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, including Annex 13 to the EU guide to GMP.
- Where necessary and in accordance with local regulations, sites should be authorised, as provided for in Article 13(1) of Directive 2001/20/EC, except where the provisions of Article 9(2) of Directive 2005/28/EC apply.
- 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.

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.).

- 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.
-

- 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.

date / /

← حكينا قبل بآخر المحاضرة السابقة عن "أيها أكبر" ونختار الأكبر دائمًا نقسم لوحدات عندي للعشر (1/10) .. ممكن أنا أقبل شي أكيد غير الـ 100 ألف تاعتك إذا إنت أثبتت إلي إنه ما تقدر تصنع 100 ألف وحدة من دواء معيّن .. وهذه هاي الحالات لما يكون عندك دواء نادر جدًا صعب تصنع منه كميات كبيرة جدًا .. ساعتها أنا بعطيك نوع صنع الحد المناسب إلك، وداح أقبلها منك.

← لما أخلص الـ bioequivalence وطلعت النتائج تاعتها وبدي أسجل هاي النتائج ملف التسجيل يروح مع عينات التسجيل .. إذا ما كانت عينات التسجيل مثل ما طلع مع بالنتائج، داح نكلفها Testing مقارنةً بالباتش تفت لبيوإكوفيلنس ..

هسّا إنت سجلت وبدّك تصنّع خلص، لازم أول ٣ من العينات لازم ينعملهم Comparative dissolution

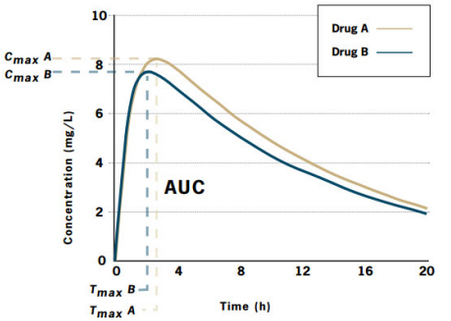
← هسّا إنت صنعت هدول الـ 100 ألف وحدة وبك تودهم على مركز الدراسات عشان يعطوها للمرضى .. كل Single بك تعمل إلها ليبل بكيس خاص فيها، ويكون Dose عليها المعلومات الكافية والمهمة عنها، وعليها كمان أهنيف باركود، طبعًا هاد البكج بيكون طالع من الشركة مصنوعه توافر حيوي أو بالمركز تاع الدراسات

طبعًا العدد تاع الـ Subjects للـ bioequivalence لازم يكون عددهم 12 والـ BMI تاعتهم لازم تكون = 18.5 وما يكون عندهم History ولا مشاكل بنضع يكونوا كلهم إناث أو كلهم ذكور أو مختلط.

ممنوع لفترة الـ Testing يكون يوخذ أدوية، غير أدوية مسموح فيها .. مثل الأدوية يلي تعالج الأعراض الجانبية يلي ممكن تنتج من الدواء الـ Test ..

ليش نختار healthy volunteers لأنه أي Data تطلع منهم بتسوي مشاكل على الـ non-healthy

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).

- 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.

- 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.

date / /

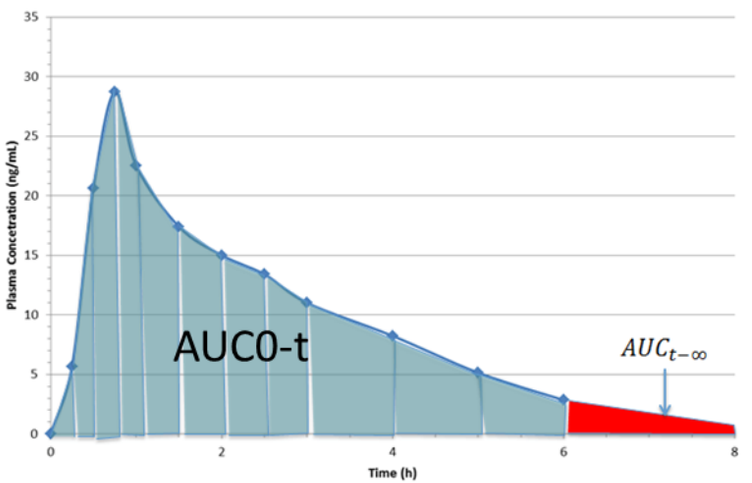
Study conduct – Standardisation

← بالنسبة للأكل، معني في حالة fast وفي حالة intake (Feed)، لو الدواء مكتوب عليه take with food بدك تعمل bioequavilance study تخص هاد الموضوع، لو على معدة فاضية، بدك تعمل على الـ fast ولو قالك ما تفرق بدك تعمل على الحالتين

