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)
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Bioavailability / Bioequivalence

- **Selection of CROs**

  - General Suitability of the CRO
    - Location (Accessability, Duration of getting IEC and Regulatory Approval, Catchment Area, Sample Shipment).
    - Years in Business?
    - The bigger is not essentially the better!
    - Study Personell (Experience, Continuing Education, Fluctuation).
    - Technical Equipment (State-of-the-Art, Maintenance).

Bioavailability / Bioequivalence

- **Selection of CROs**

  - Adherence to G*x*P (GCP, GMP, GLP)
    - ✦ Successful Audits?
    - ✦ Regulatory Inspections?
    - ✦ Current Certificates?

  - Volunteer Data Base
    - ✦ Large, up-to-date, no nominal members.
    - ✦ Special Populations (*e.g.*, post-menopausal women, aged subjects).
    - ✦ Pheno-/genotyped?

Es werden nachstehende Untersuchungen durchgeführt:

Prüfungen	Testsysteme
Pharmakokinetische Untersuchungen, Bioäquivalenzuntersuchungen: Körperflüssigkeiten von Mensch und Tier wie z.B. Urin-, Blut-, Plasmaproben, fallweise Biopsiematerial	HPLC

Es wird hiemit bescheinigt, dass die Prüfeinrichtung die Grundsätze der Guten Laborpraxis der OECD/EU bei den vorgenannten Prüfsystemen einhält.

Für die Bundesminister

BODMANN

Bioavailability / Bioequivalence

- **Selection of CROs**

  - Scientific and Statistical Expertise
    - Set-up of Protocol.
    - Evaluation of Study.
    - Handling of subsequent questions (deficiency letters, addenda to reports).

  - Standardization in the Conduct of the Study
    - Adherence to SOPs.
    - Working QUA-System.
    - Handling of Deviations to Protocol/SOPs.

Bioavailability / Bioequivalence

- **Selection of CROs**

  - Timelines

    - Should be set realistically.
    - Should be agreed upon <u>and adhered to (!)</u>.

  - Financial Issues

    - Anticipate the unexpected (*e.g.*, repeated subjects, additional bioanalytics or biostatistical evaluations, publications).
    - Investing in quality is often worth the money!

Bioavailability / Bioequivalence

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Bioavailability / Bioequivalence

- **Selection of a Reference Product**

  - Pharmaceutical Equivalents, Pharmaceutical Alternatives (EU Definition).

    - Medicinal products are <u>pharmaceutically equivalent</u> if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or compar-able standards.

    - Medicinal products are <u>pharmaceutical alternatives</u> if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength.

Bioavailability / Bioequivalence

- **Selection of a Reference Product**

  - Inovator's Product marketed in Turkey.

  - EMEA's Reference Drug Product.

    - Yes, but which country's?
    - Selection based on dissolution?
    - Bio**in**equivalence between Inovator's Products marketed in different EU countries is unlikely, but possible.

  Vlahov, V., Thyroff-Friesinger, U., Koytchev, R., Bakracheva, N. and E. Gatchev;
  Bioequivalence studies with metformin: comparability of reference tablets from different origins.
  Int. J. Clin. Pharmacol. Ther. 34(9), 457-462 (2005)

Bioavailability / Bioequivalence

- **Selection of a Reference Product**

  - FDA's Reference listed Drug Product (RLDP, 'Orange Book').

