Normativa de bioequivalencia en la Unión Europea: Estudios in vivo

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Aviso

Esta presentación representa únicamente la opinión personal del autor y puede no representar la opinión o las recomendaciones de la AEMPS, OMS, EMA o sus grupos de trabajo.

Guías

- Investigation of bioequivalence
- Pharmacokinetic and clinical evaluation of modified-release dosage forms
- Bioanalytical method validation

- Questions and answers: positions on specific questions addressed to the Pharmacokinetics Working Party

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Clinical efficacy and safety: clinical pharmacology and pharmacokinetics

Email Print Help

The European Medicines Agency's scientific guidelines on clinical pharmacology and pharmacokinetics help medicine developers prepare marketing authorisation applications for human medicines.

For the specific questions on the **pharmacokinetic evaluations** addressed to the Pharmacokinetic Working Party, see:

▸ Questions and answers: positions on specific questions addressed to the Pharmacokinetics Working Party

If you have comments on a document which is open for consultation, use the form for submission of comments on scientific guidelines.

For a complete list of scientific guidelines currently open for consultation, see Public consultations.

Draft guidelines under public consultation

▸ Qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Finalised guidelines

▸ Bioanalytical method validation

▸ Clinical investigation of the pharmacokinetics of therapeutic proteins

▸ Clinical requirements for locally applied, locally acting products containing known constituents

▸ Evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function

▸ Evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

Guías

- Clinical requirements for locally applied, locally acting products containing known constituents
- 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) in adults and for use in the treatment of asthma in children and adolescents

Product-specific bioequivalence guidance

This section includes the European Medicines Agency's (EMA) product-specific bioequivalence guidance, which summarises in a standardised format the relevant study design principles for demonstration of bioequivalence.

Product-specific guidance helps applicants meet the expectations of regulators in the European Union, particularly for **generic applications**, across all regulatory submission routes, i.e. via the centralised, decentralised, mutual recognition or national procedures. For more information about product-specific guidance, see:

▸ Concept paper on development of product-specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013).

EMA publishes finalised guidance documents for individual products on a regular basis, once the Committee for Medicinal Products for Human Use has adopted them following a public consultation. If EMA receives comments during the consultation, it publishes an overview of comments with the final guidance documents. Please refer to the individual guidance documents for their date of coming into effect.

If you have comments on a document that is open for consultation, use the form for submission of comments on scientific guidelines.

For a complete list of scientific guidelines currently open for consultation, see Public consultations.

For the specific questions on the **pharmacokinetic evaluations** addressed to the Pharmacokinetics Working Party, see:

▸ Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party

Draft guidelines under public consultation

▸ Abiraterone product-specific bioequivalence guidance

▸ Everolimus product-specific bioequivalence guidance

▸ Exenatide product-specific bioequivalence guidance

Intercambiabilidad

- Prescripción
- Sustitución
- En la UE se autorizan medicamentos por ser “prescribibles”
- La sustitución es una política nacional
  - No regulada por legislación comunitaria

Productos de referencia

- El producto de referencia debe ser de algún miembro de la Unión Europea
- No es aceptable usar productos de referencia de EEUU

- En biosimilares serían aceptables algunos estudios con la referencia de EEUU si se han comparado con la europea previamente

Productos de liberación inmediata: Ayunas o comida

- Generalmente se prefieren en ayunas
  - Ficha técnica (SPC) sólo en ayunas, o
  - SPC en ayunas o con comida
- Con comida:
  - SPC indica sólo con comida
    - Razones farmacocinéticas
    - Cuando produce molestias gastrointestinales en ayunas
      - Podría ser aceptable en ayunas (e.g. imatinib)

Requisitos adicionales en EU

- Guideline on the investigation of BE (CHMP, 2010):
- Para los productos con formulaciones con características específicas
  - Micro-emulsiones (e.g., ciclosporina),
  - Dispersiones sólidas, …
- Se requieren estudios de BE tanto en ayunas como con comida (e.g., tadalafilo)
- Salvo que el producto se tome sólo en ayunas o sólo con comida

US-FDA

- For immediate release capsule and tablet products, we recommend the following studies:

  (1) a single-dose, fasting study comparing the highest strength of the test and RLD products and

  (2) a single-dose, fed BE study comparing the highest strength of the test and RLD products (see section III.A.10).

US-FDA

- When a fasting in vivo BE study is recommended for an orally administered, immediate release product, we recommend that applicants conduct a fed study, except when the dosage and administration section of the RLD labeling states that the product should be taken only on an empty stomach (e.g., the labeling states that the product should be administered 1 hour before or 2 hours after a meal).

US-FDA

- For orally administered, immediate release products labeled to be taken only with food, fasting and fed studies are recommended, except when serious adverse events are anticipated with fasting administration.
- In these latter cases, we recommend that applicants conduct only a fed study; a fasting study is not recommended.

En ayunas y con comida

- En aquellos casos en los que se necesitan ambos estudios (en ayunas y con comida)
- Es aceptable realizar
  - Dos estudios 2x2 por separado,
    - Cada estudio con su variabilidad (ayunas / comida)
  - Un estudio cruzado de 4 periodos y 4 tratamientos
    - Con la mayor variabilidad (mayor tamaño muestral)
    - Pero permite comparar el efecto de la comida en cada producto

Composición de la comida

- En los estudios con comida, la composición de la comida debe ser la recomendada en el SPC del producto de referencia
- La composición puede depender la dieta local y las costumbres locales
- Si no se recomienda ningún tipo de comida el el SPC de la referencia, la comida debe ser alta en grasa (aprox. 50% del contenido calórico) y alta en calorías (aprox. 800 - 1000 Kcal)

Composición de la comida

- La comida deberá tener aprox. 150, 250, y 500-600 Kcal de proteínas, carbohidratos y grasa, respectivamente
- La composición de la comida se deberá describir en cuanto a contenido en proteínas, carbohidratos y lípidos (en gramos, calorías y contenido calórico relativo (%))

IR products: 5 requirements to waive

- Same manufacturing process
- Same qualitative composition in excipients
- Proportional composition in excipients
  - Except if the 5% rule applies, excipients constant
- Similar dissolution profiles
  - QC media, pH 1.2, 4.5 and 6.8
- PK linear:
  - If linear: BE study with the most sensitive strength
    - Highest strength, except if solubility is high or safety concerns
  - If non-linear, the most sensitive strength might be lowest and/or the highest.

Non-linear PK

- More than proportional increase in AUC with increasing dose
    - Highest strength (not therapeutic dose)
- Less than prpotional increase in AUC with increasing dose
  - Solubility limitation
    - Highest and lowest strength
  - Saturation of transporters
    - Lowest or in the linear part
      - If excipients are not critical

BE study required for each strength if

- The manufacturing process is different, or
- The qualitative composition in excipients is different, except aesthetic coating, shell, colorant, flavours, or
- The quantitative composition in excipients is different and the 5% rule does not apply, or
- The 5% rule applies, but excipients are not constant, except the diluent that can be used to compensate the difference in drug substance, or

BE study required for each strength if

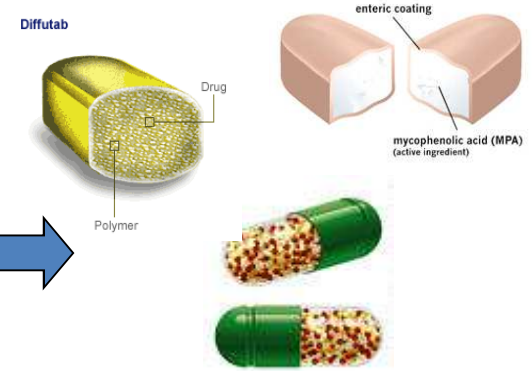
- The dissolution profiles are not similar between strength
  - QC media, pH 1.2, 5.6 and 6.8
  - Without an acceptable justification (*i.e.*, lack of sink conditions)
    - T *vs.* R at each level or
    - Same dose per vessel (2 x 5mg *vs.* 1 x 10 mg)
- Unless a bracketing approach can be used

