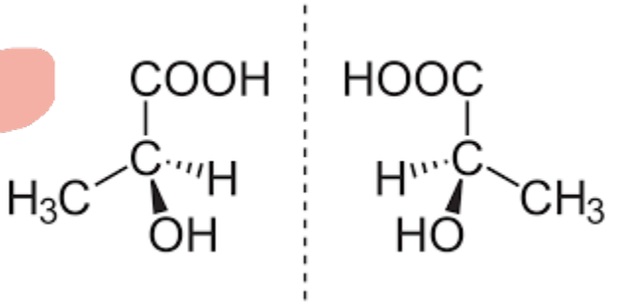
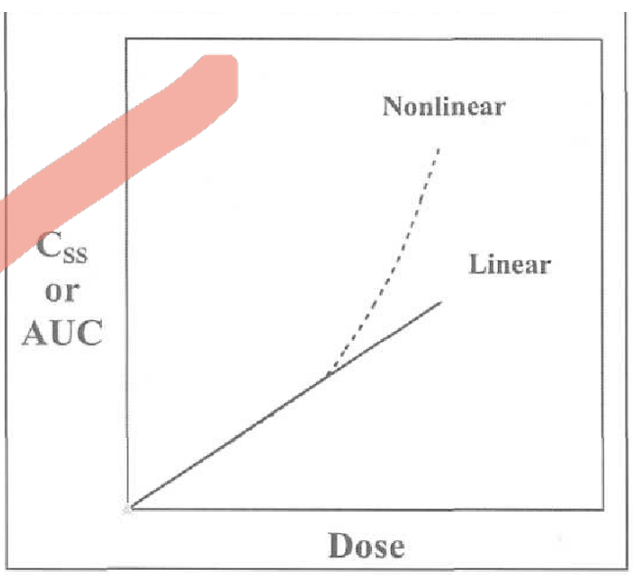
Enantiomers



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

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

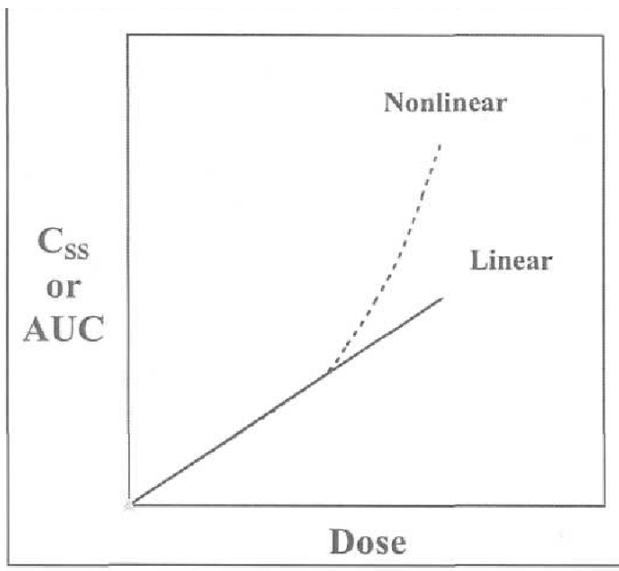


Linear pharmacokinetics

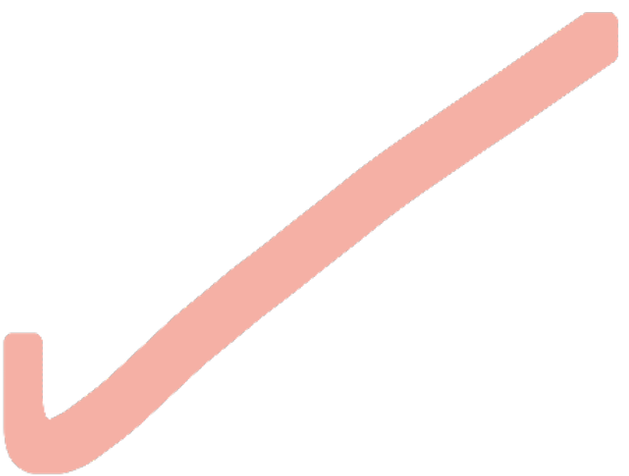
- The bioequivalence study should in general be conducted at the highest strength. For products with linear pharmacokinetics and where the drug substance is highly soluble (see Appendix III), selection of a lower strength than the highest is also acceptable.
- Selection of a lower strength may also be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

