Bioequivalence studies

SABHA MUTAN 1162122

ISRAA AWESAT 1162126

YAQEEN MUTAN 1162034

Definitions

Pharmacokinetics is how a body processes a drug. So how the drug is absorbed, distributed metabolized , and then eliminated .

Pharmacodynamics takes into account the complex interactions between the drug and the human body (biological response).

Definitions

Pharmaceutical bioequivalence:
Drug products that contain the same active ingredient(s), ie, the same salt or ester, are of the same dosage form, use the same route of administration, and are identical in strength or concentration and give the same pharmacokinetic.

Pharmaceutical Alternatives
Drug products that contain the same **therapeutic moiety** but as different salts, esters, or complexes, and different dosage forms.

Bioavailability

Means the **rate** and the **extent** to which the active substance is absorbed from a pharmaceutical form and become available in the bloodstream toward site of action.

Two terms should be understood:

- Absolute bioavailability: is the amount of drug that reaches the systemic circulation relative to an intravenous (IV) dose (100% bioavailability).
- Relative bioavailability: used when an IV formulation does not exist or cannot be made, comparison to reference listed product other than IV.

Bioequivalence

The absence of a **significant difference** in the rate and extent to which the active ingredient or active moiety in **pharmaceutical equivalents** or **pharmaceutical alternatives** becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Bioequivalence studies in human

- Subjects
- Study design
  - Standard design (Cross over)
  - Alternative design (Parallel)
- Parameters to be assessed
- Acceptance ranges

Selection of subjects(Volanteers)

- Healthy volunteers
- Age range 18-55 years
- weight within the normal range.
- Clear criteria for inclusion/exclusion should be established.
- Subjects should be of both sexes, and the risk to women will need to be considered, and they should be warned of any possible dangers to the fetus if they should become pregnant.

- Subjects should preferably be non-smokers and without a history of alcohol or drug abuse.If smokers are included, they should be identified as such.

Selection of subjects

- screening subjects for suitability by means of standard laboratory tests, a medical history, and a physical examination.
- special medical investigations before and during studies, depending on the pharmacology of the drug being investigated.
- Genetic Phenotyping and/or genotyping of subjects may be considered for safety reasons.

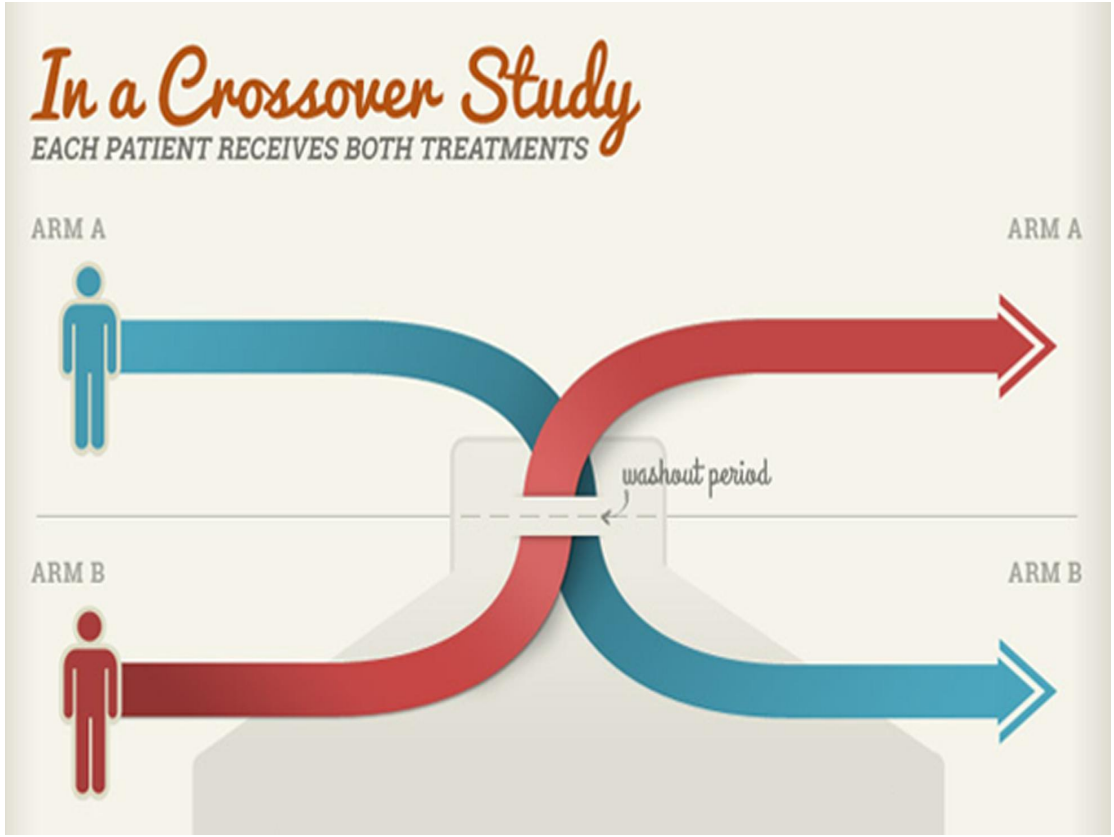
During the study, the health of volunteers should be monitored.

