on:

- – General Considerations for Clinical Trials (ICH topic E8, CPMP/ICH/291/95)
- – Guideline for Good Clinical Practice (ICH E6 (R1), CPMP/ICH/135/95)
- – Statistical Principles for Clinical Trials (ICH E9, CPMP/ICH/363/96)
- – Structure and Content of Clinical Study Reports (ICH E3, CPMP/ICH/137/95)
- – CHMP guidance for users of the centralised procedure for generics/hybrid applications (EMEA/CHMP/225411/2006)
- – Pharmacokinetic studies in man (Eudralex, Volume 3, 3CC3a)
- – Modified Release Oral and Transdermal Dosage Forms: Sections I and II (CPMP/QWP/ 604/96, CPMP/EWP/280/96)
- – Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev 1)
- – Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) (CPMP/EWP/4151/00 rev 1)
- – Clinical Requirements for Locally Applied, Locally Acting Products containing Known Constituents (CPMP/EWP/239/95)

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- The guideline should also be read in conjunction with relevant guidelines on pharmaceutical quality.
- The test products used in the bioequivalence study must be prepared in accordance with GMP regulations including Eudralex volume 4.
- Bioequivalence trials conducted in the EU/EEA have to be carried out in accordance with Directive 2001/20/EC.
- Trials conducted outside of the Union and intended for use in a Marketing Authorisation
- Application in the EU/EEA have to be conducted to the standards set out in Annex I of the community code, Directive 2001/83/EC as amended.
- Companies may also apply for CHMP Scientific Advice, via the EMEA, for specific queries not covered by existing guidelines.

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Design, conduct and evaluation of bioequivalence studies

- The number of studies and study design depend on :

1. the physico-chemical characteristics of the substance,
2. its pharmacokinetic properties
3. proportionality in composition, and should be justified accordingly.

- In particular it may be necessary to address the linearity of pharmacokinetics, the need for studies both in fed and fasting state, the need for enantioselective analysis and the possibility of waiver for additional strengths

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Study design

- The study should be designed in such a way that the formulation effect can be distinguished from other effects.
- **Standard design**
- If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended.
- The treatment periods should be separated by a **wash out period** sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period.
- Normally at least 5 elimination half-lives are necessary to achieve this.
- Example: t1/2= 6hrs---→ 2 X 6= 12 hrs

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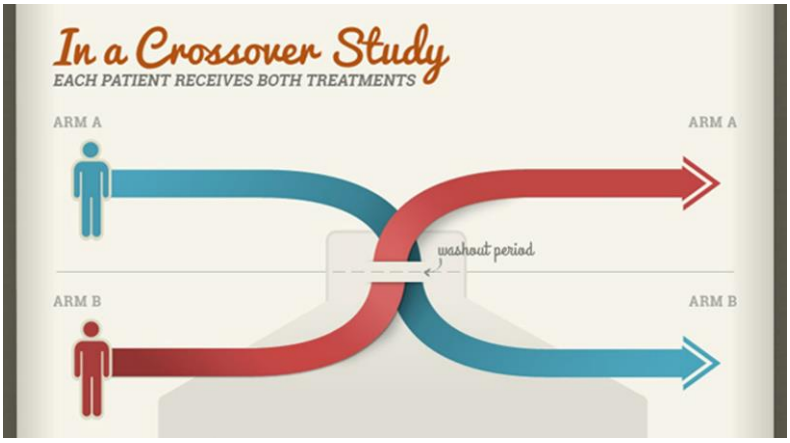

