Guideline on the Investigation of Bioequivalence

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

Dr. Isra Dmour

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.

الحوشين (6.1.2025) « بسم الله الرحمن الرحيم » date / /

"Bioequivalence"

- معناها "متكافئ حيويًا"، يعني الformula القديمة يلي مسجلة أصلًا يلي كاتبين عليها كل شي تأثير الformula الجديدة على الجسم نفسها.

- الـ SBAC من الحالات يلي نقل عليها bioequivlence، لا نقرر على formula.. المعيار تاع الدواء مثلًا أو هاي الأمور.

- الحالة الثانية يلي هي أساسية أصلًا، إنه أعمل دواء جديد (جينيريك)، قررت الشركة تعمل كبسولات بروجيستون مثلًا، بالسوق في الأصل هاي الكبسولات، إنت بدك تعمل كبسولات زرها، لازم تثبت التأثير الحيوي تاع كبسولاتك إنه زي يلي بالسوق من خلال الدراسات الكلينيكال (السريرية)

- بدنا نفرق بين مصطلح :-

① pharmaceutical equivalene

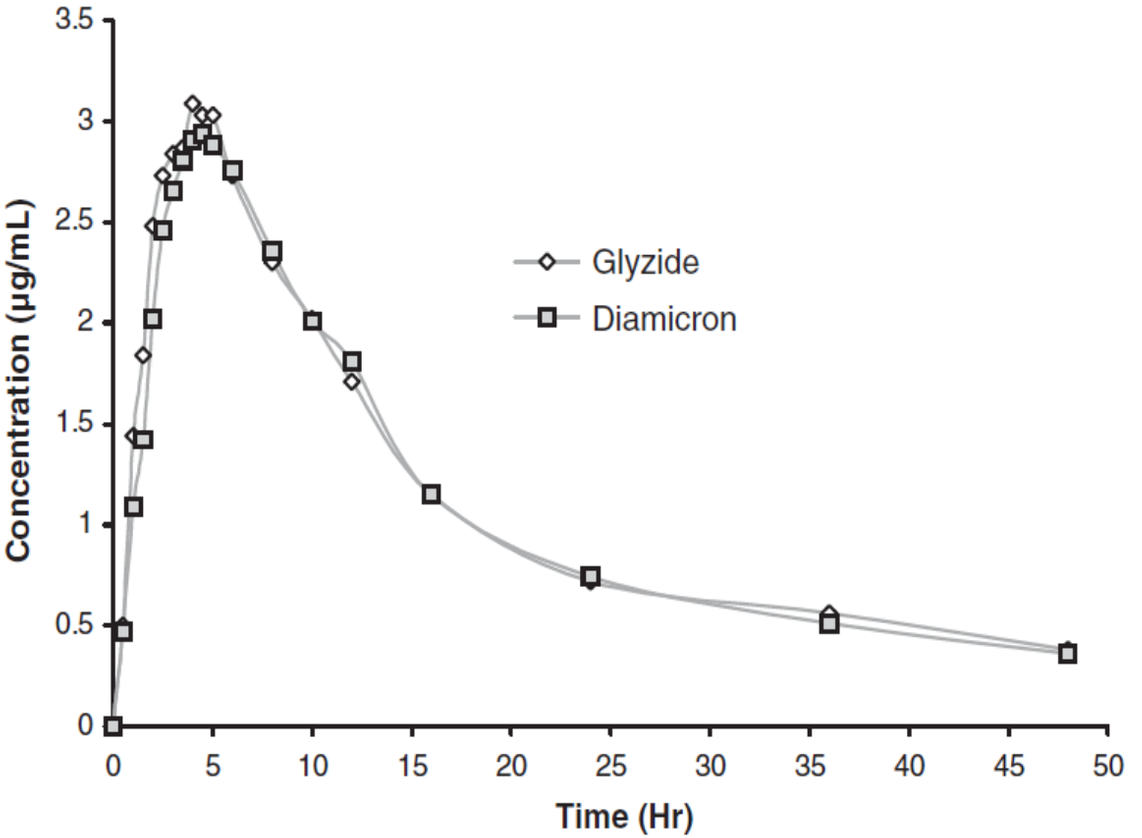
هو عبارة عن دواء إله نفس الـ AE والمعيار، هو لحد هنا مش bioequivelent وما بقدر أعتبره أصلًا لحتى أعمل دراسات bioequivalence عليه، مش شرط كل شي pharmaceutical equivalence

معناته هو bioequivalence.

