Bioavailability / Bioequivalence

- Selection of CROs
- Selection of a Reference Product
- Metrics (AUC, $C_{\text{max}}/t_{\text{max}}$, 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
Highly Variable Drugs (HVDs)

- Defined at the BioInternational '89 (Toronto) with intra-subject CV of $\geq 30\%$, 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
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 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)**
  - HVDPs

![Diagram showing ANOVA %CV intra-subject for various formulations of Diclofenac]
Highly Variable Drugs (HVDs)

- Turkey
  
  Extended Acceptance Range (0.75 – 1.33)
  
  - Sample Sizes for $\Delta \pm 5\%$, power 80\%
  - CV 30\%: 22
  - CV 40\%: 38
  - CV 50\%: 58

- EMEA
  
  Extended Acceptance Range (0.75 – 1.33)?
  
  - if based on clinical 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)
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.
Highly Variable Drugs (Add-On Designs)

- EMEA

Group Sequential Designs

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

*) L.A. Gould;
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).
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 $CV_{\text{intra}}$)
  - Mentioned only in South African Guideline.
  - Sample Size?
  - Acceptance?
Highly Variable Drugs

• Assessment of $AUC \cdot k_{el}$
  - For drugs with highly variable Clearance, assessment of $AUC \cdot k_{el}$ 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.
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...
Advanced Topics

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