- Randomization

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Alternative designs

- Under certain circumstances, provided the study design and the statistical analyses are scientifically sound, alternative well-established designs could be considered such as parallel design for substances with very long half-life and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics.
- Conduct of a multiple dose study in patients is acceptable if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients.
- In the rare situation where problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single dose administration and where the concentrations at steady state are sufficiently high to be reliably measured, a multiple dose study may be acceptable as an alternative to the single dose study.
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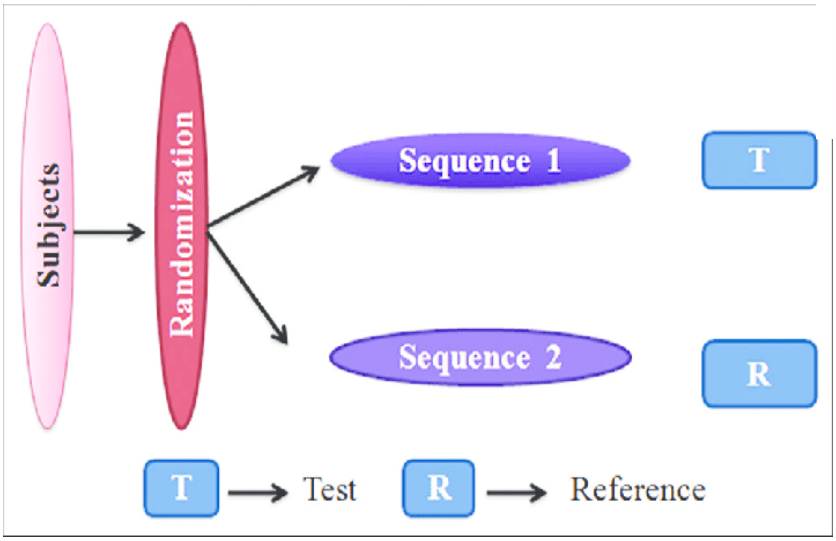

Alternative designs

- However, given that a multiple dose study is less sensitive in detecting differences in Cmax, this will only be acceptable if the applicant can adequately justify that the sensitivity of the analytical method cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration taking into account also the option of using a supra-therapeutic dose in the bioequivalence study
- Due to the recent development in the bioanalytical methodology, it is unusual that parent drug cannot be measured accurately and precisely.
- Use of a multiple dose study instead of a single dose study, due to limited sensitivity of the analytical method, will only be accepted in exceptional cases.

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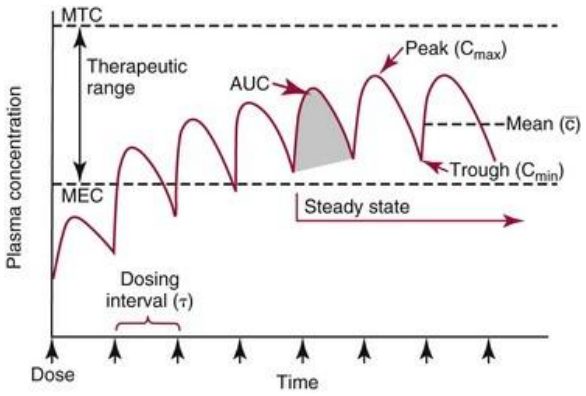
- In steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least 5 times the terminal half-life).



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Reference and test product

- **<u>Reference Product</u>**
- In the marketing authorisation applications, reference must be made to the dossier of a reference medicinal product for which a marketing authorisation is regestered
- The product used as reference product in the bioequivalence study should be part of the global marketing authorisation of the reference medicinal product
- The choice of the reference medicinal product identified by the applicant is appropriate in bioavailability studies, should be justified “Information for generic, hybrid or bio-similar applications”.
- Test products in an application for a generic or hybrid product or an extension of a generic/hybrid product are normally compared with the corresponding dosage form of a reference medicinal product, if available on the market.

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- when there are several dosage forms of this medicinal product on the market, it is recommended that the dosage form used for the initial approval of the concerned medicinal product (and which was used in clinical efficacy and safety studies) is used as reference product, if available on the market.
- The selection of the reference product used in a bioequivalence study should be based on assay content and dissolution data and is the responsibility of the Applicant.
- the assayed content of the batch used as test product should not differ more than 5% from that of the batch used as reference product determined with the test procedure proposed for routine quality testing of the test product.
- The Applicant should document how a representative batch of the reference product with regards to dissolution and assay content has been selected.
- **It is advisable** to investigate more than one single batch of the reference product when selecting reference product batch for the bioequivalence study.