Productos de liberación modificada

- Tipos:
  - Liberación prolongada: sostenida, controlada, extendida
  - Diferida: gastrorresistente
  - Otros: multifásica, pulsátil, etc.
- Se necesitan varios estudios
  - Cruzado, dosis única, en ayunas con la dosis más alta
  - Cruzado, dosis única, con comida con la dosis más alta
    - Comida rica en grasa (tiempo según SPC o 30 min antes)
  - Cruzado, dosis múltiple (si liberación prolongada y se acumula)
  - Efecto del alcohol en los perfiles de disolución *in vitro* (0% vs. 10, 20, 40%)

Productos de liberación modificada

- Tipos:
  - Formulación uniparticular
  - Formulación múltiparticular



- Formulaciones proporcionales
  - Múltiparticular: investigar la dosis alta
  - Uniparticular:
    - US-FDA: Dosis alta (antes también algunos países EU)
      - Disolución en al menos 3 medios (e.g., pH 1.2, 4.5 and 6.8)
    - EU: Todas las dosis deben investigarse en dosis única y ayunas (si se toma en ayunas) o “bracketing”
      - Dosis alta en dosis única con comida y dosis múltiple en ayunas

6.1. Prolonged release formulations for oral administration

- BE between two PR formulations should be evaluated on the basis of **studies designed to demonstrate** that:
  - the test formulation **exhibits the claimed PR characteristics** of the reference;
  - the active substance is not released unexpectedly from the test formulation (**no dose dumping**);
  - performance of the test and the reference formulation is **equivalent after single dose and at steady state**;
  - the **effect of food** on the in vivo performance is **comparable** for both formulations **when a single dose study is conducted**

6.1.1. Studies **generally required** to demonstrate BE

- a **single-dose fasting** study comparing test and reference drug product
- a **single-dose fed** study using a **high-fat** meal (see 5.1.4.1) comparing test and reference drug product
- a **multiple-dose** study comparing test and reference drug product.

6.1.1.1. Single dose studies

- **One of the following schemes** is recommended for **single dose** evaluation **in fasting and fed** state:

  ➢ A **four-period cross-over** trial with **four complementary sequences** of four treatment conditions

  Both the **test and reference** products should be assessed in the **fasting** state as well as **after** the administration of a **high fat meal** at a specified time before taking the drug

6.1.1.1. Single dose studies

➢ **Two cross-over trials**

The **first trial** should compare the **test and reference** products under **fasting** conditions

The study treatments should be administered during two periods and with two sequences of treatment conditions

The **second trial** should compare the **test and reference** formulations following the administration of a **high-fat meal** at a specified time before taking the study treatment, **as well as the test** formulation under **fasting** conditions to generate intraindividual data describing a possible food effect

6.1.1.1. Single dose studies

➢ **Two cross-over trials**, both with **two periods and two sequences** of **test and reference** product administration

One trial should be conducted in the **fasting** state

The **other trial** should be conducted after the administration of a **high fat meal** at a specified time before taking the study treatment

6.1.1.2. Multiple dose studies

- A **multiple dose** study is **needed unless** a **single dose** study has been performed with the **highest strength** which has **demonstrated** that the **mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference**, and consequently a **low extent of accumulation** is expected

6.1.1.2. Multiple dose studies

- In this case **bioequivalence needs to be demonstrated for additional parameters representing the shape** of the plasma concentration versus time curve **in the single dose study** (see also section 6.8.2)

6.1.1.2. Multiple dose studies

- An **early $_{\text{partial}}AUC_{(0\text{-cut-off t})}$ and a terminal $_{\text{partial}}AUC_{(\text{cut-off t - tlast})}$ separated by a predefined cut-off time point**, e.g. **the half** of the dosage interval is recommended, **unless** otherwise scientifically **justified**

6.1.1.2. Multiple dose studies

- In all other cases, **where accumulation is likely** ($AUC_{(0-\tau)}$ after the first dose covers less than 90% of mean $AUC_{(0-\infty)}$) **a multiple dose study is required**
- Generally, steady-state studies should be performed **under** the **conditions** concerning **concomitant food intake** recommended in the **SmPC for the originator** product

6.1.1.2. Multiple dose studies

- **If the SmPC states** that the product has to be taken **in fed condition only** the study should be **performed in fed conditions (standard meal) including the day of profiling**
- **If the SmPC states** that the product should be taken **in fasted state or irrespective** of food intake the studies should be **performed in fasted conditions**

6.1.1.2. Multiple dose studies

- **Fasting conditions in a multiple dose** study needs to be adapted to realistic situations, i.e. morning administration requires an 10 hour fasting interval whereas for all other **administrations 4 hour fasting prior to administration is sufficient**
- **Fasting after** each administration should be defined as **2 hour minimum**

6.1.1.2. Multiple dose studies

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

6.1.1.2. Multiple dose studies

- Whether the **steady-state has been achieved** is **assessed by comparing at least three pre-dose concentrations** for each formulation.
- The **apparent half-life** should also be taken into account

6.1.2. Strength(s) to be evaluated

- **6.1.2.1. Single unit formulations**
  A. **Single dose studies**
  – If the reference SmPC recommends intake in the **fasting state or irrespective** of food intake
  – If the reference SmPC recommends intake under **fed conditions only**
  B. **Multiple dose studies**
- **6.1.2.2. Multiple Unit formulations**

6.1.2.1. Single unit formulations
A. Single dose studies

- If the reference SmPC recommends intake in the **fasting state or irrespective** of food intake:
  - Fasting state: **a single dose study under fasting** conditions is required **for each strength**
    - However a **bracketing** approach (see section 6.6) is also possible if justified

6.1.2.1. Single unit formulations
A. Single dose studies

- Fed state: **One single dose** bioequivalence study **at the highest strength/most sensitive strength** conducted in **fed state** may be sufficient
  - The **other strength(s) can be waived if** the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled
  - However, **if** the strengths of the test product **do not fulfil these criteria or if proportional strengths have different shape** two strengths representing the **most extreme difference** should be tested **in fed state**

Strengths with large difference in size may have different GI transit time. How much different do they need to be?
Dissolution profiles perhaps not discriminative to differences in release due to differences in surface.
FDA withdrew a higher strength approved based only in dissolution data

6.1.2.1. Single unit formulations
A. Single dose studies

- If the reference SmPC recommends intake under **fed conditions**,
  - Fed state: **a single dose study** under **fed conditions** is required **for each strength**
    - However, **a bracketing** approach (see section 6.6) is also possible if justified.
  - Fasting state: **One single dose** bioequivalence study at the **highest strength** conducted **in fasting state** may be sufficient
    - The **other strength(s) can be waived if** the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled
    - However, **if** the strengths of the test product **do not fulfil these criteria or if proportional strengths have different shape** two strengths representing the **most extreme difference** should be tested **in fasting state**

6.1.2.1. Single unit formulations
B. Multiple dose studies

- A **multiple dose** study should be performed with the **highest strength** (**unless** it is shown that there is **no accumulation** as detailed in section 6.1)
- In case of safety concerns the study should be conducted in patients.
- The **other strength(s) can be waived if** the criteria for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled
- However a bracketing approach (see section 6.6) is also possible if justified.

May difference in size / shape affect the final release of the dosage form?
Dissolution profiles perhaps not discriminative to differences in final release due to differences in surface

Prolonged release single unit (**fasting or irrespective of food**)

Strength	Single dose fasting study**	Single dose fed Study	Multiple dose study*
high	yes	yes	yes
middle	yes	waiver	waiver
low	yes	waiver	waiver

* see criteria for necessity in section 6.1

** bracketing approach possible if criteria (see section 6.6) are met

Prolonged release single unit (**fed conditions**)

Strength	Single dose fasting study	Single dose fed Study**	Multiple dose study*
high	yes	yes	yes
middle	waiver	yes	waiver
low	waiver	yes	waiver

* see criteria for necessity in section 6.1

** bracketing approach possible if criteria (see section 6.6) are met

EMA más exigente que FDA

- La FDA sólo requiere estudiar una dosis en dosis única (ayunas y comida).
- Se extrapola con perfiles de disolución
- La FDA ha tenido que retirar un genérico de bupropion: Budeprion XL 300mg tablets (Teva)
- Se aprobó con un estudio con 150 mg, pero hubo notificaciones sobre la dosis de 300 mg
- FDA: AUC_{0-t}: 76.71-95.82 y C_{max}: 65.24-86.81

Woodcock J, Khan M, Yu LX. Withdrawal of generic budeprion for nonbioequivalence. N Engl J Med. 2012 Dec 27;367(26):2463-5

Lin et al. 2016. *AAPS J.* 18(2): 333-345

- Influence of Drug Properties and Formulation on *In Vivo* Drug Release and Biowaiver Regulation of Oral Extended Release Dosage Forms

- One out of four additional 300-mg strength product was withdrawn from the market due to bioinequivalence

Lin et al. 2016. *AAPS J.* 18(2): 333-345

- La diferencia en S/V entre las distintas potencias con composición proporcional afecta a la liberación de estos sistemas de liberación prolongada.

