7. Clinical Trial Assessment
Bioequivalent Studies (Generic)

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Disclaimer:

The information within this presentation is based on the presenter’s expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Overview

• Regulations & Guidance
• Objective & characteristics of bioequivalence studies
• Data requirements
• Study designs
• Essential components in the review
Guideline for Bioequivalence Studies of...

- Generic Products
- Topical drug for skin as new formulation
- New content in oral solid forms
- Change of ingredients in oral solid forms
- Generic of topical drug for skin
- Change of manufacturing in controlled release dosage forms
- Change of controlled release dosage forms

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Purpose of BE study

- Assure therapeutic equivalence of generic products to innovator products
  - Bioavailability should be compared for innovator and generic products.
  - If this is not feasible, pharmacological effects supporting efficacy or therapeutic effectiveness in major indications should be compared.
  - For oral drug products, dissolution tests should be performed, since they provide important information concerning bioequivalence.
Study methods

- Bioequivalent studies
- Pharmacodynamic studies
- Clinical studies
Pharmacodynamic studies

• For drugs do not produce measurable concentrations of the parent drug
• For drugs active metabolite in blood or urine and those whose bioavailability does not reflect therapeutic effectiveness
• The Acceptance criteria of equivalence in this study should be established by considering the pharmacological activity of each drug.
Clinical studies

• Performed to establish the equivalence of an index

• If bioequivalence studies and pharmacodynamic studies inappropriate, this study is applied.

• The Acceptance criteria of equivalence in this study should pharmacological characteristics and activity of each drug.
BE Study Design

• Appropriate study protocol including the required number of subjects and sampling intervals should be determined according to preliminary studies and previously reported data.

• Design
  – Randomized crossover studies
    • more than 5 times the elimination half life of the parent drug or active metabolites.
  – Parallel designs can be employed for drugs with extremely long half-lives.

• Dose: Single dose by one dose unit or a clinical usual dose
Sampling

• Sampling points should be at least 7, including zero time, 1 point before Cmax, 2 points around Cmax and 3 points during the elimination phase. Sampling should be continued until AUCt is over 80% of AUC∞ (normally more than 3 times the elimination half life after tmax).
Bioequivalence range

- AUC and Cmax are logarithmically distributed
  - 0.8–1.25 as the ratios of average AUC and Cmax of test product to reference product
- AUC and Cmax are normally distributed
  - -0.2 – +0.2 as the ratio of the relative difference in the mean AUC and Cmax between reference and test products to those of the reference product
Reference

• Guideline for Bioequivalence Studies of Generic Products
  – http://www.nihs.go.jp/drug/be-guide(e)/Generic/be97E.pdf