previous Lecture

next Lecture

Bioavailability / Bioequivalence

- Selection of CROs
- Selection of a Reference Product
- Metrics (AUC, C_{max}/t_{max}, Shape of Profile)
- Acceptance Ranges (0.80 – 1.25 and beyond)
- Sample Size Planning (Literature References, Pilot Studies)
- Steps in bioanalytical Validation (Validation Plan, Pre-Study Validation, In-Study Validation)
- Study Designs
- Protocol Issues
- Evaluation of Studies
- **Advanced Topics**
- Avoiding Pitfalls

Bioavailability / Bioequivalence

- **Advanced Topics**
  - Highly Variable Drugs (Add-On Designs, Reference-Scaled Average Bioequivalence, Replicate Designs)
  - Assessment of Metabolites
  - Chiral Drugs
  - Dose Proportionality

Bioavailability / Bioequivalence

- **Highly Variable Drugs** (HVDs)
  - Defined at the BioInternational ’89 (Toronto) with intra-subject CV of ≥30 %, elaborated at the BioInternational ’92 (Bad Homburg)
    - Various methods were discussed
      - → Potential reduction of variability in steady-state
      - → Replicate designs
      - → Add-on designs
      - → Stable isotope techniques

Bioavailability / Bioequivalence

- **Highly Variable Drugs** (HVDs)
  - K. Midha (BioInternational ’94 Munich) distinguished between Highly Variable Drugs (HVDs), and Highly Variable Drug Products (HVDPs)
    - HVD
      - → Drugs with low and variable absorption,
        e.g., biphosphonates (etidronate, aledronate, clodronate,…)
      - → Drugs with variable clearance,
        e.g., verapamil, spironolactone,…
    - HVDP
      - → Drug Products where the the galenic principle may lead to an increased variability as compared to an oral solution,
        e.g., diclofenac