If the 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 use patients under treatment instead. This alternative should be explained by the sponsor.

Study design

Standard design (Cross-over)

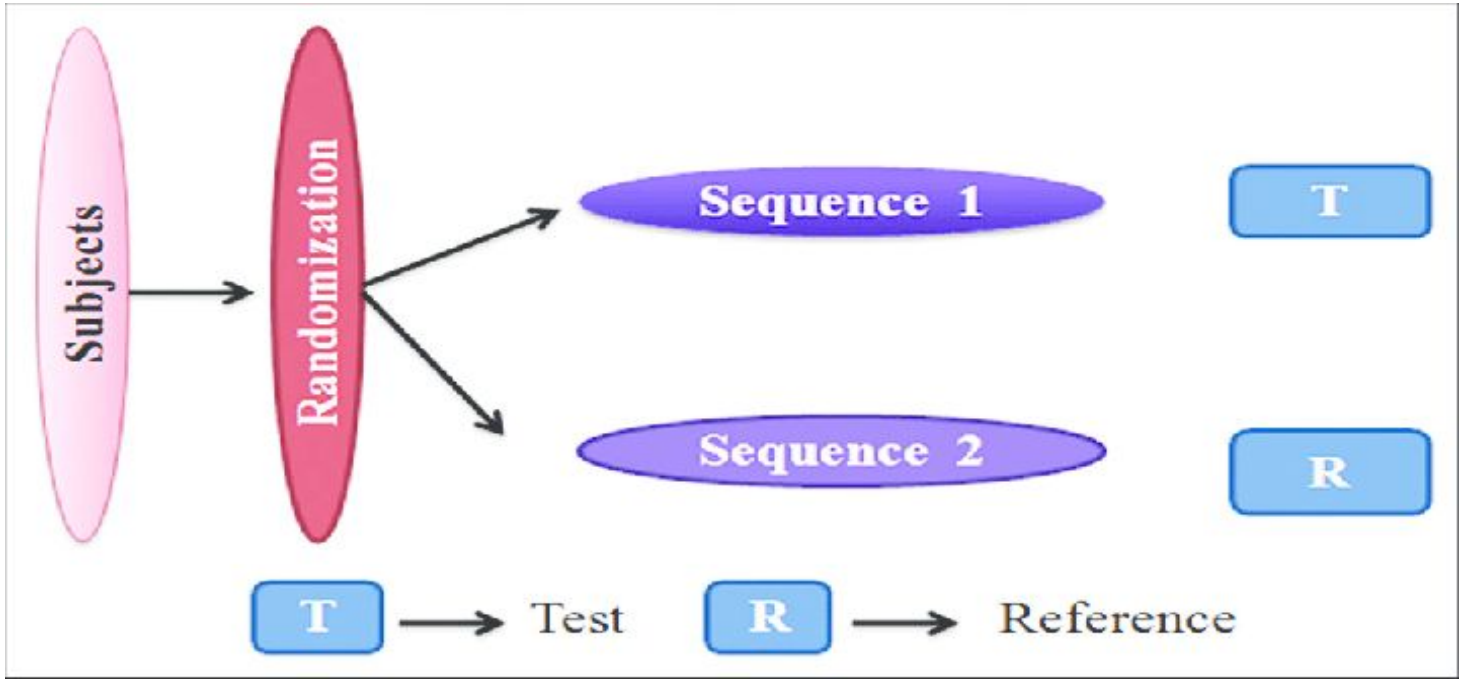
- If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period.