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Test product

- The test product used in the study should be representative of the product to be marketed and this should be discussed and justified by the applicant.
- For example, for oral solid forms for systemic action:
- a) The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified.
- b) The production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale.
- In case of a production batch smaller than 100,000 units, a full production batch will be required.
- c) The characterisation and specification of critical quality attributes of the drug product, such as dissolution, should be established from the test batch, i.e. the clinical batch for which bioequivalence has been demonstrated.

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- d) Samples of the product from additional pilot and / or full scale production batches, submitted to support the application, should be compared with those of the bioequivalence study test batch, and should show similar in vitro dissolution profiles when employing suitable dissolution test conditions
- Comparative dissolution profile testing should be undertaken on the first three production batches.
- If full scale production batches are not available at the time of submission, the applicant should not market a batch until comparative dissolution profile testing has been completed.
- The results should be provided at a Competent Authority's request or if the dissolution profiles are not similar together with proposed action to be taken.
- For other immediate release pharmaceutical forms for systemic action, justification of the representative nature of the test batch should be similarly established.

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Packaging of study products

- The reference and test products should be packed in an individual way for each subject and period, either before their shipment to the trial site, or at the trial site itself.
- Packaging (including labelling) should be performed in accordance with good manufacturing practice, (GMP).
- Where necessary and in accordance with local regulations, sites should be authorised
- Third country sites should be able to demonstrate standards equivalent to these GMP requirements compliant with local requirements.
- It should be possible to identify unequivocally the identity of the product administered to each subject at each trial period.
- Packaging, labelling and administration of the products to the subjects should therefore be documented in detail.
- This documentation should include all precautions taken to avoid and identify potential dosing mistakes.
- The use of labels with **a tear-off portion is recommended.**

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Subjects

- **Number of subjects**
- The number of subjects to be included in the study should be based on an appropriate sample size calculation.
- The number of evaluable subjects in a bioequivalence study should not be less than **12**.
- **Selection of subjects**
- The subject population for bioequivalence studies should be selected with the aim of permitting detection of differences between pharmaceutical products.
- In order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers unless the drug carries safety concerns that make this unethical.
- This model, *in vivo* healthy volunteers, is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the reference medicinal product is approved (the elderly, children, patients with renal or liver impairment, etc.).

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- The inclusion/exclusion criteria should be clearly stated in the protocol.
- Subjects should be 18 years of age or older and preferably have a Body Mass Index (BMI)between 18.5 and 30 kg/m2.
- The subjects should be screened for suitability by means of clinical laboratory tests, a medical history, and a physical examination.
- Depending on the drug's therapeutic class and safety profile, special medical investigations and precautions may have to be carried out before, during and after the completion of the study.
- Subjects could belong to either sex; however, the risk to women of childbearing potential should be considered.
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- Subjects should preferably be non-smokers and without a history of alcohol or drug abuse.
- Phenotyping and/or genotyping of subjects may be considered for safety or pharmacokinetic reasons.
- **In parallel design studies**, the treatment groups should be comparable in all known variables that may affect the pharmacokinetics of the active substance (e.g. age, body weight, sex, ethnic origin, smoking status, extensive/poor metabolic status).
- This is an essential pre-requisite to give validity to the results from such studies.
- If the investigated active substance is known to have adverse effects, and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to include patients instead, under suitable precautions and supervision.

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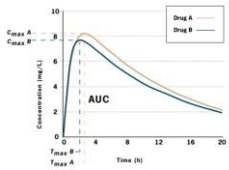
Study conduct- Standardisation



- The test conditions should be standardised in order to minimise the variability of all factors involved except that of the products being tested.
- Therefore, it is recommended to standardise diet, fluid intake and exercise.
- The time of day for ingestion should be specified.
- Subjects should fast for at least 8 hours prior to administration of the products, unless otherwise justified.
- 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).
- It is recommended that water is allowed as desired except for one hour before and one hour after drug administration and no food is allowed for at least 4 hours post-dose.
- Meals taken after dosing should be standardised in regard to composition and time of administration during an adequate period of time (e.g. 12 hours).