② pharmaceutical alternative

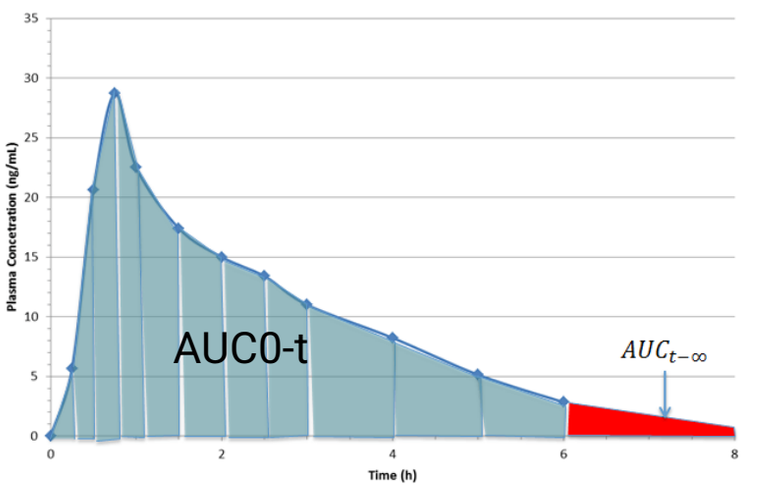
- هم الأدوية يلي تكون من نفس العائلة، زي الديكوفينات، مثلًا ديكلوفين صوديوم وديكلوفين بوتاسيوم أو إيستر، كلهم يكونوا ديكوفينات بس مش بدائل عن بعض مش نفس الـ AE

- 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(!!) concentration time curve is generally used to assess the rate and extent of absorption.



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;
$t_{1/2}$:	Plasma concentration half-life;
λ_z:	Terminal rate constant;
SmPC	Summary of Product Characteristics



INTRODUCTION

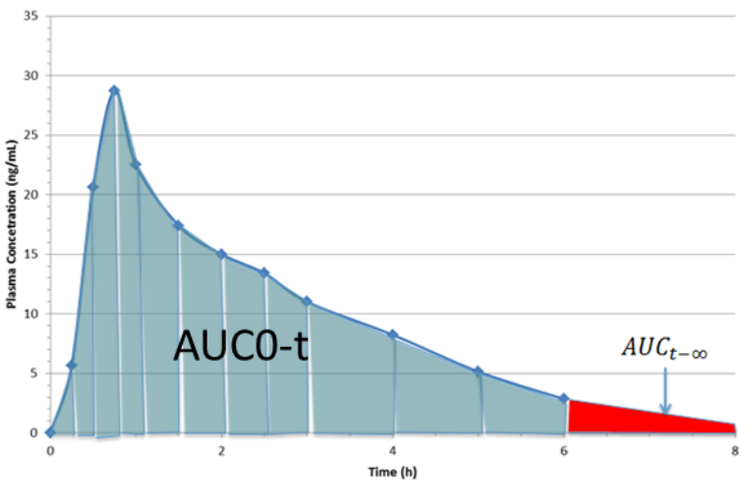
Selected pharmacokinetic parameters and preset acceptance limits allow the final decision on bioequivalence of the tested products.

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!



← واضح عنا هون بالرسمة، عندي profile للتركيز بالبلازما مع الوقت لدوايين Orginator و Generic، بيقيسوا فيها الـ AUC يلي هي المساحة تحت الـ curve و الـ C_{max} ، T_{max} ... بهيني هنن الثلاث (AUC, C_{max}, T_{max}) بدهن bioequi...

ما بدي أعمل دراسة سريرية، بدي أعطي ناس الدواء مختبرين، بحدين بيسحب منهم دم بحلل تركيز الدم بالبلازما على كل point، عشان أعرف الـ bioequivalence يلي هي نفسها (rate and extent of absorption)

← من كل المذكورين، أهم شي عندي الـ AUC، الـ Cmax، الـ Tmax

لـ rate of absorption مع الـ Tmax بحسبه

→ The possibility of using in vitro instead of in vivo studies is also addressed.

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.

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.

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.

- 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.