- Los mismo ocurre en el producto de referencia de Divalproex sódico (*J Pharm Sci*. 2003; 92(11):2317-25)

6.2.2.2. Multiple unit formulations

- For multiple unit formulations of a medicinal product with several strengths, it is **sufficient** to conduct the studies listed in section 6.1.1 **only at the highest/most sensitive strength** if the compositions of the strengths are **proportional**, the formulations contain identical **beads or pellets** (and these are produced by the same manufacturer) and the **dissolution profiles are similar**

Prolonged release multiple unit (**fasting or irrespective of food**)

Strength	Single dose fasting study	Single dose fed Study	Multiple dose study*
high	yes	yes	yes
middle	waiver	waiver	waiver
low	waiver	waiver	waiver

* see criteria for necessity in section 6.1

Prolonged release multiple unit (**fed conditions**)

Strength	Single dose fasting study	Single dose fed Study	Multiple dose study*
high	yes	yes	yes
middle	waiver	waiver	waiver
low	waiver	waiver	waiver

* see criteria for necessity in section 6.1

6.2. **Delayed** release formulations

- Bioequivalence between two delayed release formulations should be evaluated on the basis of studies designed to demonstrate that:
  - the test formulation exhibits the claimed delayed release characteristics of the reference
  - the active substance is not released unexpectedly from the test formulation (to ensure the aimed location of release)
  - performance of the test and the reference formulation is equivalent after a single dose
  - the effect of food on the in vivo performance is comparable for both formulations when a single dose study is conducted.

6.2. **Delayed** release formulations

- 6.2.1. Studies generally required to demonstrate bioequivalence:

  ➢ a **single-dose fasting** study comparing test and reference product

  ➢ a **single-dose fed** study using a **high-fat** meal (see 5.1.4.1) comparing test and reference product

- A similar approach as detailed for prolonged release forms regarding study design of single dose studies can be used (see 6.1.1.1).

6.2.2. Strength(s) to be evaluated

- **6.2.2.1. Single unit** formulations

  A. Single dose studies

  – If the reference SmPC recommends intake under **fasting state or irrespective** of food intake

  – If the reference SmPC recommends intake under **fed conditions only**

  B. Multiple dose studies

- **6.2.2.2. Multiple unit** formulations

6.2.2.1 Single unit formulations
A. Single dose studies

- If the reference **SmPC** recommends intake **under fasting state or irrespective of food** intake,
  - **Fasting state**: a **single dose** study under **fasting** conditions is required **for each strength**
    - However a **bracketing** approach (see section 6.6) is also possible if justified
    - In case of safety concerns in healthy volunteers, studies should be conducted in patients, that may require steady state conditions.

6.2.2.1 Single unit formulations
A. Single dose studies

- If the reference **SmPC** recommends intake **under fasting state or irrespective of food** intake,
  - **Fed state**: One **single dose** bioequivalence study **at the highest/most sensitive strength** conducted in **fed state** may be sufficient
    - The **other strength(s) can be waived if** the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled
    - However, if the strengths of the test product **do not fulfil these criteria or if proportional strengths have different shape** two strengths representing the **most extreme difference** should be tested in **fed state**

6.2.2.1 Single unit formulations
A. Single dose studies

- If the reference **SmPC** recommends intake under **fed conditions only**:
  - **Fed state**: a **single dose** study under **fed conditions** is required for **each strength**
    - However a bracketing approach (see section 6.6) is also possible if justified

6.2.2.1 Single unit formulations
A. Single dose studies

- If the reference **SmPC** recommends intake under **fed conditions only**:
  - **Fasting state**: One **single dose** bioequivalence study **at the highest strength** conducted in **fasting state** may be sufficient
    - The **other strength(s) can be waived if** the criteria for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled
    - However, if the strengths of the test product **do not fulfil these criteria or if proportional strengths have different shape** two strength representing the **most extreme** difference should be tested in **fasting state**.

6.2.2.1. Single unit formulations

B. **Multiple dose studies**

In principle there is **no need** for multiple dose studies except if single dose studies cannot be performed because of safety concerns

6.2.2.1. Single unit formulations

– When evaluating **proportionality in composition**, the proportionality of **gastro-resistant coating with respect to the surface area** (**not to core weight**) should be considered to have the same gastro-resistance (coating layer in **mg/cm²** surface).

The same applies for prolonged release coatings

Delayed release single unit (fasting or irrespective of food)

Strength	Single dose fasting study**	Single dose fed Study
high	yes	yes
middle	yes	waiver
low	Yes	waiver

* see criteria for necessity in section 6.1

Delayed release single unit (fed conditions)

Strength	Single dose fasting study	Single dose fed Study**
high	Yes	yes
middle	waiver	yes
low	waiver	yes

* see criteria for necessity in section 6.1

6.2.2.2. Multiple unit formulations

- For multiple unit formulations of a medicinal product with several strengths, it is **sufficient** to conduct the studies listed under 6.2.1 **at highest/most sensitive strength**, **if** the compositions of the strengths are **proportional**, the formulations contain **identical beads or pellets** (and these are produced by the same manufacturing process) and the **dissolution profiles are similar**

Delayed release multiple unit (fasting or irrespective of food)

Strength	Single dose fasting study	Single dose fed Study
high	yes	yes
middle	waiver	waiver
low	waiver	waiver

* see criteria for necessity in section 6.1

Delayed release multiple unit (fed conditions)

Strength	Single dose fasting study	Single dose fed Study
high	yes	yes
middle	waiver	waiver
low	waiver	waiver

* see criteria for necessity in section 6.1

6.2.3. Prolonged residence time in the stomach

- **Gastric emptying of modified release dosage forms** that do **not disintegrate in the stomach** (e.g. enteric coated tablets) may be **prolonged** and highly **erratic**
- The consequences of this effect on the enteric coating of delayed release formulations are largely **unpredictable** and can result in non-existing or aberrant concentration profiles.

6.2.3. Prolonged residence time in the stomach

- If the **incidence of this outlier behaviour** is observed with a **comparable frequency (e.g. the number of cases is not numerically higher in the test product) in both**, test and reference product, **data of a period with non-existing profile can be excluded** from statistical analysis **provided that it has been pre-specified** in the study protocol

6.2.3. Prolonged residence time in the stomach

- In a **2-period trial** this will result in the subject being **removed from the analysis**
- If the percentage of excluded subjects **exceeds 20%** for a particular study, the validity of the study may need to be **discuss**ed
- Furthermore the release of the active substance may be **considerably delayed due to a prolonged residence in the stomach**
- Therefore the **sampling period** should be designed such that measurable concentrations are obtained, **taking into consideration not only the half-life of the active substance but the possible occurrence of this effect as well**

6.3. **Multiphasic** modified release products

- The regulatory criteria mentioned in this Guideline are also applicable in the assessment of bioequivalence for modified release products designed to achieve **sequential release** combining **immediate and modified** characteristics (e.g. biphasic-/ pulsatile-release)
- **If one of the release phases is prolonged**, the **type and number of studies required** are those described above for this specific release mechanism
- However **additional pharmacokinetic parameters are needed to demonstrate bioequivalence for all phases** (see section 6.8.1)

6.4. **Intramuscular/Subcutaneous** Depot Formulations

- Studies generally required to demonstrate BE

  ➢ a **single-dose** study comparing test and reference products

  ➢ a **multiple-dose** study comparing test and reference products.