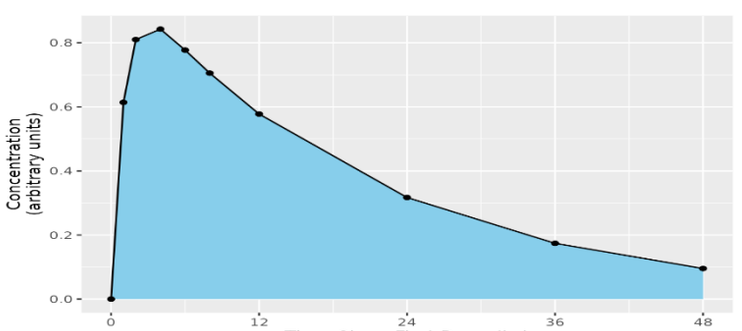
← بالنسبة في حالة الصيام، لازم يكون الـ subject معني صايم قبل بـ 8 ساعات بس مسموح الي عادي .. أما قبل ما ياخذ الـ Dose قبل بساعة ممنوع يشرب مي أو بعد الـ Dose بساعة برضه ممنوع الي .. حتى الي يلي لازم يوخذوها الـ subject 150 ml وكلهم متساويين لازم .. لأنه حتى الي تأثر على الامتصاص وهاي لازم ممنوع يوكل قبل أو بعد 8 ساعات .. 20 ساعة صايم بعضي .. حتى الأكل يلي يلي راح ياكلوه قبل عدد السعرات محدد طبعًا .. وأي شي يأثر على النتائج تاعت الكبد زي الكحول ممنوعة

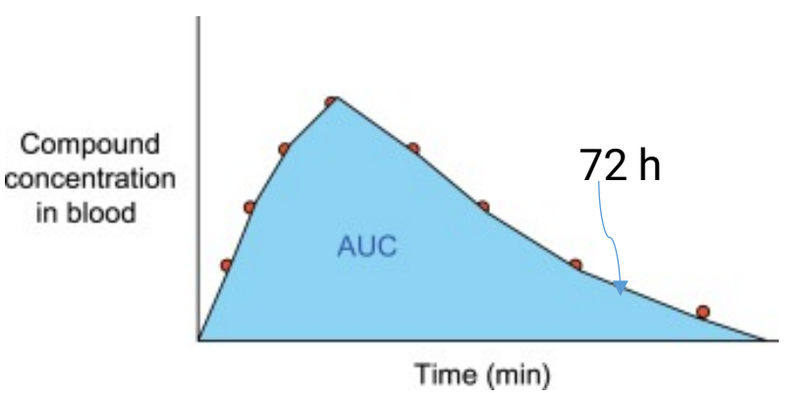
• Sampling times

- 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-∞).



- 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.





- 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.

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.

- 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 (%)).

date / /

→ Sampling time

متى أسحب سحبات الدم أنا؟ بسحبهم بوقت مثالي.. مش بوقت الـ C_{max} مثلاً
لازم الـ Sample على رابع point مثلاً..
وراح تغطي العينة عندي على الأقل 80٪ من الـ AUC.

← اغلب الأدوية لما immediate يكون (0-∞) على 72، يعني من Time
zero للـ 72.. إذا مش 72 يكون عندي مشاكل بالسبسفيكيشن.

← لو أنا عندي multiple-dose لازم آخذ pre-dose قبل خلال 5min

طيب لو ما بدي أسحب للدم، بدي أسحب عينة بول، نفترض (elimination half life) يساوي 5 ساعات
وبدي أسحب ٣ عينات، تكون العينة الأخيرة بعد كم ساعة.

→ BE for endogenous substances

← أحيانًا الواحد يحظر يوخذ هورمون من برّا، زي مثلاً هرمون الثايروكسين، فش
حدا بيكون الثايروكسين عنده صفر، يكون في شوي بجسمه.. لما يوخذ حبة الثايروكسين
قبل ما يوخذها للحبة، أسحب منه عينتين دم على شكل بيزلاين.. لو أنا ما أخذت
عينة قبل ما يوخذ لحبة، راح نفكر إنه ارتفاع الثايروكسين كله جاي من الحبة..
بس إنه آخذ عينتين من الدم قبل ما يوخذ لحبة، هكي مش دقيق بالمرّة
الأصح إنه قبل ما تعطيه لحبة بيومين أو على مدار يومين.. آخذ عينات دم
عشان أعرف كيف غط الثايروكسين عنده.. عكين بالوقت يلي بسحب فيه العينة
الأولى.. مرتفع عنده الثايروكسين زيادة.

→ Fasting or Fed

← لازم لما بدنا نسجل Composition of the meal تكون بالـ Calories، grams
و الـ relative caloric content %

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.

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.