- 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.

date / /

← شو هو ال Generic ؟ هلا البدائل، نفس ال AE ونفس العيّنة، بينفعش أحكي إنه البنادول الكابسول، نفسه التابلت من البنادول ما بنقدر أحكي إنه Generic، باختصار هو نفس ال AE ونفس النوع ونفس ال dosage form، وإنت ما تعتبره generic إذا ما إله نفس ال bioequivalence.

← مثلاً دواء (X) صوديوم، الشركة عملت منه دواء (X) بوتاسيوم، هل (X) بوتاسيوم دواء جديد ومطلوب أعمل دراسات سريرية عليه من جديد؟ لأ، بعتبر الصوديوم هو المرجع والبوتاسيوم الجديد هو ال Generic، بشرط يكون إلهم نفس الفعالية والأمان.
هلا هدول الأدوية نفس الشي ونفس ال AE حتى تأثر عندهم الفعالية والأمان تاعهم

← طبعاً بهاد الشابتر راح نغطي ال bioequivalence لل immediat فقط ما راح نغطي الأنواع الأخرى مثل ال modified وهاي الأمور لأنه إلها guidelines خاص فيها.

← بعتبر الأدوية same pharm form إذا إلها Dosage form تنعطى عن طريق الفم، بعتبرهم كلهم تحت هاد البند، فقط بكون oral + immediat غير هيك مش مشمول في هاد القايدلاين.

← ليه نقل bioequivalance؟ للمقارنة فقط بين الأدوية وأتأكد إنه الفعالية والأمان تمام.

← شو هي ال herbal medicine؟ عشان أسجلها بحتاج إلى bioequivalance و دراسة سريرية ما بستغني عنهم أبداً.

← ال bioequivalence study لازم تخضع لل GMP، كل ما ينطبق وتعرفنا عليه بال GMP بنطبق على bioequivalence

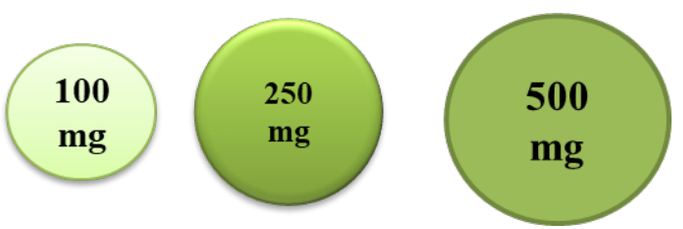
← الدكتورة حكت ما بهمني التنظيمات الأوروبية بهمني فقط الأردن حتى عنهم بعدين.

MAIN GUIDELINE TEXT
Design, conduct and evaluation of bioequivalence studies

- The number of studies and study design depend on :