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- In case the study is to be performed during fed conditions, the timing of administration of the drug product in relation to food intake is recommended to be according to the SmPC of the originator product. If no specific recommendation is given in the originator SmPC, it is recommended that subjects should **start the meal 30 minutes prior** to administration of the drug product and **eat this meal within 30 minutes.**
- 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.

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- The subjects should abstain from food and drinks, which may interact with circulatory, gastrointestinal, hepatic or renal function (e.g. alcoholic drinks or certain fruit juices such as grapefruit juice) during a suitable period before and during the study.
- Subjects should not take any other concomitant medication (including herbal remedies) for an appropriate interval before as well as during the study. Contraceptives are, however, allowed.
- In case concomitant medication is unavoidable and a subject is administered other drugs, for instance to treat adverse events like headache, the use must be reported (dose and time of administration) and possible effects on the study outcome must be addressed.
- In rare cases, the use of a concomitant medication is needed for all subjects for safety or tolerability reasons (e.g. opioid antagonists, anti-emetics).
- In that scenario, the risk for a potential interaction or bioanalytical interference affecting the results must be addressed.

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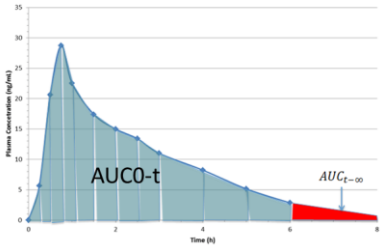
- **Sampling times**
- A sufficient number of samples to adequately describe the plasma concentration-time profile should be collected.
- The sampling schedule should include frequent sampling around predicted tmax to provide a reliable estimate of peak exposure.
- In particular, the sampling schedule should be planned to avoid **Cmax** being the first point of a concentration time curve.
- The sampling schedule should also cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved if AUC(0-t) covers *at least 80%* of AUC(0-∞).



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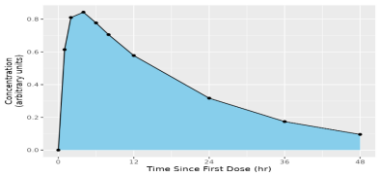
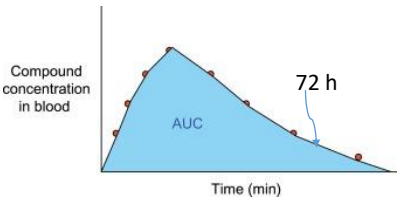
- **Sampling times**
- At least 3-4 samples are needed during the terminal log-linear phase in order to reliably estimate the terminal rate constant (which is needed for a reliable estimate of AUC(0-∞)).
- AUC truncated at 72 h (AUC(0-72h)) may be used as an alternative to AUC(0-t) for comparison of extent of exposure as the absorption phase has been covered by 72 h for immediate release formulations.
- A sampling period longer than 72 h is therefore not considered necessary for any **immediate** release formulation irrespective of the half life of the drug.





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- In multiple-dose studies, the pre-dose sample should be taken immediately before (within 5 minutes) dosing and the last sample is recommended to be taken within 10 minutes of the nominal time for the dosage interval to ensure an accurate determination of AUC(0-τ).
- If urine is used as the biological sampling fluid, urine should normally be collected over no less than 3 times the terminal elimination half-life.
- However, in line with the recommendations on plasma sampling, urine does not need to be collected for more than 72 h.
- If rate of excretion is to be determined, the collection intervals need to be as short as feasible during the absorption phase.
- BE for endogenous substances,
- the sampling schedule should allow characterisation of the endogenous baseline profile for each subject in each period. Often, a baseline is determined from 2-3 samples taken before the drug products are administered.
- In other cases, sampling at regular intervals throughout 1-2 day(s) prior to administration may be necessary in order to account for fluctuations in the endogenous baseline due to circadian rhythms.