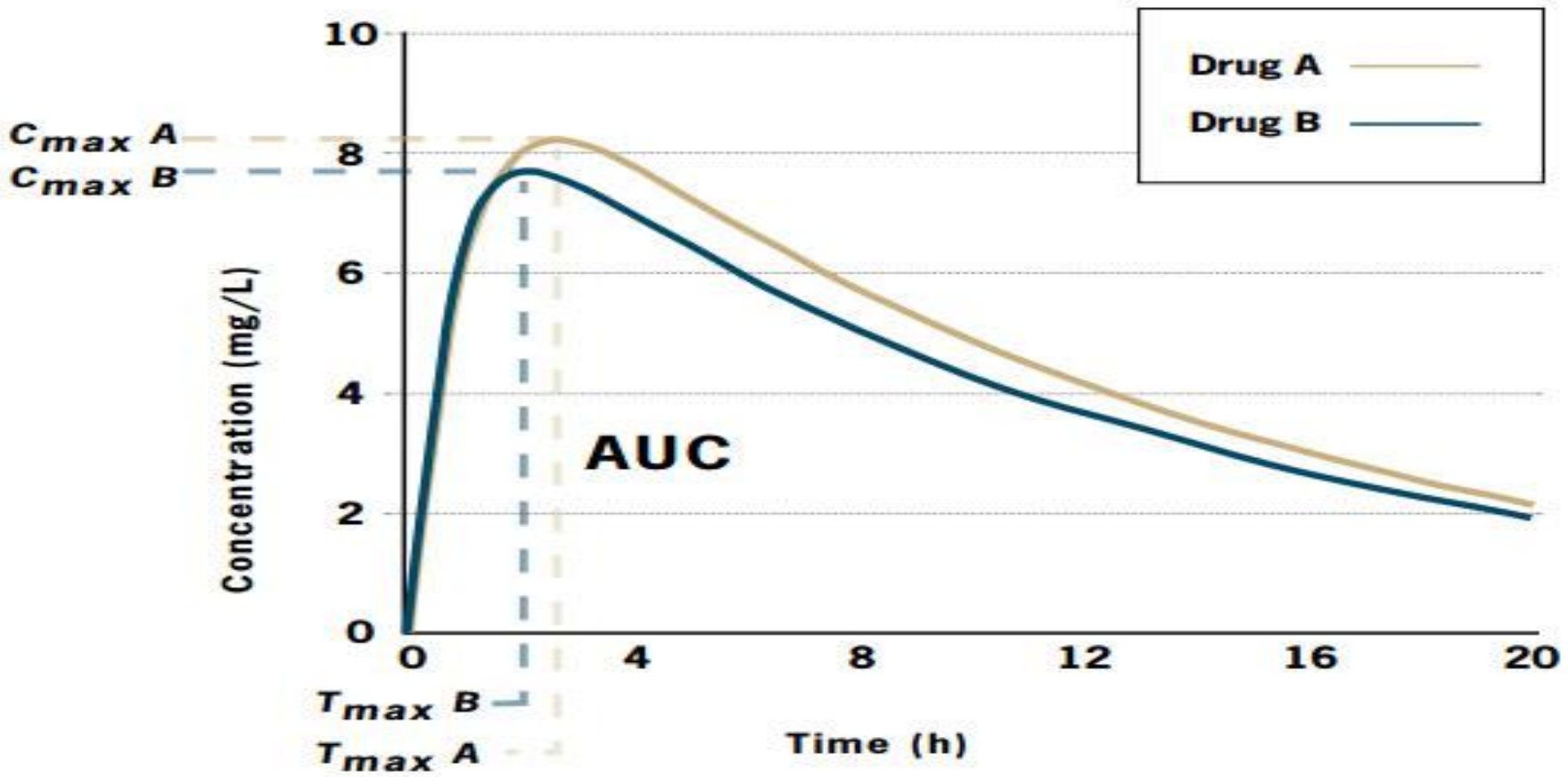
Alternative designs

Sometimes cross study cannot be applied, as for long half life drugs (as Clofazimine) , so parallel study is the alternative.