Non-linear pharmacokinetics

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



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



Bioanalytical methodology

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

Subject accountability

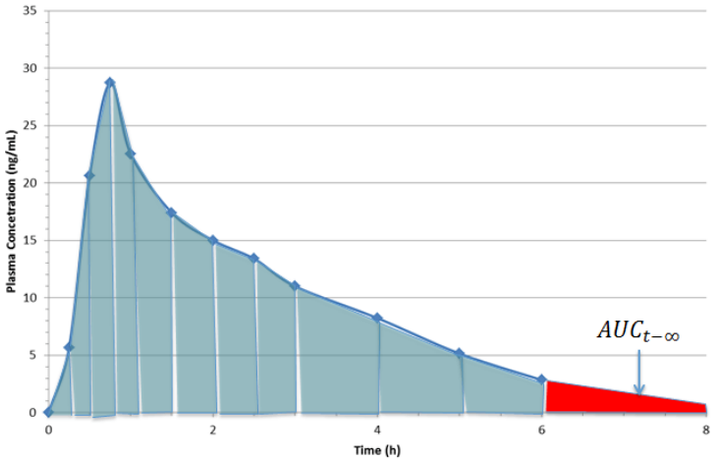
- The data from all treated subjects should be treated equally.
- It is not acceptable to have a protocol which specifies that ‘spare’ subjects will be included in the analysis only if needed as replacements for other subjects who have been excluded.
- It should be planned that all treated subjects should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

- 24 + 2(alternate)

Reasons for exclusion

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

Collected data



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

Statistical analysis

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

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

date / /

← لازم يكون عدد ال subject بالتجربة مثالي، عشان ما نجمع تحت الخطأ، يعني لأجل نتجنب الأخطاء.. وحكينا إنه ممنوع أعطي أدوية فوق الأدوية يلي بدي أجربها عليهم؟ مثلاً إلا إذا صار عندي side effect معينة.. ← مثل vomating إلخ

← ما بدك تحسب الكاينتيك للدواء، لو كانت عندك AUC أقل من 80% تحت أي ظروف ممنوع تعمل Exclusion.. معناه إنه ال Data تاعتك مش عن المطلوب

← لو صار معنا خطأ وتكررت هاي الحالة بأكثر من subject يعني فوق 20% من الحالات الدراسة بتعتبر كلها خطأ.

→ Statistical analysis

← إحنا نحسب 90% من ال Confidence.. يعني باختصار 90% من الحالات خلال التجربة أنا حسبتلهم النسبة Test / reference ..

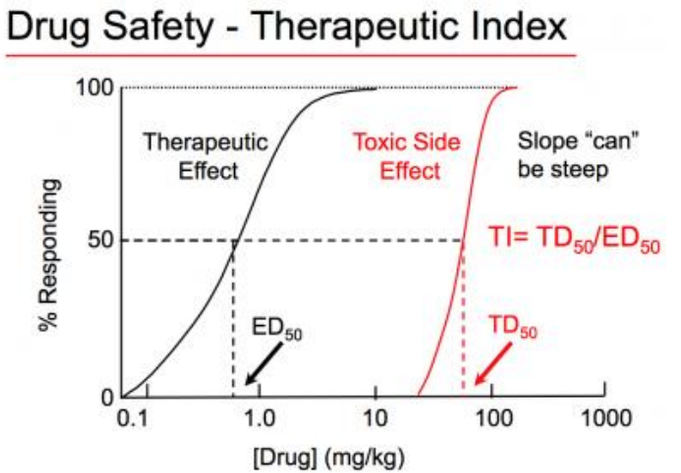
لازم كمان نحسب شي اسمه ANOVA.. عشان أقدر أحسب ال ANOVA لازم شو أحدد؟ أحدد كم مقدار ال null hypothesis عند 5% من ال Significance level

لما نحسب ال ANOVA لازم نوخذ بالاعتبار.. عشان استخدم اللوغريتم وأطلع رقم

← أي إنسحاب أو withdrawal.. يعني بنص الدراسة واحد من المرضى أو يلي حكي عنهم subject قرر ينسحب، هل بقدر أشيله لا.