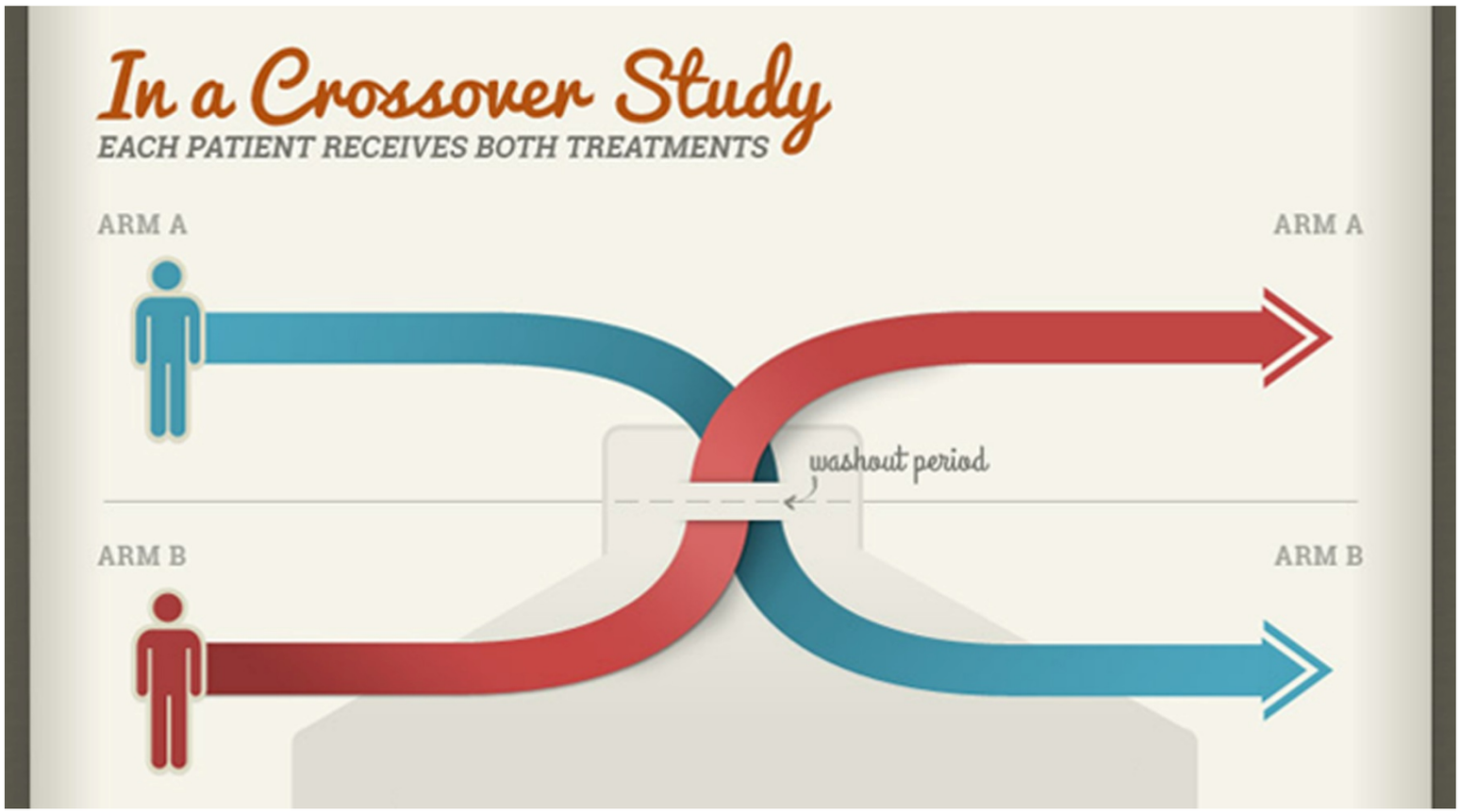
1. the physico-chemical characteristics of the substance,
2. its pharmacokinetic properties
3. proportionality in composition, and should be justified accordingly.