Bioavailability / Bioequivalence

- **Highly Variable Drugs** (HVDs)
  - HVD

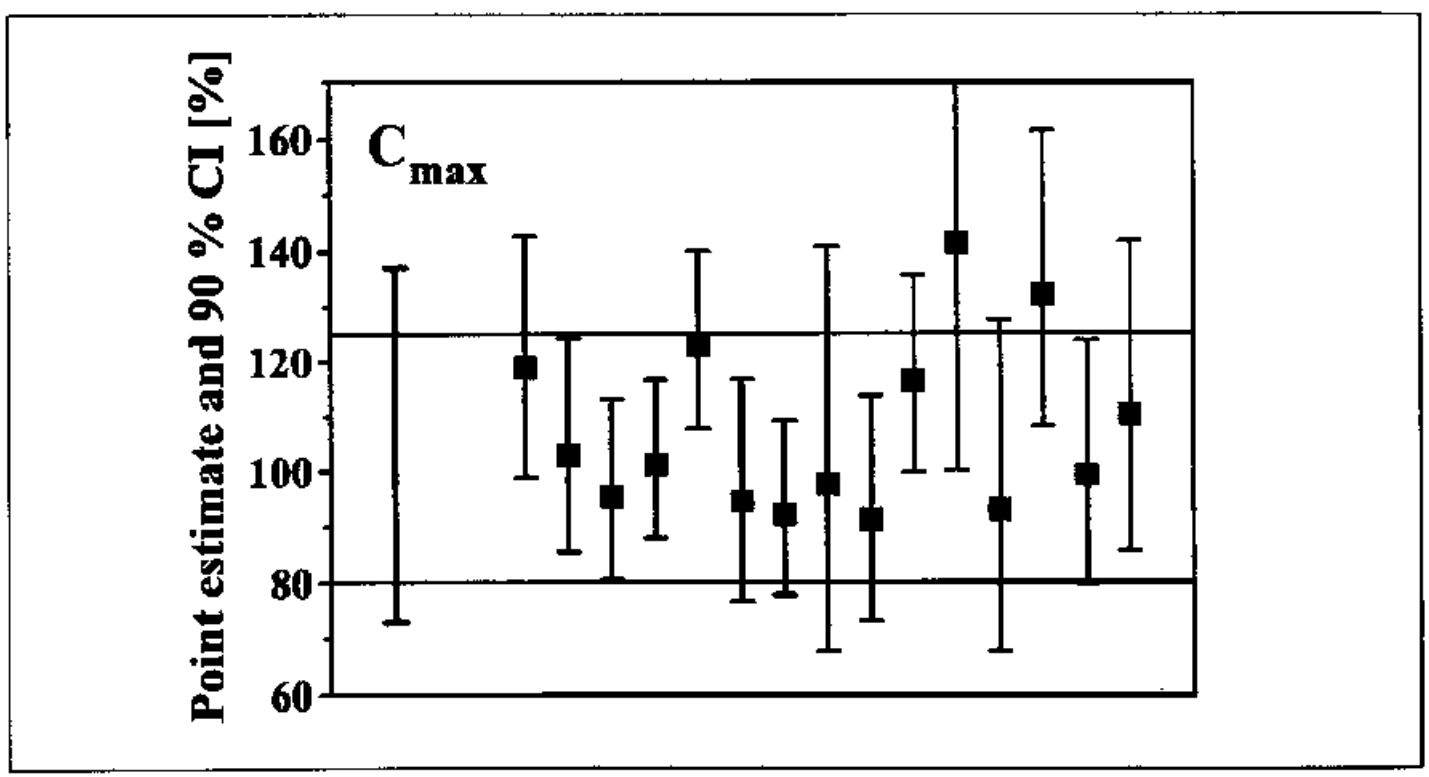
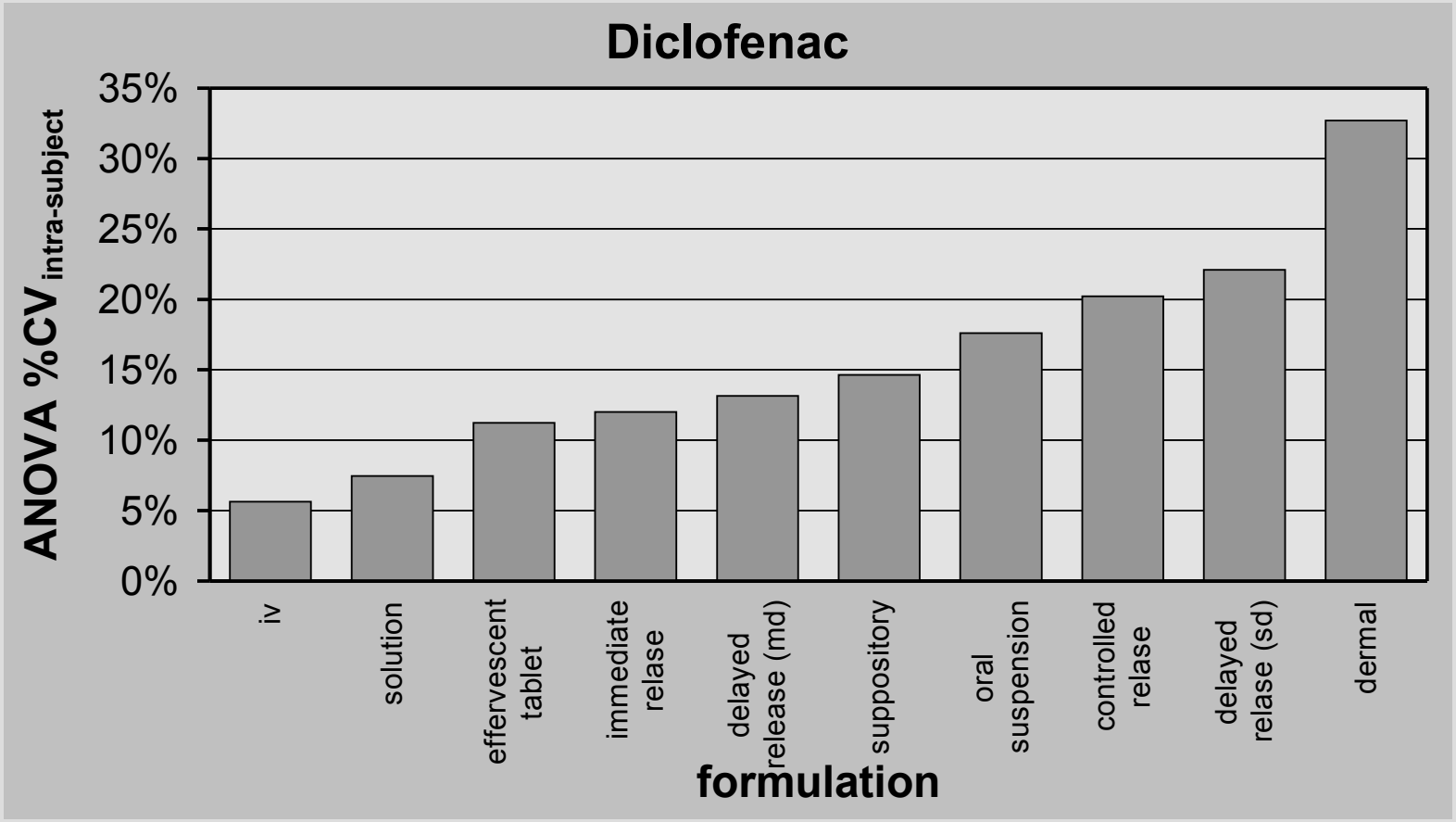