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Fasting or fed conditions

- In general, a bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations.
- For products intake of the reference medicinal product on an empty stomach or irrespective of food intake, the bioequivalence study should hence be conducted under fasting conditions.
- For products intake of the reference medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions.
- However, for products with specific formulation characteristics (e.g. microemulsions, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required unless the product must be taken only in the fasted state or only in the fed state.
- In cases where information is required in both the fed and fasted states, it is acceptable to conduct either two separate two-way cross-over studies or a four-way cross-over study.

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- In studies performed under fed conditions, **the composition of the meal** :
- the meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal.
- This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively.
- The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).

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Characteristics to be investigated - Pharmacokinetic parameters

- Actual time of sampling should be used in the estimation of the pharmacokinetic parameters. In studies to determine bioequivalence after a single dose, AUC(0-t), AUC(0-∞), residual area, Cmax and tmax should be determined.
- In studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, AUC(0-∞) and residual area do not need to be reported; it is sufficient to report AUC truncated at 72h, AUC(0-72h).
- Additional parameters that may be reported include the terminal rate constant, λz, and t1/2.
- In studies to determine bioequivalence for immediate release formulations at steady state, AUC(0-τ), Cmax,ss, and tmax,ss should be determined.
- When using urinary data, Ae(0-t) and, if applicable, Rmax) (Maximum rate of **urinary** excretion), should be determined.
- **Non-compartmental methods** should be used for determination of pharmacokinetic parameters in bioequivalence studies.
- The use of compartmental methods for the estimation of parameters is ***not*** acceptable.

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Parent compound or metabolites

General recommendations

- In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound.
- The reason for this is that Cmax of a **parent** compound is usually more sensitive to detect differences between formulations in absorption rate than Cmax of a metabolite.
- **Inactive pro-drugs**
- for inactive prodrugs, demonstration of bioequivalence for parent compound is recommended.
- The active metabolite does not need to be measured.
- However, some pro-drugs may have low plasma concentrations and be quickly eliminated resulting in difficulties in demonstrating bioequivalence for parent compound. In this situation it is acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound.
- a parent compound can be considered to be an inactive pro-drug if it has no or very low contribution to clinical efficacy.

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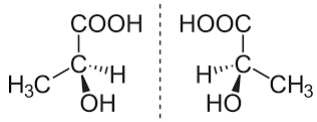
Enantiomers



- The use of achiral bioanalytical methods is generally acceptable. However, the individual enantiomers should be measured when all the following conditions are met:
- (1) the enantiomers exhibit different pharmacokinetics
- (2) the enantiomers exhibit pronounced difference in pharmacodynamics
- (3) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.
- The individual enantiomers should also be measured if the above conditions are fulfilled or are unknown.
- If one enantiomer is pharmacologically active and the other is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer.

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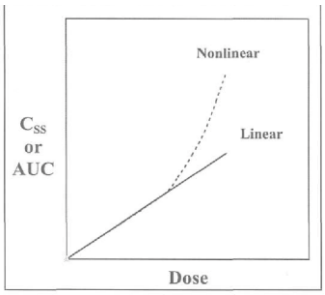
- **Strength to be investigated**
- If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the **proportionality in composition** between the different strengths and other product related issues described below.
- The strength(s) to evaluate depends on the linearity in pharmacokinetics of the active substance.



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Linear pharmacokinetics

- The bioequivalence study should in general be conducted at the highest strength. For products with linear pharmacokinetics and where the drug substance is highly soluble (see Appendix III), selection of a lower strength than the highest is also acceptable.
- Selection of a lower strength may also be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons.
- Further, if problems of sensitivity of the analytical method preclude sufficiently precise plasma concentration measurements after single dose administration of the highest strength, a higher dose may be selected (preferably using multiple tablets of the highest strength).
- The selected dose may be higher than the highest therapeutic dose provided that this single dose is well tolerated in healthy volunteers and that there are no absorption or solubility limitations at this dose.