كل concentration data and pharmacokinetic لكل subjects لازم يكونوا as individual listings وما يكونوا summary statistics.

Narrow therapeutic index drug



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

Highly variable drugs or drug products

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

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

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

date / /

Narrow therapeutic index drug

الأدوية يلي إلها narrow therapeutic لازم نقلل ونضيق الـ rang الـ Generic نضيق الرينج (tightened) 90-111.11% والافتلاف بين الـ Orgenator و

← وفي حالة كان الدواء عندي الـ variable فيها كتير عالي، والسبب يكون الدواء نفسه.. استجابته تختلف من شخص لآخر.. لهيك هاي مشكلة.. بحل إنه لو حللنا فيه C_{max} وكانت مرّة 200 mg مرة يلي بعدها كانت 90 mg/mL الفرق كبير.. ولكن أحيانًا في مبرر لهيك شي mL والسبب للدواء نفسه ... have intrasubject variable

الجدول مش حفظ أبدًا .. حتجيبه بالامتحان بس.

مش مطلوب حفظ المعادلة. $CV(\%) = 100\sqrt{e^{MSE} - 1}$

إنه إذا كان النسبة 30% اعرف شو الـ Limit تبعك .. يلي هو 80-125

Study report
Bioequivalence study report

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

Other data to be included in an application

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

Biowaivers

In vitro studies

Only *in vitro* studies sufficient to surrogate

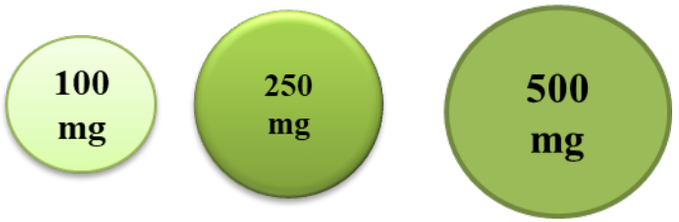
In vivo studies

exemption to in vivo studies is biowaiver

Biowaivers

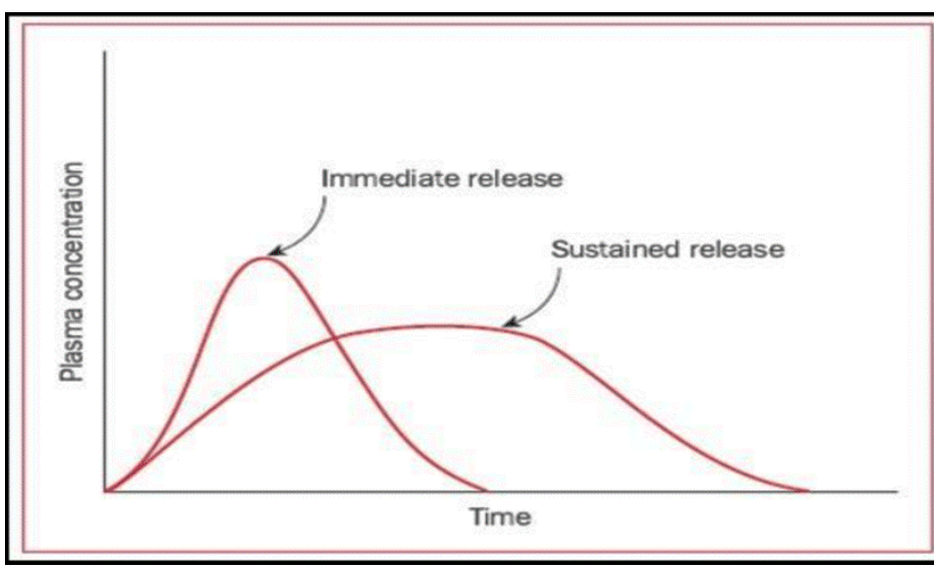
- Biowaiver based on biopharmaceutical classification system (BCS)
- **Goals of the BCS guidance**:
  - To recommend methods for classification according to dosage form dissolution, along with the solubility and permeability characteristics of the drug substance
  - Predict ***in vivo*** performance of drug products from in vitro measurements of permeability and solubility
  - To recommend a class of immediate-release (IR) solid oral dosage forms for **which bioequivalence may be assessed** based on in vitro dissolution tests
  - **To improve** the efficiency of drug development and the review process by recommending a strategy for identifying expandable clinical bioequivalence tests