  – A multiple dose study is needed **unless a single dose** study has been performed with the **highest strength** which has demonstrated that:

  – the **mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both** test and reference, and consequently a **low extent of accumulation** is expected

6.4.2. Strength to be evaluated

- **Only one strength** has to be investigated **if** the different strengths are **proportional** in composition and exhibit a **similar in vitro dissolution profile**
- The **strength** should be selected based on the pharmacokinetic **linearity and safety**

6.4.1. Strength to be evaluated

- If there are several **non-proportional strengths** a **bracketing** approach is possible, but the formulation strategy of the reference product should be taken into account

6.4.1. Strength to be evaluated

- If the originator product is **marketed in only one concentration** and the **different doses** are achieved by choosing the **total volume** to be injected **any dose** should be acceptable for a bioequivalence trial in case **dose proportionality has been shown for the reference**

6.4.1. Strength to be evaluated

- In case therapeutic doses cannot be administered to healthy volunteers, **non-therapeutic doses may be acceptable for safety reasons**

6.4.1. Strength to be evaluated

- In situations where it is not possible to perform single dose studies with an intramuscular/subcutaneous depot formulation in healthy volunteers **for safety or ethical reasons, multiple dose studies in patients are acceptable to show bioequivalence.**

6.5. Transdermal Drug Delivery Systems (**TDDS**)

- A generic TDDS is defined by having the **same amount** of active substance **released per unit time** as compared to the reference TDDS
- It is to note that this definition is different to the general definition of a generic since the overall amount of active substance could differ while the labelled amount of active substance released per unit time should be the same between a generic and the innovator TDDS

6.5. Transdermal Drug Delivery Systems (TDDS)

- Equivalence testing of TDDS should comprise both **non-inferiority in terms of adhesion (see appendix IV)** and **bioequivalence**
- It is **advisable** to ensure **comparable or better adhesion properties prior to bioequivalence** investigations in volunteers since inferior adhesion could invalidate the pharmacokinetic results and question the acceptability of the product

6.5.1 Studies generally required to demonstrate bioequivalence

- a single-dose study comparing test and reference products
- a multiple-dose study comparing test and reference products

Transdermal Drug Delivery Systems (TDDS)

- Bioequivalence of TDDS should generally be assessed after **single dose** as well as after **multiple dose** application.
- A **multiple dose study is needed unless** a single dose study has been performed with the highest strength which has demonstrated that the mean **$AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$** for both test and reference, and consequently a low extent of accumulation is expected

Transdermal Drug Delivery Systems (TDDS)

- The study design including the **site of application** should be justified in terms of its **sensitivity** to detect formulation differences
- The application site should be **standardized and be the same** for both test and reference
- Due to rotation of patches between several sites a different site in the same region is typically used for the cross-over
- **The adhesion behaviour of the patch should not be altered by e.g. <u>over-taping</u>.**

6.5. Transdermal Drug Delivery Systems (TDDS)

- Bioequivalence should be assessed using the **same main characteristics, pharmacokinetic parameters and statistical procedures** as for prolonged release formulations
- The test product should demonstrate a similar or lower degree of local irritation, phototoxicity, sensitization, and similar or better adhesiveness to the skin as the reference product

6.5. Transdermal Drug Delivery Systems (TDDS)

- In order to ensure equivalence in terms of safety, comparative state-of-the-art studies are required to investigate
  - cutaneous tolerability, irritation and sensitisation (see appendix I)
  - the potential to produce phototoxic reactions
  - adhesion characteristics (for details regarding comparative adhesion tests see appendix IV)
- **unless otherwise justified by e.g. very similar quantitative and qualitative composition.**

6.5.2. Strength to be evaluated

- When the marketing authorisation of multiple strengths is required, a bioequivalence study can be performed with the **highest/most sensitive strength** provided that:

  ➢ the **qualitative composition** is the **same** for all strengths;

  ➢ the **strengths are proportional** to the effective **surface area of the patch** and the lower dose strengths can be considered as ''partial'' areas of the highest dose strength;

  ➢ there are **similar dissolution/release profiles**

6.5.2. Strength to be evaluated

- In case of **safety / tolerability limitations** at the highest strength, the use of a **lower strength** is acceptable for size proportional formulations

6.6. Bracketing approach

- **In case** bioequivalence **assessment at more than two strengths** is **needed**, e.g. because of **deviation from proportional composition and/or if dissolution profiles are not similar**, **or for single unit formulations with proportional composition**, a **bracketing approach** may be used if **the other waiver criteria** (see Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98) **are fulfilled**

Factors to take into account: composition, dissolution, man. process, size /shape, weight, ratio drug/excipient

6.6. Bracketing approach

- In this situation it can be **acceptable to conduct two bioequivalence studies**, if the strengths selected represent the **extremes**, e.g. the highest and the lowest strength or the two strengths **differing most** in composition, dissolution or size, so that any **difference**s in composition or dissolution **in the remaining strengths is covered by the two conducted studies**

6.6. Bracketing approach

- However, for prolonged release formulations **release-controlling excipients and mechanism should be the same for all strengths**.
- The same is required for release controlling coatings for delayed release formulations

6.8. Evaluation

6.8.1. Parameters to be analysed

- Single dose studies
- Steady state studies

Single dose studies

- In studies to determine bioequivalence after a **single dose, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, Cmax , $_{partial}$AUC and tmax** should be determined
- A **truncated $AUC_{(0-72h)}$ is not acceptable for MR products**

Single dose studies

- For **multiphasic** modified release products additional parameters to be determined include $_{\text{partial}}$**AUC, Cmax and tmax in all phases**
- The **time point for truncating the** $_{\text{partial}}$**AUC** should be **based on the PK profile for the IR and the MR parts respectively** and should be **justified and pre-specified** in the study protocol

Multiple dose studies

- In studies to determine bioequivalence after a **multiple dose** administration **$AUC_{(0-\tau)}$, $t_{max,ss}$, $C_{max,ss}$, $C_{\tau,ss}$, and fluctuation** should be determined
- In contrast to the need of characterisation of **$C_{min,ss}$ for new MR formulations**, a comparison of **$C_{\tau,ss}$**, which **is easier** to determine, should be **sufficient**

Multiple dose studies

- $C_{t,ss}$ is required to assess shape of the curve for generic applications and replaces the need to also evaluate $C_{min,ss}$ in those circumstances

6.8.2. Evaluation characteristics and acceptance criteria

- Bioequivalence for **prolonged release products with accumulation** should be demonstrated by showing equivalence after **statistical** evaluation of the following parameters:
  - **Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}**
  - **Multiple dose: $AUC_{(0-\tau)}$, $C_{max,ss}$, $C_{\tau,ss}$**

6.8.2. Evaluation characteristics and acceptance criteria

- Products that are also intended for one single application, bioequivalence has to be proven also for a metric of the shape of the curve (e.g. $_{partial}$AUCs) after single dose

	Single dose fasting study	Single dose fed Study	Multiple dose study
C_{max}	yes	yes	no
$AUC_{(0-t)}$	yes	yes	no
$AUC_{(0-\infty)}$	yes	yes	no
$_{partial}AUCs$	no	no	no
$C_{max,ss}$	no	no	Yes
$C_{\tau,ss}$	no	no	yes
$AUC_{(0-\tau)ss}$	no	no	yes

6.8.2. Evaluation characteristics and acceptance criteria

- For **prolonged release products** with **no risk of accumulation** (see section 6.1) or that are intended for once only use exclusively a **statistical** evaluation of the following parameters has to show bioequivalence:
  - **Single dose:** **$AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}** and a representative metric of the shape of the curve (**early and terminal $_{partial}$AUCs**)

	Single dose fasting study	Single dose fed Study	Multiple dose study
C_{max}	yes	yes	no
$AUC_{(0-t)}$	yes	yes	no
$AUC_{(0-\infty)}$	yes	yes	no
$_{partial}AUCs$	yes	yes	no
$C_{max,ss}$	no	no	no
$C_{\tau,ss}$	no	no	no
$AUC_{(0-\tau)ss}$	no	no	no

6.8.2. Evaluation characteristics and acceptance criteria

- Bioequivalence for **delayed release products** should be demonstrated by showing equivalence after statistical evaluation of the following parameters:
- Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max},

	Single dose fasting study	Single dose fed Study	Multiple dose study
C_{max}	yes	yes	no
$AUC_{(0-t)}$	yes	yes	no
$AUC_{(0-\infty)}$	yes	yes	no
$_{partial}AUCs$	no	no	no
$C_{max,ss}$	no	no	no
$C_{\tau,ss}$	no	no	no
$AUC_{(0-\tau)ss}$	no	no	no

6.8.2. Evaluation characteristics and acceptance criteria

- For **multiphasic modified release products** a statistical evaluation of the following parameters has to show bioequivalence:
- Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $_{partial}AUC$ and C_{max} in all phases.