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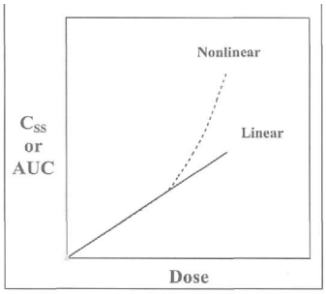
Non-linear pharmacokinetics

- For drugs with non-linear pharmacokinetics characterised by a more than proportional increase in AUC with increasing dose over the therapeutic dose range, the bioequivalence study should in general be conducted at the highest strength.
- As for drugs with linear pharmacokinetics a lower strength may be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons.



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- Selection of other strengths may be justified if there are analytical sensitivity problems preventing a study at the lowest strength or if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons.

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Bioanalytical methodology

- The bioanalytical part of bioequivalence trials should be performed in accordance with the principles of Good Laboratory Practice (GLP).
- The bioanalytical methods used must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted. Within study validation should be performed using Quality control samples in each analytical run.
- The main characteristics of a bioanalytical method that is essential to ensure the acceptability of the performance and the reliability of analytical results are: **selectivity, LOQ lower limit of quantitation, the response function (calibration curve performance), accuracy, precision and stability.**
- The lower LOQ (limit of quantitation)should be 1/20 of Cmax or lower, as pre-dose concentrations should be detectable at 5% of Cmax or lower
- Reanalysis of study samples should be predefined in the study protocol (and/or SOP) before the actual start of the analysis of the samples. Normally reanalysis of subject samples because of a pharmacokinetic reason is not acceptable.
- This is especially important for bioequivalence studies, as this may bias the outcome of such a study. Analysis of samples should be conducted without information on treatment (**Blinded**).

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Subject accountability

- The data from all treated subjects should be treated equally.
- It is not acceptable to have a protocol which specifies that 'spare' subjects will be included in the analysis only if needed as replacements for other subjects who have been excluded.
- It should be planned that all treated subjects should be included in the analysis, even if there are no drop-outs.

- 24 + 2(alternate)

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Reasons for exclusion

- In principle any reason for exclusion is valid provided it is specified in the protocol and the decision to exclude is made before bioanalysis.
- However the exclusion of data should be avoided, as the power of the study will be reduced and a minimum of 12 evaluable subjects is required.
- Examples of reasons to exclude the results from a subject in a particular period are events such as vomiting and diarrhoea which could render the plasma concentration-time profile unreliable.
- In exceptional cases, the use of concomitant medication could be a reason for excluding a subject.
- Exclusion of data cannot be accepted on the basis of statistical analysis or for pharmacokinetic reasons alone, because it is impossible to distinguish the formulation effects from other effects influencing the pharmacokinetics.

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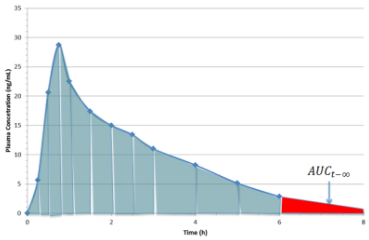
Collected data



- AUC(0-t) should cover at least 80% of AUC(0-∞).
- Subjects should not be excluded from the statistical analysis if AUC(0-t) covers less than 80% of AUC(0-∞), but if the percentage is less than 80% in more than 20% of the observations then the validity of the study may need to be discussed.
- This does not apply if the sampling period is 72 h or more and AUC(0-72h) is used instead of AUC(0-t).

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Statistical analysis

- The assessment of bioequivalence is based upon 90% confidence intervals for the ratio of the population geometric means (test/reference) for the parameters under consideration.
- This method is equivalent to two one-sided tests with the null hypothesis of bioinequivalence at the 5% significance level.
- The pharmacokinetic parameters under consideration should be analysed using **ANOVA**.
- The data should be transformed prior to analysis using a logarithmic transformation.
- A confidence interval for the difference between formulations on the log-transformed scale is obtained from the ANOVA model.