Biowaivers



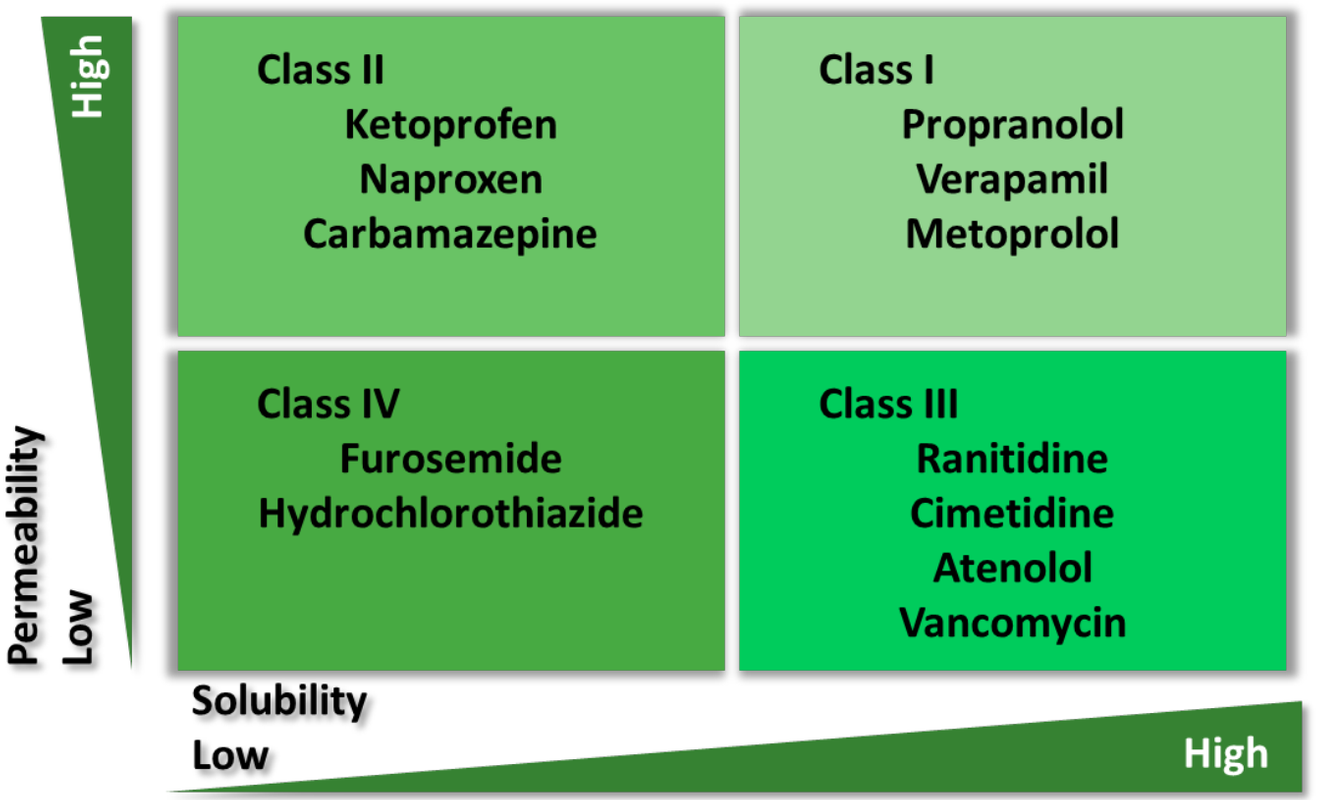
- Composition proportionality
- Basis of biowaivers for additional strength
  - API and excipients must be qualitatively the same and quantitatively proportional
  - Manufactured by the same process