- 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



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



- Randomization

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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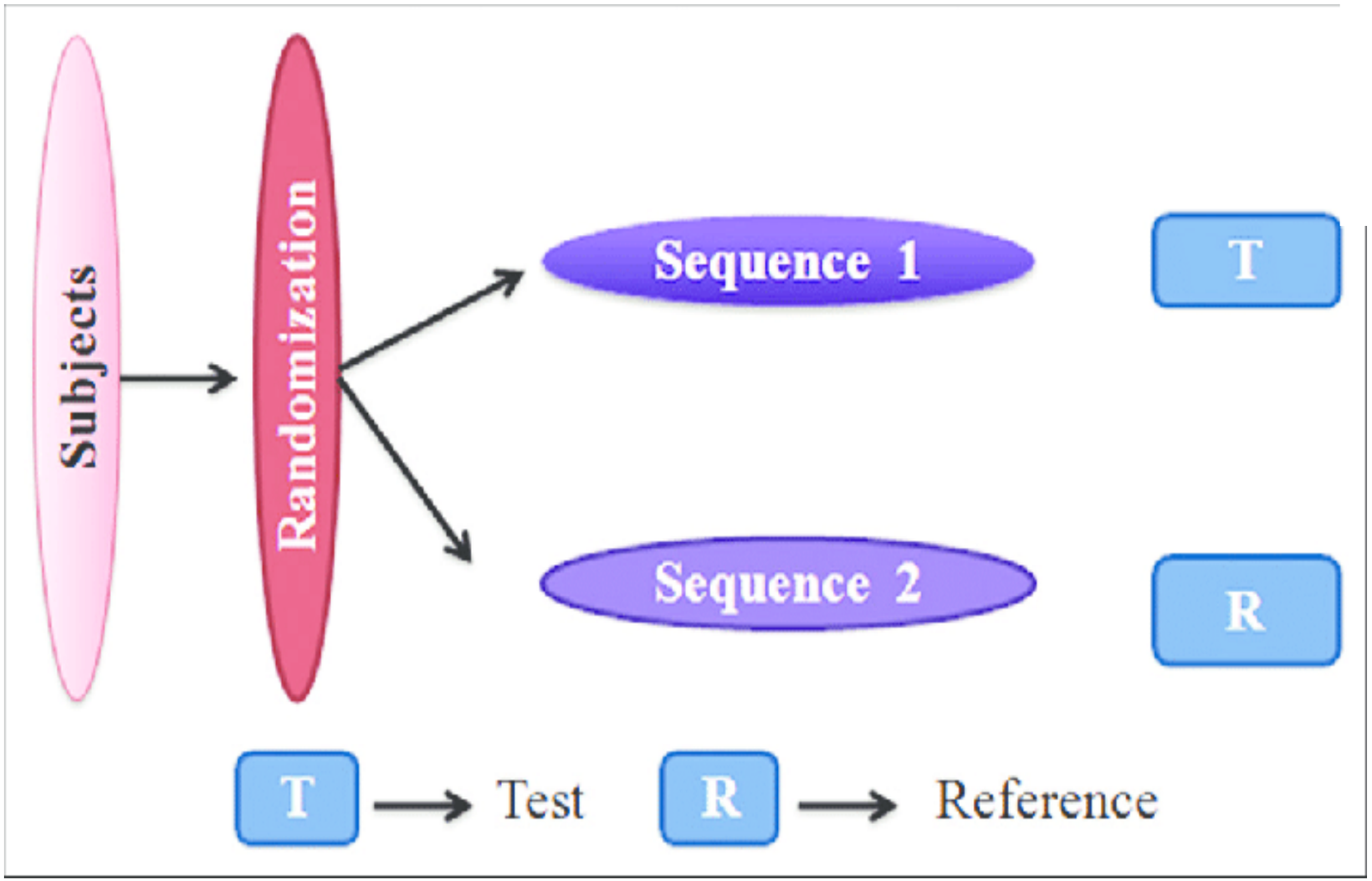
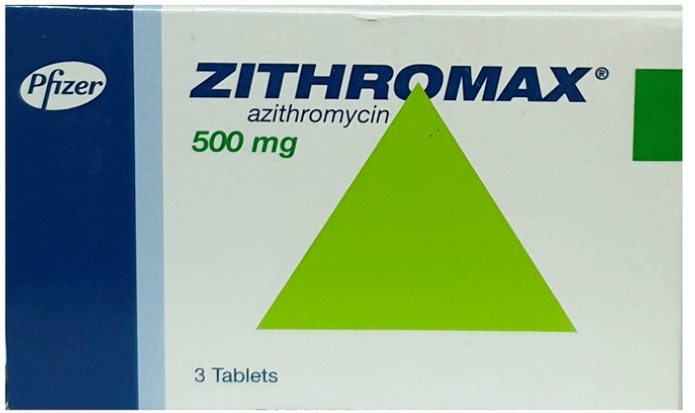
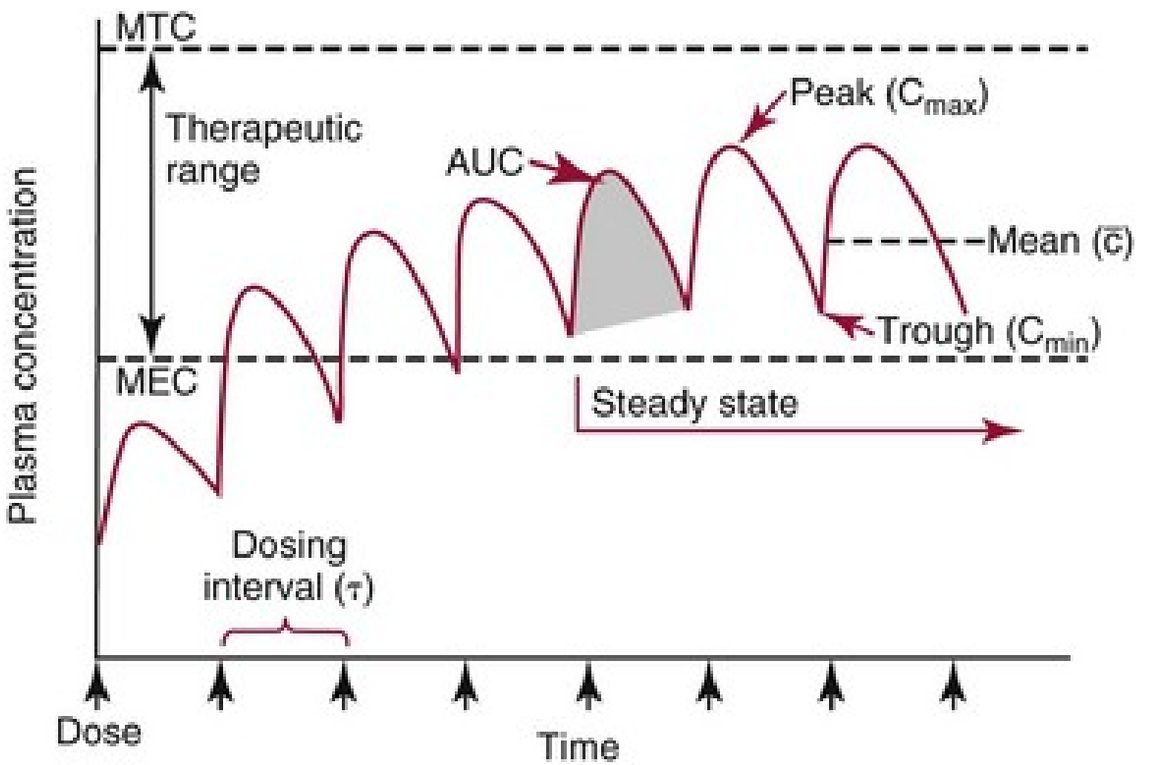