Fig. 4: Confidence intervals for C_{max}-values from 15 T vs. R studies after single dose administration of different verapamil 80 mg IR formulations: Assessment of bioequivalence considering 80–125 % acceptance limits [for reference: confidence interval of replicate R vs. R study]

Bioavailability / Bioequivalence

- **Highly Variable Drugs** (HVDs)
  - HVDP



Bioavailability / Bioequivalence

- **Highly Variable Drugs** (HVDs)
  - Turkey

    Extended Acceptance Range (0.75 – 1.33)
    - Sample Sizes for Δ ±5 %, power 80 %
      - CV 30 %: 22
      - CV 40 %: 38
      - CV 50 %: 58
  - EMEA

    Extended Acceptance Range (0.75 – 1.33) ?
    - if based on clinicial grounds
      - see lecture 2-1-1 (slides 29-30)
      - but: see lecture 2-1-1 (slides 32-33), lecture 2-2-1 (slides 28-31)

Bioavailability / Bioequivalence

- **Highly Variable Drugs** (HVDs)
  - EMEA

    Multiple dose studies to decrease variability ?
    - …may be considered,
      - → see lecture 2-1-1 (slide 33)
      - → but: see lecture 2-1-3 (slide 3/5)
    - are successful in most cases,
    - but in rare cases may also fail:
      - → van Hoogdalem *et al.*;
        Multiple dose bioequivalence study with josamycin propionate, a drug with highly variable kinetics, in healthy volunteers.
        Int. J. Clin. Pharmacol. Ther. 34(5), 202-207 (1996)

Bioavailability / Bioequivalence

- **Highly Variable Drugs** (Add-On Designs)
  - EMEA

    Group Sequential Designs
    - Although discussed at BioInternationals ’89 to ’96, no concensus was reached.
    - Group sequential designs are standard in clincial research.
    - Personal Experience:
      - → A proposed method*) was not accepted in the planning phase (3 cases, German BfArM).

*) L.A. Gould;
Group Sequential Extension of a Standard Bioequivalence Testing Procedure.
J. Pharmacokin. Biopharm. 32(1), 57-86 (1995)

Bioavailability / Bioequivalence

- **Highly Variable Drugs** (Add-On Designs)
  - EMEA

    Group Sequential Designs
    - Personal Experience:
      - ➔ Evaluation of first part by an independent statistician (CV only!), performance of a second part, evaluation of pooled data without Bonferroni-correction – 90 % CI (2 cases Germany, 1 case France).
      - ➔ May be a reasonable approach, since Add-On Designs are in practice in Canada (since 1991), and Japan (since at least 1997).

Bioavailability / Bioequivalence

- **Highly Variable Drugs** (Reference-Scaled Average Bioequivalence)
  - EMEA

    Reference-Scaled ABE
    - Proposed by L. Endrenyi and L. Tothfalushi; not only in replicate designs, but also in standard 2×2 Cross-over (scaling to CV_{intra})
      - → Mentioned only in South African Guideline.
      - → Sample Size?
      - → Acceptance?

Bioavailability / Bioequivalence

- **Highly Variable Drugs**
  - Assessment of AUC·k_{el}
    - For drugs with highly variable Clearance, assessment of AUC·k_{el} instead of AUC was proposed.
      - → Must my decided on a case-to-case basis (does not work for all drugs!)
      - → Acceptance?