Parallel study:
At least 24 volunteer
12 takes the innovator
12 takes the tested



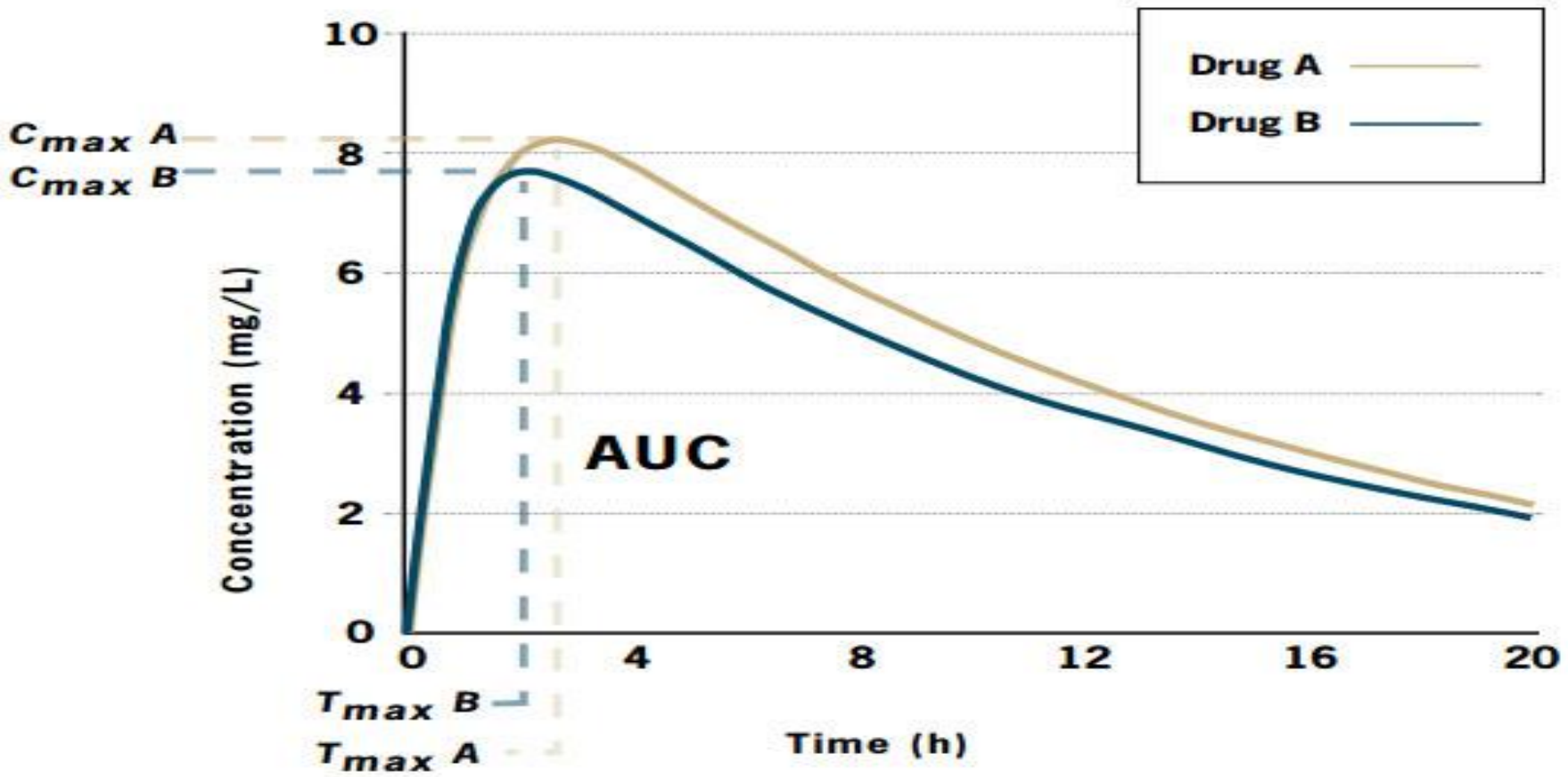
Parameters to be assessed



Acceptance range

For these parameters (**AUC , T max and C max**) the 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of **80.00- 125.00%.**

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.


Drug A
Drug B
C_{max} A
C_{max} B
10
8
6
4
2
0
Concentration (mg/L)
AUC
0
4
8
12
16
20
T_{max} B
T_{max} A
Time (h)

Is the quality of a generic drug the same as that of the brand drug?

(FDA) requires generic drugs to have the same performance and quality as brand name drugs.

The FDA says: “When a generic drug product is approved, it has met rigorous standards established by the FDA with respect to identity, strength, quality, purity, and potency.”

When bioequivalence study in vivo not needed?

- For oral solutions, elixirs, syrups, tinctures, or other solubilized forms.
- Parenteral solutions.
- Gases for inhalation.
- Locally applied products without systematic effect

Strength to be investigated

In linear pharmacokinetics : bioequivalence with only one strength and in general be conducted at the highest strength .

where the drug substance is highly soluble or highest strength cannot be administered to healthy volunteers for safety/tolerability reasons , selection of a lower strength than the highest is also acceptable

In non - linear pharmacokinetics: bioequivalence should in most cases be established both at the highest strength and at the lowest strength

Referencies

- ★ World Health Organization resource

  https://apps.who.int/medicinedocs/en/d/Jh1813e/3.4.5.1.html

- ★ Bioequivalence testing of immunosuppressants: concepts and misconceptions

  Uwe Christians1 , Jelena Klawitter1 and Claudia F. Clavijo1 1 Clinical Research and Development, Department of Anesthesiology, University of Colorado Denver, Aurora, Colorado, USA

- ★ https://www.ema.europa.eu/en/documents/scientific-guideline/draft-note-guidance-investigation-bioavailability-bioequivalence_en.pdf?fbclid=IwAR3OKCoOrtZYZ-zbBKA2OaQ6zBTrzjDmO8agpCRxkf8gFObRuObrJwd4evg
- ★ https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

The End

Any Question ?