Alternative designs

- 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.
- Hence, 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.

- 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).



← Study design تعتمد على الخصائص الكيميائية، الفيزيائية للدواء، والخصائص الكينيتك ذي ADME

← أول Study deasp هو:-

① Standard design

من الصفات لـ Standard، إنه يكون "two sequence" "two period" "randomised". معناه أنا بجيب two group عندي two drugs راح يأخذوا واحد Drug يكون reference و Drug يكون test وعندي group A وعندي group B راح أعطي لـ قروب A وراح أعطي قروب B الـ Test. reference

في كل قروب عندي 20 شخص مثلاً نفترض، بلش معهم عشوائياً، بعدين راح يصير عندي ستي

اسمه wash period كل واحد منهم أخذ حبة من الدواء، بعدين أعمل wash out-period بدي تأكد إنه الدواء صار له elimination من الدم.

wash out period = half life *5

لنفترض إنه بلشنا معاه المريض بدواء Test وكان الـ half life تاعته 30min يروح أضربها بـ 5 = يطلع عندي ساعتين ونص، يعني بعد ساعتين ونص من إعطاء الدواء تاع الـ Test بعطيه الـ reference والعكس صحيح

هاي هي الـ Standard design.. متى ما نقدر نخلي الـ half life تاعته طويل يعني hours 12 مثلاً! يروح في هاي الحالة على Design ثاني اسمه parallel والـ parallel بنعطي مرة وحدة زي ذي الـ Standard

② parallel design

ببعض الأحيان ما نقدر أعطي Single dose لسبب أنه الدواء مثلاً إنه دواء ضغط بنزل الضغط كثير، هل من المنطق أعطيه لناس هالشي؟ لأ، متى أعطي multiple؟ إذا كان عندي مريض فقط، لأنه ما ينفع أوقف عنه الدواء اللي يوخذه وأعطيه جرعة واحدة؟

والسبب الثاني هو التركيز تاع الدواء

Reference and test product

- Reference Product
- For Article 10(1) and 10(3) marketing authorisation applications reference must be made to the dossier of a reference medicinal product for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC, as amended.
- The product used as reference product in the bioequivalence study should be part of the global marketing authorisation of the reference medicinal product (as defined in Article 6(1) second subparagraph of Directive 2001/83/EC).
- The choice of the reference medicinal product identified by the applicant in Module 1.2 Application form for which bioequivalence has been demonstrated by appropriate bioavailability studies, should be justified in section 1.5.2 “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.

- 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.

لو الإنتاجية ٥٠ ألف، شو عشرها؟
٥ الآلف، أيهما أكبر ؟
ال ١٠٠ ألف.

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.
- 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 (see Appendix I).

- 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.