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- Drop-out and withdrawal of subjects should be fully documented.
- If available, concentration data and pharmacokinetic parameters from such subjects should be presented in the individual listings, but should not be included in the summary statistics.
- The bioanalytical method should be documented in a pre-study validation report.
- A bioanalytical report should be provided as well.
- The bioanalytical report should include a brief description of the bioanalytical method used and the results for all calibration standards and quality control samples.
- Arepresentative number of chromatograms or other raw data should be provided covering the whole concentration range for all standard and quality control samples as well as the specimens analysed.
- This should include all chromatograms from at least 20% of the subjects with QC samples and calibration standards of the runs including these subjects.

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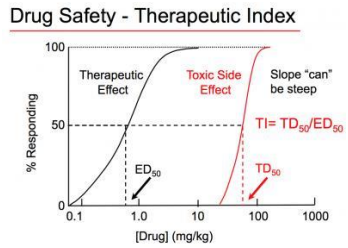
Narrow therapeutic index drugs



- In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. Where Cmax 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 narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations.

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Highly variable drugs or drug products

- Highly variable drug products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a drug product can be considered as highly variable in its rate and/or extent of absorption**, a replicate cross-over design study can be carried out.**
- Those HVDP for which a wider difference in Cmax is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case the acceptance criteria for **Cmax can be widened to a maximum of 69.84 – 143.19%.**

Within-subject CV (%)*	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

$$*\,CV(\%) = 100\sqrt{e^{s^2_{WR}} - 1}$$

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Study report
Bioequivalence study report

- The report of the bioequivalence study should give the complete documentation of its protocol, conduct and evaluation.
- It should be written in accordance with the ICH E3 guideline and be signed by the investigator .
- Names and affiliations of the responsible investigator(s), the site of the study and the period of its execution should be stated.
- Audits certificate(s), if available, should be included in the report.
- The study report should include evidence that the choice of the reference medicinal product is in accordance with Article 10(1) and Article 10(2) of Directive 2001/83/EC as amended.
- This should include the reference product name, strength, pharmaceutical form, batch number, manufacturer, expiry date and country of purchase.
- The name and composition of the test product(s) used in the study should be provided. The batch size, batch number, manufacturing date and, if possible, the expiry date of the test product should be stated.
- Certificates of analysis of reference and test batches used in the study should be included in an appendix to the study report.
- Concentrations and pharmacokinetic data and statistical analyses should be presented in the level of detail described before (*Presentation of data*).

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Other data to be included in an application

- The applicant should submit a signed statement confirming that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for authorization.
- A confirmation whether the test product is already scaled-up for production should be submitted.
- Comparative dissolution profiles should be provided.
- The validation report of the bioanalytical method should be included in Module 5 of the application.
- Data sufficiently detailed to enable the pharmacokinetics and the statistical analysis to be repeated, e.g. data on actual times of blood sampling, drug concentrations, the values of the pharmacokinetic parameters for each subject in each period and the randomization scheme

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Biowaivers

In vitro studies

Only *in vitro* studies sufficient to surrogate

In vivo studies

exemption to in vivo studies is biowaiver

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Biowaivers

- Biowaiver based on biopharmaceutical 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

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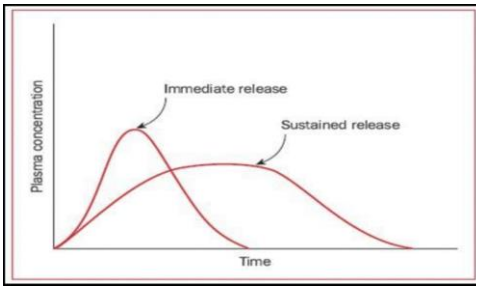
Biowaivers

- Composition proportionality
- Basis of biowaivers for additional strength
  - API and excipients must be qualitatively the same and quantitatively proportional
  - Manufactured by the same process

- *In vitro- in vivo* correlation (*IVIVC*)
- Used for biowaiver grants of
  - Modified release products or
  - Products subject to change in manufacturing procedure.