    http://www.fda.gov/cder/ob/default.htm

  - If possible different batches of the reference should be selected based on Dissolution.
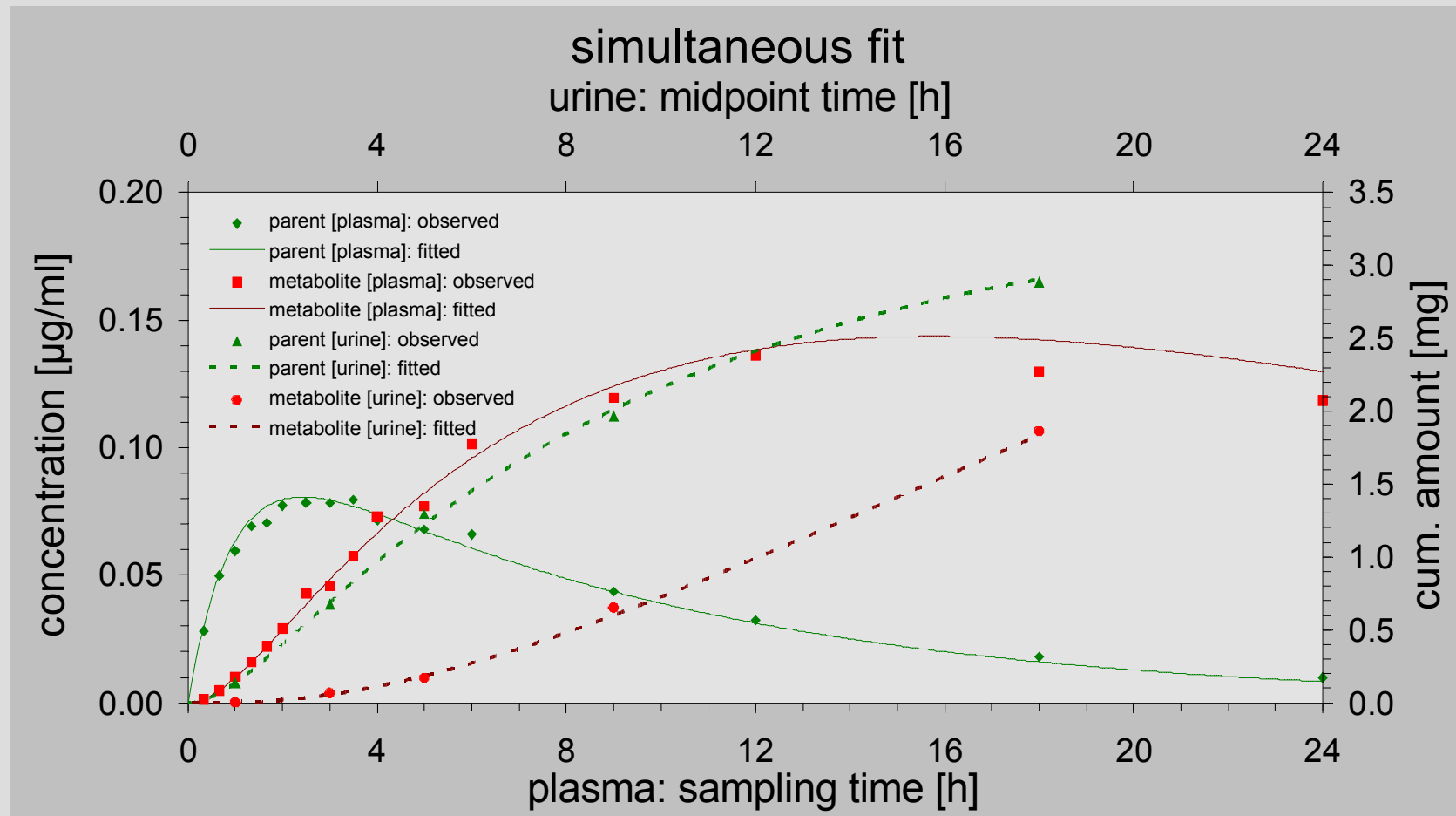
Bioavailability / Bioequivalence

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Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

  - EMEA

    - Two medicinal products are bioequivalent if they are phar-maceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.

    - In bioavailability studies, the <u>shape of and the area under the plasma concentration *versus* time curves</u> are mostly used to assess <u>extent and rate of absorption</u>.

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

simultaneous fit
urine: midpoint time [h]

parent [plasma]: observed
parent [plasma]: fitted
metabolite [plasma]: observed
metabolite [plasma]: fitted
parent [urine]: observed
parent [urine]: fitted
metabolite [urine]: observed
metabolite [urine]: fitted

concentration [µg/ml]

cum. amount [mg]