*and in case of accumulation in

- Multiple dose: $AUC_{(0-t)}$, $C_{max,ss}$, $C_{t,ss}$

	Single dose fasting study	Single dose fed Study	Multiple dose study*
$C_{max(x)}$	yes	yes	no
$C_{max(x+1)}$	yes	yes	no
$AUC_{(0-t)}$	yes	yes	no
$AUC_{(0-\infty)}$	yes	yes	no
$_{partial}AUC_{(x)}$	yes	yes	no
$_{partial}AUC_{(x+1)}$	yes	yes	no
$C_{max,ss}$	no	no	yes
$C_{\tau,ss}$	no	no	yes
$AUC_{(0-\tau)ss}$	no	no	yes

Statistical Evaluation characteristics and acceptance criteria

- The bioequivalence approach considering usual acceptance limits (**80 – 125 %**) is applicable for generic MR products (see CPMP/EWP/QWP/1401/98)
- Any widening of the acceptance criteria for **Cmax** should follow the recommendations on **highly variable drug products** in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98).
- A **similar approach** can be used for widening the acceptance criteria for **$C_{max,ss}$, $C_{\tau,ss}$, and $_{partial}$AUC**

Statistical Evaluation characteristics and acceptance criteria

- Calculation of the intra-subject variability in multiple dose studies can be based on two consecutive administrations of the same product after reaching steady state

6.8.2. Evaluation characteristics and acceptance criteria

- For **delayed and multiphasic** release formulations **differences in t_{max}** is also recommended to be assessed, especially for products **where a fast onset of action is important**
- A **formal statistical evaluation of t_{max} is not required**
- However, there should be **no apparent difference in median t_{max} and its range** between test and reference product

6.9. Effects of alcohol

- **For generic** oral formulations, **in vitro studies** of the release in alcohol solutions should be performed
- Where **accelerated** active substance **release** is seen in vitro **either at high or low alcohol concentrations** over a **short period of time** or at **lower alcohol** concentrations over a **longer period** of time, the product should be **reformulated**
- If the alcohol effect **cannot be avoided** and it is present **also in the reference** product, the applicant should **justify / demonstrate** that it **lacks of clinical relevance or discuss the possible relevance in comparison to the reference product**

In vitro or in vivo? Justify

¡Muchas gracias por su atención!

¿Preguntas?

DIAPOSITIVAS ADICIONALES

Submission

- *Module 2.7.1 should list all relevant studies carried out with the product applied for, i.e. bioequivalence studies comparing the formulation applied for (i.e. same composition and manufacturing process) with a reference medicinal product marketed in EU.*
- *Studies should be included in the list regardless of the study outcome.*
- *Full study reports should be provided for all studies, except pilot studies for which study report synopses (in accordance with ICH E3) are sufficient.*

Submission

- *Full study reports for pilot studies should be available upon request.*
- *Study report synopses for bioequivalence or comparative bioavailability studies conducted during formulation development should also be included in Module 2.7.*
- *Bioequivalence studies comparing the product applied for with non-EU reference products should not be submitted and do not need to be included in the list of studies.*

Presentation of data

- *If for a particular formulation at a particular strength multiple studies have been performed some of which demonstrate bioequivalence and some of which do not, the body of evidence must be considered as a whole.*
- *Only relevant studies, as defined in section 4.1, need be considered.*
- *The existence of a study which demonstrates bioequivalence does not mean that those which do not can be ignored.*

Submission

- The results of in vitro dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study should be reported.
- Particular dosage forms like ODT may require different experimental conditions

Presentation of data

- The applicant should thoroughly discuss the results and justify the claim that bioequivalence has been demonstrated.
- Alternatively, when relevant, a combined analysis of all studies can be provided in addition to the individual study analyses.
- It is not acceptable to pool together studies which fail to demonstrate bioequivalence in the absence of a study that does.

Selection of the reference

- *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.*

Design

- Single dose 2x2 cross-over
- Multiple dose if HV do not tolerate and single dose is not feasible in patients
- Sensitivity problems:
  - Supra-therapeutic dose in single dose?
    - Tolerable? Solubility? Linear PK?
  - Steady state (last option)

Parent or metabolite : General recommendations

- In principle, parent
- Even if inactive (pro-drug)
- Metabolite does not need to be measured

Parent or metabolite: Inactive pro-drugs

- 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.

Parent or metabolite: metabolite as a surrogate for active parent

- Use of metabolite as surrogate for active parent is not encouraged.
- Justify sensitivity of the analytical method cannot be improved
  - Taking into account the option of using a higher single dose.
- Unusual. Only in exceptional cases.
- Justify that the metabolite exposure will reflect parent drug and that the metabolite formation is not saturated at therapeutic doses.

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.

Enantiomers

- 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.

Strength to be investigated: biowaiver of additional strengths

- Immediate release products
- Modified release products
  - Multiple-unit formulations
  - Single-unit formulations
  - Transdermal patches
  - Injectables

Clarifications

- What is bracketing?
- What is linear PK?
- What strength is the most sensitive?
- What is the 5% rule?
- How to compare dissolution profiles?
- How to compare compositions in FDC?

Bracketing approach

- *Where BE assessment at more than two strengths is needed, e.g. because of deviation from proportional composition, a bracketing approach may be used*
- *In this situation it can be acceptable to conduct two BE studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, so that any differences in composition in the remaining strengths is covered by the two conducted studies*

Bracketing approach

- *Where BE assessment is needed both in fasting and in fed state and at two strengths due to nonlinear absorption or deviation from proportional composition, it may be sufficient to assess BE in both fasting and fed state at only one of the strengths*

Bracketing approach

- *Waiver of either the fasting or the fed study at the other strength(s) may be justified based on previous knowledge and/or pharmacokinetic data from the study conducted at the strength tested in both fasted and fed state*
- *The condition selected (fasting or fed) to test the other strength(s) should be the one which is most sensitive to detect a difference between products*

Linear PK for BE waivers only

- *In case of non-linear PK (i.e. not proportional increase in AUC with increased dose) there may be a difference between different strengths in the sensitivity to detect potential differences between formulations*
- *In the context of the guideline, PK is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength (or strength in the planned BE study) and the strength(s) for which a biowaiver is considered*

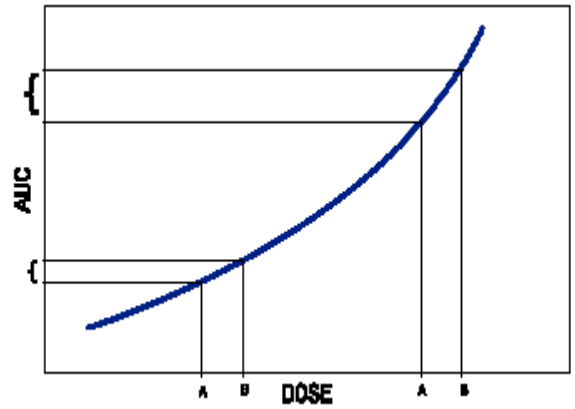
Linear PK for BE waivers only

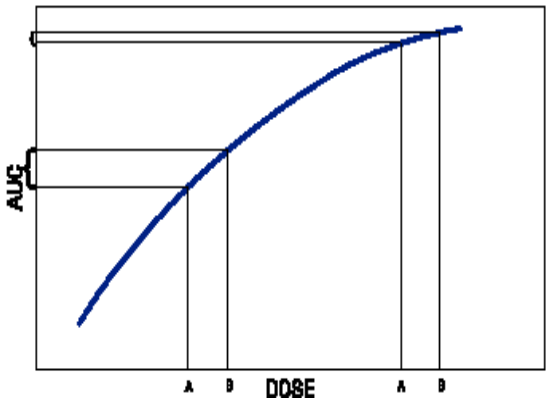
- *In order to assess linearity, the applicant should consider all data available in the public domain with regard to the dose proportionality and review the data critically*
- *Assessment of linearity will consider whether differences in dose-adjusted AUC meet a criterion of ± 25%*