H.Y. Abdalah;
An Area Correction Method To Reduce Intrasubject Variability In Bioequivalence Studies.
J. Pharm. Pharmaceut. Sci. 1(2), 60-65 (1998)

Bioavailability / Bioequivalence

- **Highly Variable Drugs** (Replicate Designs)
  - EMEA
    - …under certain circumstances and provided the study design and the statistical analyses are scientifically sound, alternative well-established designs could be considered such as […] replicate designs for substances with highly variable disposition.
      - ➔ Scaling the acceptance range according to the variability of the reference.
      - ➔ but: contact with the respective Regulatory Authority in a ‘Scientific Advisory Meeting’ is highly recommended!
      - ➔ Acceptance in *all* EU countries doubtful…

Bioavailability / Bioequivalence

- **Advanced Topics**
  - Highly Variable Drugs (Add-On Designs, Reference-Scaled Average Bioequivalence, Replicate Designs)
  - Assessment of Metabolites
  - Chiral Drugs
  - Dose Proportionality

Bioavailability / Bioequivalence

- **Assessment of Metabolites**
  - Turkey
    - BA Studies
      - → Both the parent drug and its major active metabolite.
    - BE Studies
      - → Only parent drug is sufficient.
    - Exemptions
      - → If parent drug is not measurable by the analytical method used, measurement of a metabolite (active/inactive) is recommended.

Y. Çapan;
BE Practice and Issues in Turkey.
BioInternational 2005, London (26 October 2005)

Bioavailability / Bioequivalence

- **Assessment of Metabolites**
  - Turkey
    - Exemptions
      - → If metabolite contributes meaningfully to safety and/or efficacy, both parent drug and metabolite should be measured.
      - → Active metabolite should be measured
        - in case of a prodrug,
        - if the parent drug is transformed extremely to the active metabolite,
        - if pharmacokinetics of the parent drug is non-linear.

Y. Çapan;
BE Practice and Issues in Turkey.
BioInternational 2005, London (26 October 2005)

Bioavailability / Bioequivalence

- **Assessment of Metabolites**
  - EMEA
    - BA / BE
      - → Parent drug.
    - Exemptions
      - → Active or inactive metabolite should be measured if the concentration of the active substance is too low to be accurately measured in the biological matrix.
        - major difficulty in analytical method,
        - if product is unstable in the biological matrix,
        - if half life of the parent compound too short.

Bioavailability / Bioequivalence

- **Assessment of Metabolites**
  - EMEA
    - Exemptions
      - → BE determinations based on metabolites should be justified in each case bearing in mind that the aim of a BE study is intended to compare the *in vivo* performance of test and reference products.
        In particular if metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non-linear, it is necessary to measure both parent drug and active metabolite plasma concentrations and evaluate them separately.

Bioavailability / Bioequivalence

- **Advanced Topics**
  - Highly Variable Drugs (Add-On Designs, Reference-Scaled Average Bioequivalence, Replicate Designs)
  - Assessment of Metabolites
  - Chiral Drugs
  - Dose Proportionality

Bioavailability / Bioequivalence

- **Chiral Drugs**
  - FDA
    - **BA Studies**: measurement of individual enantiomers may be important.
    - **BE Studies**: measurement of the racemate using an achiral assay is recommended. Measurement of individual enantiomers in BE studies is recommended only when **all** of the following conditions are met:
      - enantiomers exhibit different PD characteristics,
      - enantiomers exhibit different PK characteristics,
      - primary efficacy and safety activity resides with the minor enantiomer,
      - nonlinear absorption is present for at least one of the enantiomers.

Bioavailability / Bioequivalence

- **Chiral Drugs**
  - EMEA
    - **BA Studies**: individual enantiomers (?)
    - **BE Studies**: enantiomeric bioanalytical methods *unless*:
      - → both products contain the same stable single enantiomer, or
      - → both products contain the racemate **and** both enantiomers show linear pharmacokinetics.
      - → Remark:
        the last point may in the NfG be a nasty trap, since *pharmacokinetics of single enantiomers are simply not known for the majority of drugs.*

Bioavailability / Bioequivalence

- **Chiral Drugs**
  - Turkey?