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



Biowaivers

❑Biopharmaceutical Classification System (BCS)



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Study report bioequivalence

← شو لازم يحتوي الريبورت ؟
لازم يحتوي عل Documentation فيه ال protocol, conduct, evaluation
ويكون فيها اسم المسؤول عن الدراسة .. وال QA والرخصة تاعته، وكل شي
يخصه.. و شهادة تحاليل .. وكل شي .. حتى ال specefication
حتى ال Validation و ال pharmacokinetic .. إلخ

Biowaivers.

← يلي هي in vitro .. وطبعًا إله شروط حتى يقبلوه منك .. الشروط هاي تعتمد على
BCS class .. هي هم :-

- Class 1 high S high P
- class 2 low S high P
- class 3 high S Low P
- class 4 Low Low

S = Solubility
P = permeability

متى بعمل biowaver ؟ إني أجيب اورجنيتر وتعمل biowaver إله مع new your product
إنت أصلاً مادفعت مصاري لل BE .. ما عملت تصميم للتجربة.

الحالة الثانية .. إنه انت عندك دواء إله أكثر من عيار .. بعمل بس لل high biowaver أما ال Low ؟ .. ال biowavers ممنوع فقط ل class 1 ..

Biowaivers

- application of biowaivers based on :

❑**Biopharmaceutical Classification System (BCS)**

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

❑IVIVC

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

❑Composition proportionality

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

Biowaivers

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

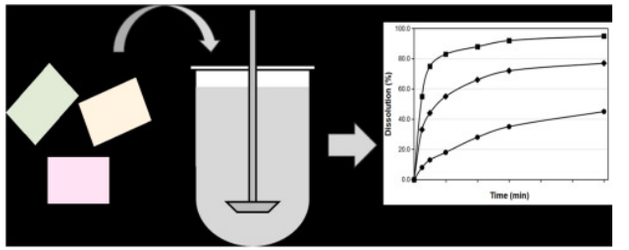
Conditions for BCS Biowaivers

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

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

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

In vitro dissolution tests in support of biowaiver of strengths



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

الاختبارات الدوائية لدعم الإعفاء من اختبارات التكافؤ الحيوي الإضافية

1. الهدف من الاختبارات

تأكيد كفاية التنازل عن الاختبارات الحيوية الإضافية.

2. بيئة الاختبار

قيم الحموضة المختلفة:

pH 1.2 (بيئة معدية).

pH 4.5 (بيئة معتدلة الحموضة).

pH 6.8 (بيئة معوية).

إذا تم تبريرها، يمكن استخدام قيم مختلفة.

3. التشابه في الذوبانية

المقارنة بين التركيزات:

تحقيق تشابه في الذوبانية بين جميع التركيزات المطبقة (المنتجات الإضافية والمنتجات المستخدمة في اختبارات التكافؤ الحيوي).

إثبات التشابه في جميع ظروف الاختبار.

4. الحالات التي قد لا تتحقق فيها ظروف الذوبان المثالية

اختلاف الذوبانية بين التركيزات:

إذا لم تتحقق شروط الذوبان المثالي، يجب إثبات أن السبب مرتبط بالمادة الفعالة وليس بالتركيبة الدوائية.

المقارنة مع المنتج المرجعي:

يجب أن تؤكد المقارنة مع التركيز المرجعي أن الاختلاف متعلق بالمادة الفعالة.

5. خيارات إضافية لإثبات التشابه

المقارنة عند نفس الجرعة:

مثال: مقارنة قرصين بتركيز 5 ملغ مع قرص واحد بتركيز 10 ملغ.

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  Enter at least 3 characters | Search

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- **Search by Dosage Form (for example: *TABLET*)**
- **Search by Route of Administration (for example: *ORAL*)**

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