Dose	AUC (ng·h/ml)	AUC / Dose	Ratio of dose-normalised AUC
10 mg	498	49,8	0,94857143
20 mg	1045	52,25	0,9952381
40 mg	2100	52,5	

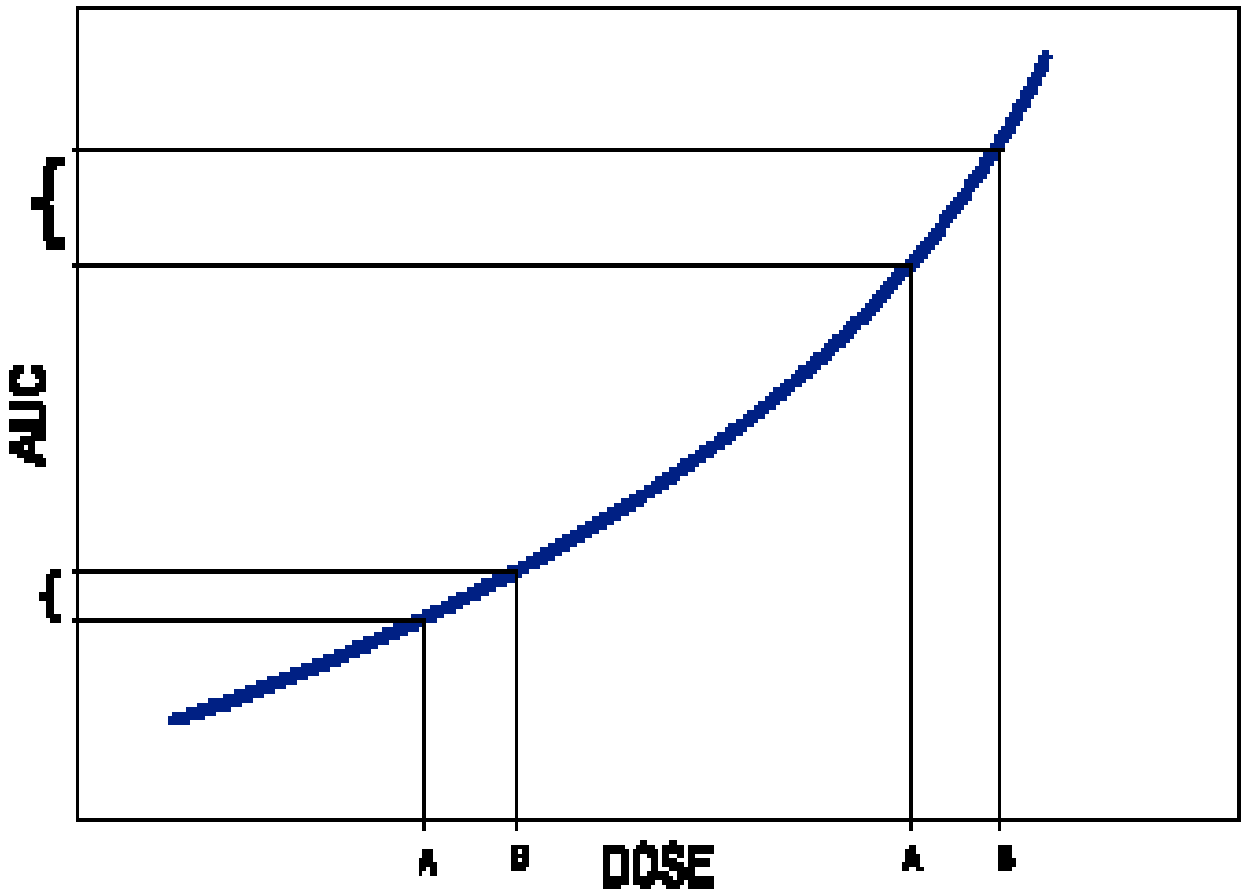
Strength to be tested

- FDA: Orange Book
- Canada: The most sensitive strength to detect differences
  - Linear PK: any strength – highest strength
  - Non-linear PK:





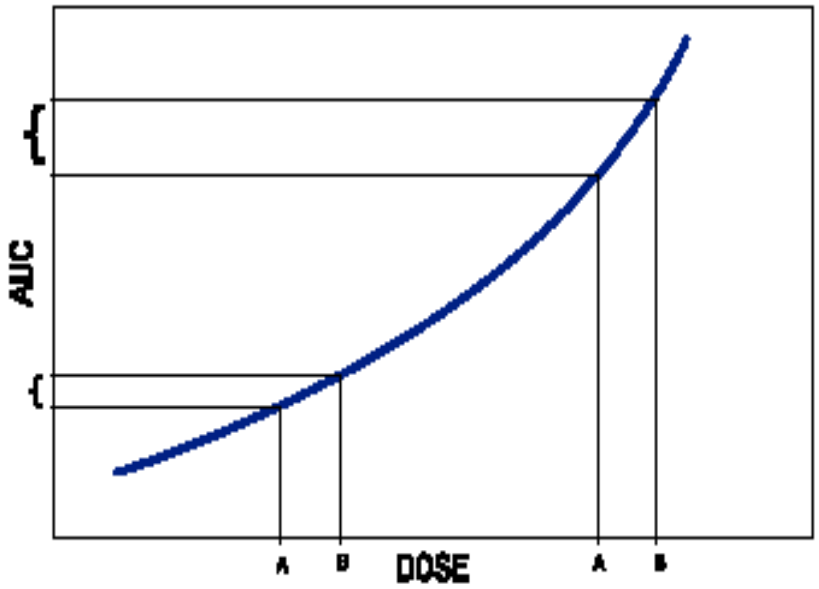
More than proportional AUC



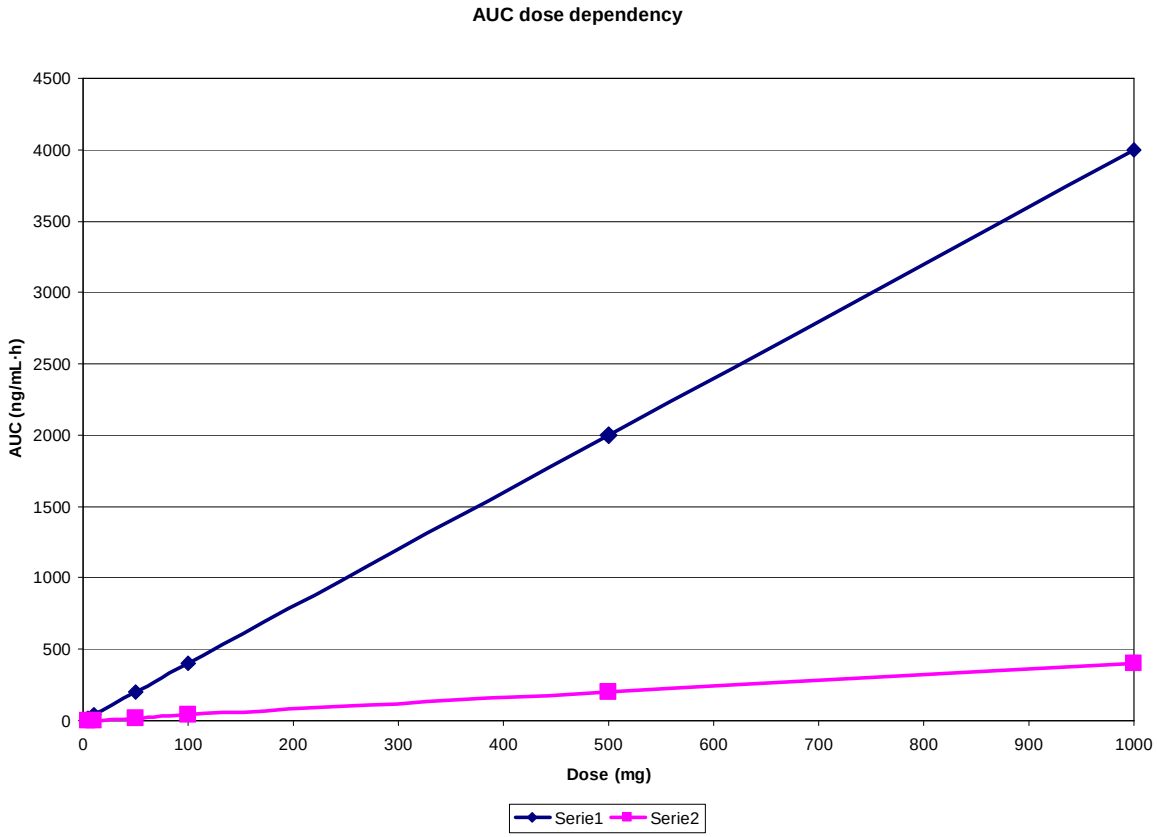
- *e.g.,* saturation of first-pass effect.

