Bioavailability and Bioequivalence Studies

" Standard Approach"

Part I: Design and Conduct

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Note for Guidance on the Investigation of Bioavailability and Bioequivalence

CPMP/EWP/QWP/1401/98 (London 26 July 2001)

From the Introduction:

"The bioavailability of an active substance from a pharmaceutical product should be *known* and *reproducible*"

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Preamble

- Reference to other guidances relating to PK or clinical studies
- Good Clinical Practice, Ethics Committee
- Bioavailability: normally established by comparing the target product to another type of formulation (Example: if target IR, then reference drug solution)
- Bioequivalence: normally established by comparing the target product to a reference product of the same type of formulation

Necessity to file BA (or BE) Data

- For all new chemical entities
- For new formulations of active substances
- For new dosage forms of a registered drug
- For Type II Variations of a marketed product:
  change of main excipients or manufacturing process, change of salt or ester, line extension, etc
- For the administration in another population, i.e. children
- For the acceptance of wider than standard side batch ranges
- (Criteria for biowaivers exist)

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Study Design

- Statistically robust design: most common is the cross-over design. If long half-life: parallel design, if highly variable data: replicate design
- Normally single dose, steady-state study if for PK or analytical reasons
- Number of subjects: calculated based on data variation and desired significance level
- Minimum number : 12 (completed)

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Study Design (cont'd)

- (Highest) Dose administered with defined amount of water
- Adequate wash-out periods / build-up in steady-state studies
- Plasma sampling: adequate estimation of C_{max} and 80% of AUC
- Terminal half-life to based on at least 3-4 data points
- Adjustments for special PK properties

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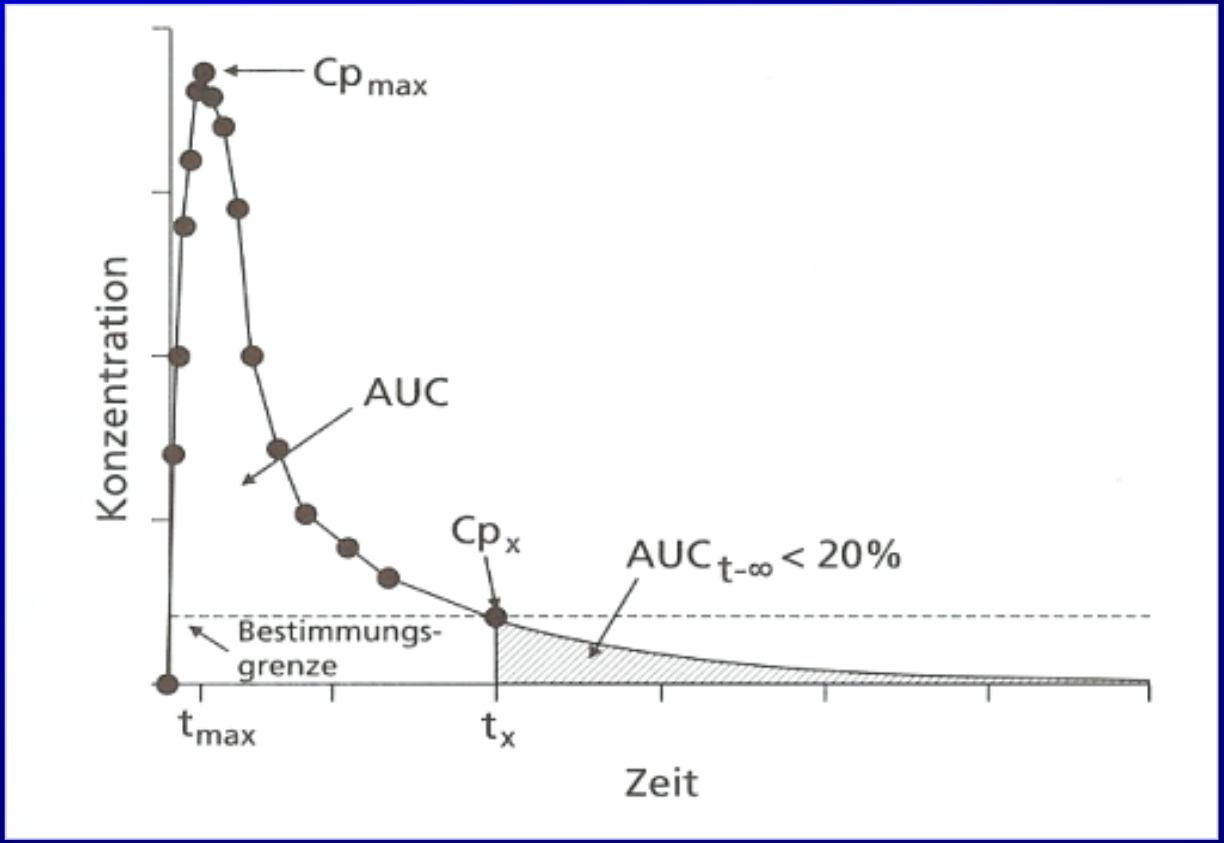
Illustration of BA Assessment



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Study Subjects

- Overall aim: to minimize variability introduced by subjects
- Healthy, both sexes, 18-55 years old, non-smokers, no history of alcohol or drug abuse
- Standardization of food and fluid intake
- No other medication
- If BE study: follow food intake recommendations of reference product
- Selection of subpopulation (fast or slow metabolizers)
- Reasons for enrolling patients

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Study Characteristics

- Clearly define *primary* and *secondary* study parameters, normally based on unchanged substance in plasma or urine
- Normal primary parameters: AUC_t, AUC_{inf}, C_{max}, T_{max}, A_{et}, Ae_{inf}, as appropriate
- Also recommended: t½, MRT and in steady-state studies: AUC_{tau}, C_{max}, C_{min}, fluctuation index
- Describe intended statistical data treatment and acceptance criteria
- Define outlier criteria
- (Compartmental PK analysis not recommended)

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Chemical Analysis

- Follow GLP Practices
- Validated analytical method: stability of analytes, specificity, accuracy, precision, limit of quantification, response function
- Calibration curves from pre-study and study phase
- Method well described in SOP
- Special considerations for chiral active substances

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Selection of Test Products

- GMP material
- *In vitro* characterization of test product(s) (“batch control results to be on file”)
- Limited stability data
- Show evidence that reference product is “typical”
- (Originator product from one EU member state may suffice, supported by in vitro similarity between products from different countries)
- Preferably of biobatch size
- (Retention of samples from tested products)

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Aspects for *New* Active Substances

- BA from final pharmaceutical form, compared to i.v. administration or oral solution
- When prodrug: reference should be made of active moiety
- Bridging BE studies for formulations in early clinical trials

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Aspects for *Products containing Approved* Active Substances

- Criteria for assessing whether a BE study need not be conducted (solubility, permeability, safety, efficacy)
- BE requirements for various dosage forms
- BE of combination products
- *In vitro* dissolution
- BE always needed for generic product in comparison to innovator product
- Dose proportionality: criteria for biowaiver

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