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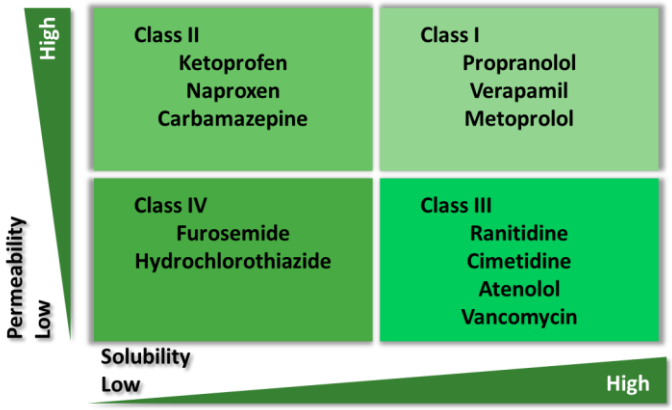
Biowaivers

- **Biopharmaceutical Classification System (BCS)**



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Biowaivers

- application of biowaivers based on :

❑**Biopharmaceutical Classification System (BCS)**

❑Consider the dose: solubility ratio, permeability and dissolution behaviour.

❑IVIVC

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

❑Composition proportionality

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

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Biowaivers

- **High solubility**
  - The **highest single dose** is completely soluble in 250 mL or less of the aqueous solution at pH 1-6.8 (37 °C)
- **High permeability**
  - EMA : extent of absorption ≥ 85% (absolute BA or mass balance data)
  - FDA: absolute BA ≥ 90%
- **Very rapid dissolution**
  - When ≥ 85% of the labeled amount of drug substance dissolves in 15 min.
- **Rapid dissolution**
  - When ≥ 85% of the labeled amount of drug substance dissolves in **30** min.

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Conditions for BCS Biowaivers

- Should contain Class 1 drug substance
- Drug products must meet the following criteria:
  - Immediate release solid oral dosage form
  - Highly soluble, highly permeable drug substance
  - Rapid *in vitro* release
- **Not less than (NLT)85% dissolves within 30 min**
- **Similarity factor (f_2) for test v. reference profile comparison should> 50**

- Important Waivers are **not applicable** for narrow therapeutic range (Digoxin, Lithium, phenytoin, warfarin) drug

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- Eligibility for the biowaiver procedure based on the solubility and permeability characteristics of the active pharmaceutical ingredients
- According to the Health and Human Services (HHS):
  - **Class I: Eligible**
  - **Class II: Not eligible**
  - **Class III: Not eligible**
  - **Class IV: Not eligible**
- According to the WHO:
  - **Class I: Eligible**
  - **Class II: Eligible only if the dissolution of the dose in 250 mL or lower at pH 6.8**
  - **Class III: Eligible if very rapidly dissolving**
  - **Class IV: Not eligible**

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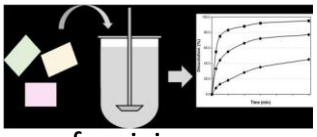
In vitro dissolution tests in support of biowaiver of strengths



- Appropriate *in vitro* dissolution should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.
- Accordingly, dissolution should be investigated at different pH values (normally pH 1.2, 4.5 and 6.8) unless otherwise justified.
- Similarity of *in vitro* dissolution should be demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength(s) (i.e. batch(es)) used for bioequivalence testing.
- At pH values where sink conditions may not be achievable for all strengths *in vitro* dissolution may differ between different strengths.
- However, the comparison with the respective strength of the reference medicinal product should then confirm that this finding is drug substance rather than formulation related.
- In addition, the applicant could show similar profiles at the same dose (e.g. as a possibility two tablets of 5 mg versus one tablet of 10 mg could be compared).

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