But this plot is wrong

- 1. Visually evident that the difference is higher with the higher slope, but false because we work with ratios in y-axis. The ratio is the same as long as it is a straight line
- 2. In x-axis we work with %, then the width should be double if we double the dose in order to be comparable (bigger difference, more visual, equally wrong).



If it were a matter of slope we should use poor metabolizers



AUC = F · Dose / Cl

Steep slope	Dose	AUC
Poor metaboliser	5	20
y=4x	10	40
	50	200
	100	400
	500	2000
	1000	4000
Flat slope	5	2
extensive metaboliser	10	4
y=0,4x	50	20
	100	40
	500	200
	1000	400

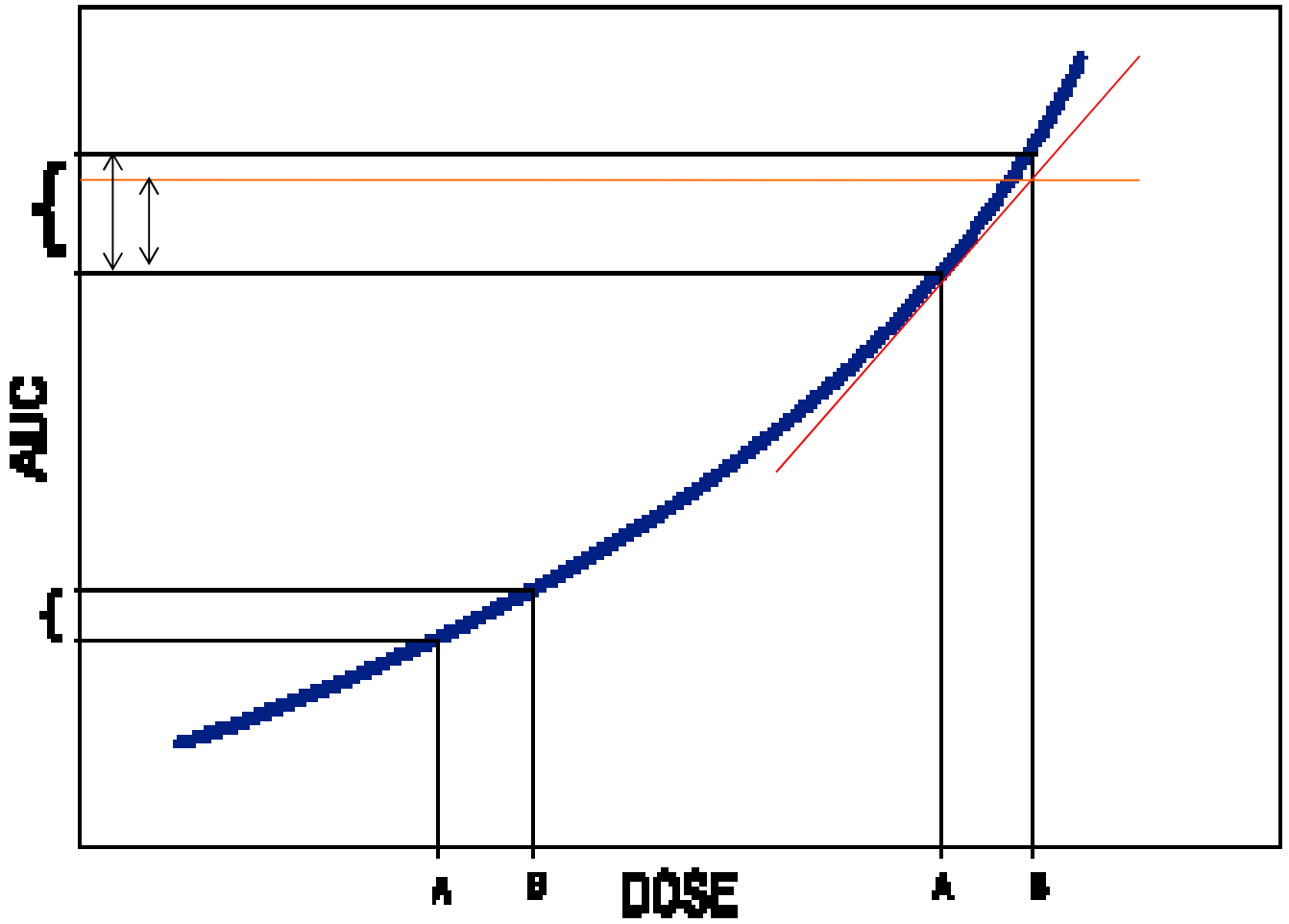
Poor metabolisers have lower clearance and steeper slope

But the sensitivity is the same

Y=4x	DOSE	AUC test	AUC ref	ratio T/R
	10	36	40	0.9
	50	180	200	0.9
	100	360	400	0.9
	250	900	1000	0.9
	500	1800	2000	0.9
	1000	3600	4000	0.9
Y=2x	DOSE	AUC test	AUC ref	ratio T/R
	10	18	20	0.9
	50	90	100	0.9
	100	180	200	0.9
	150	270	300	0.9
	500	900	1000	0.9
	1000	1800	2000	0.9

AUC = F · Dose / Cl

The difference observed in the linear part is amplified in the non-linear part

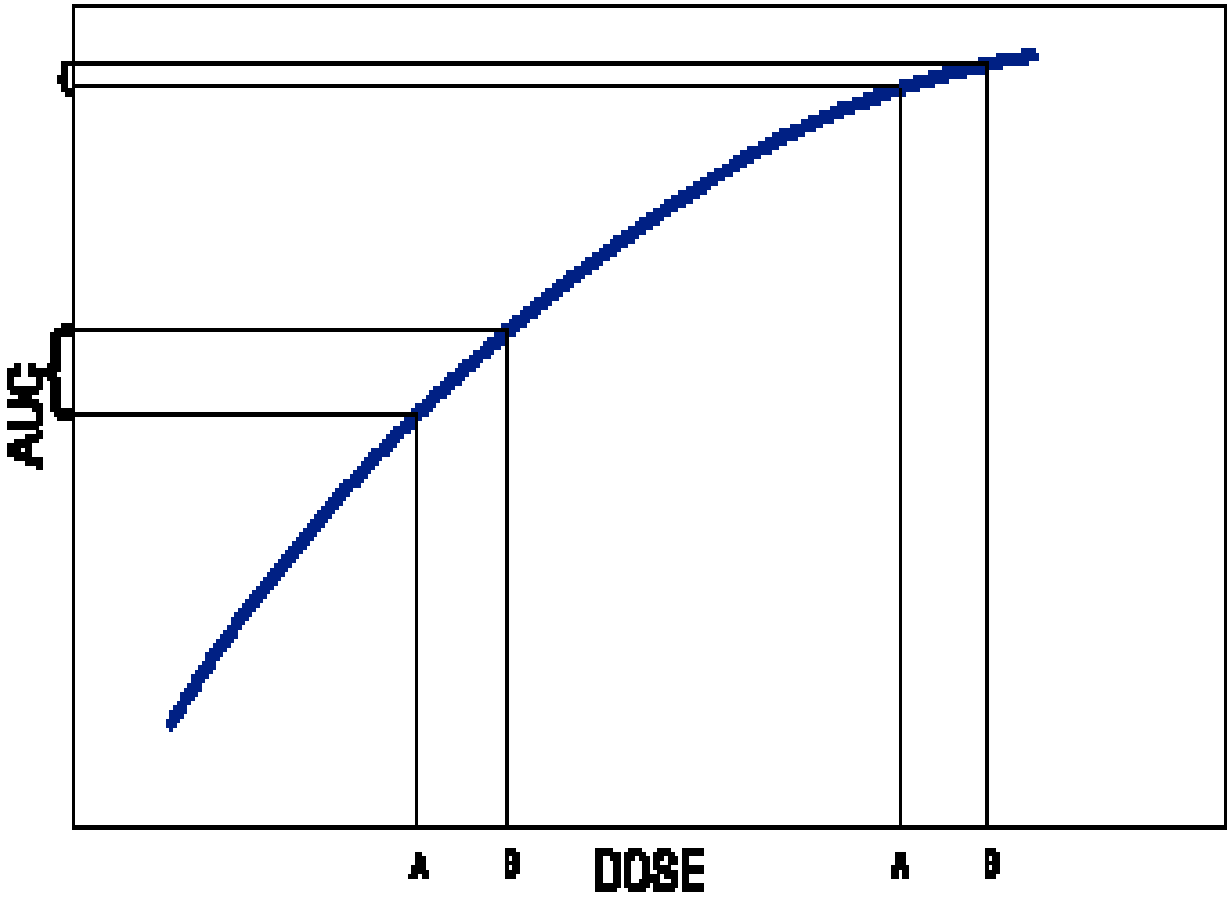


Numerical example

- Let's assume a 10% less bioavailable test product
  - Ratio T/R for AUC is 0.9 in the linear part
- Let's assume that Clearance changes a 10% due to saturation
  - Cl = 1 for the reference and 1.1 for the test

$$\frac{AUC_T}{AUC_R} = \frac{F_T \times Dose/Cl_T}{F_R \times Dose/Cl_R} = \frac{F_T \times Cl_R}{F_R \times Cl_T} = \frac{0.9 \times 1}{1.0 \times 1.1} = 0.82$$

Less than proportional AUC



- *e.g.,* low solubility or saturation of absorption

Less than proportional AUC

- Low solubility drug:
  - Highest strength (if the test is more linear)
    - “Investigate if the test is better”
  - Lowest strength (if saturation occurs in both)
    - “Investigate if the test is worse”
- Saturation of absorption
  - Lowest strength or a strength in the linear part
  - What if excipients saturate the transporter or affect motility?
    - Higher saturation or effect with the highest strength in proportional formulations

Exceptions

- A lower strength is acceptable if the highest strength has safety / tolerability problems in healthy volunteers
- A supra-therapeutic dose with multiple units of the highest strength for analytical reasons if there is neither absorption / solubility problems nor safety concerns

What about Cmax?

- Is the Cmax comparison independent of Clearance, like in case of AUC?
  - No
  - The difference in absorption rate (k_a) are detected better in drugs with quick clearance (or distribution)
  - Cmax differences are detected better in extensive metabolisers or patients with induced metabolism
    - Tothfalusi L, Endrenyi L. 2013. Approvable generic carbamazepine formulations may not be bioequivalent in target patient populations. Int J Clin Pharmacol Ther. 51(6):525-528

5% rule

- If the amount of the active substance(s) is less than 5 % of the tablet core weight or capsule content
  - the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed
  - the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths

Exceptions?

- *e.g.*, antioxidant: the amount of a particular excipient is directly correlated with the amount of active substance and the excipient does not have any effect on the BA of the active substance
- *e.g.,* solid dispersions: excipients that cannot be kept constant because they affect bioavailability and should be proportional

Glimepiride

Glimepiride	1 mg	2 mg	3 mg	4 mg	6 mg
Lactose monohydrate	a	2a-0.75	2a-1	4a-0.2	4a-1.9
Microcrystalline cellulose	b	2b	2b	4b	4b
Na starch glycollate	c	2c	2c	4c	4c
Povidone K25	d	2d	2d	4d	4d
Red Ferric oxide	x	16x	2x		
Indigotine		y		3y/4	
Mg stearate	e	2e	2e	4e	4e

Studies at a dose of 6 mg with 3 and 6 mg strengths

	Test 1	Test 2	Ref	T1/R log	IC 90% T1/R	T2/R log	IC 90% T2/R
AUC_{0-t} (ng h/ml)	2023.30	2026.60	2102.85	**96.1**	**91.6 - 100.8**	**97.4**	**92.8 – 102.1**
$AUC_{0-\infty}$ (ng h/ml)	2067.58	2069.50	2145.57	**96.4**	**92.0 - 101.1**	**97.5**	**93.0 – 102.2**
C_{max} (ng/ml)	339.43	345.23	395.74	**85.4**	**78.4 - 93.1**	**88.4**	**81.1 – 96.4**
t_{max} (h) mediana	4.0	4.0	4.0		**-1.25 - 0.25**		**-1.00 - 0.00**
$T_{1/2}$ el (h)	8.00	7.90	8.23				

Studies at a dose of 4 mg with 2 and 4 mg strengths

	Test 1	Tes 2	Ref	T1/R log	IC 90% T1/R	T2/R log	IC 90% T2/R
AUC_{0-t} (ng h/ml)	1668.49	1684.23	1646.10	**100.8**	**96.4 – 105.4**	**101.8**	**97.4 – 106.4**
$AUC_{0-\infty}$ (ng h/ml)	1702.62	1726.19	1675.62	**101.1**	**96.8 – 105.6**	**102.5**	**89.3 – 103.5**
C_{max} (ng/ml)	283.36	291.86	305.97	**92.3**	**85.7 – 99.3**	**96.1**	**88.1 – 107.0**
t_{max} (h) mediana	4.0	2.5	3.0		**-1.00 – 0.25**		**-0.25 – 0.75**
$T_{1/2}$ el (h)	7.24	8.60	7.03				

Study at a dose of 1 mg with the 1 mg strength (Canada)

	Test	Ref	T/R log	IC 90% T/R
AUC_{0-t} (ng h/ml)	278.36	287.31	**97.63**	**92.34 – 103.21**
$AUC_{0-\infty}$ (ng h/ml)	329.78	316.61	**106.51**	**99.18 – 114.38**
C_{max} (ng/ml)	42.54	44.99	**93.90**	**83.77 – 105.26**
t_{max} (h) mediana	6.00	6.00		
$T_{1/2}$ el (h)	4.11	3.06		

Study at a dose of 3 mg with the 3 mg strength

	Test	Ref	T/R log	IC 90% T1/R
AUC_{0-t} (ng h/ml)			**98.9**	**95.5 – 102.4**
$AUC_{0-\infty}$ (ng h/ml)			**98.8**	**95.3 – 102.3**
C_{max} (ng/ml)			**90.3**	**81.6 – 100.0**
t_{max} (h) mediana				**-1.50 – 0.00**
$T_{1/2}$ el (h)				

- The proportional formulations of 1, 2 and 4 mg are similar: 93.9, 92.3 and 96.1% (>90%)
- Although composition is similar between 3 and 6 and 2 and 4 mg strengths, the difference is larger with 3 and 6 mg: 85.4 or 88.4 *vs.* 92.3 or 96.1%
- Cmax of the 3 mg strength depends on the dose: 85.4 *vs.* 90.3
- No trend can be detected with dissolution profiles.

Dissolution profile comparison

- In low solubility drugs dissolution is not complete in any condition (pH 1.2, 4.5, 6.8, QC)
  - The same incomplete dissolution is expected
- Different strengths will have different non-sink conditions which precludes similarity
  - Compare T *vs.* R to show that the same limitation occurs in the reference (drug dependent)
  - Compare the same dose per vessel
    - 1 x 10 mg *vs.* 2 x 5 mg

Fixed dose combinations

- When considering the amount of each drug the other drug(s) can be considered as excipients
  - *e.g.* 80/25 and 40/12.5 should be proportional
  - *e.g.* 80/25 and 80/12.5: 25 and 12.5 should meet the 5% rule (*i.e.,* core of 500 mg)
  - *e.g.* 40/25 needs another BE study if 80 does not meet the 5% rule (*i.e.*, core <1600 mg)
- Bi-layer tablets are considered as two different tablets