plasma: sampling time [h]
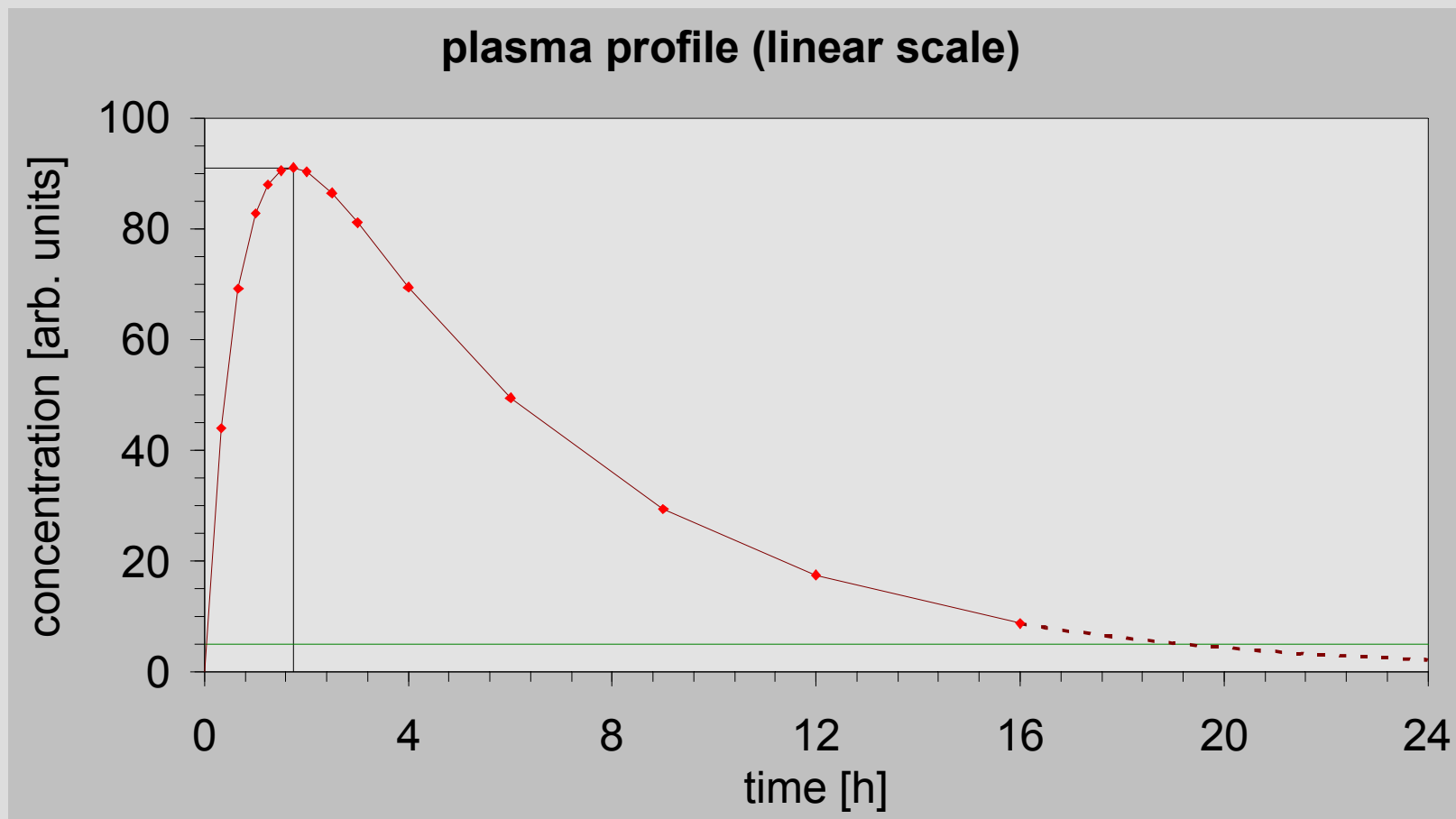
Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

  - Calculation of PK parameters by Noncompart-

    mental Analysis (NCA) only; no PK modelling!

  - Calculation of Moments of Curve (AUC, MRT)

    - Linear trapezoidal rule, or

    - Log-linear trapezoidal rule (lin-up, log-down).

  - Estimation of elimination half life

    - (Unweighted) log-linear regression.

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

  - 'Classical Metrics' (single dose)
    - AUC_t Area Under the Curve (from time of adiministration to the time of the last quantifiable concentration).
    - AUC_∞ Area Under the Curve extrapolated to infinite time.
    - C_{max} Highest observed concentration.
    - t_{max} Time point of C_{max}.
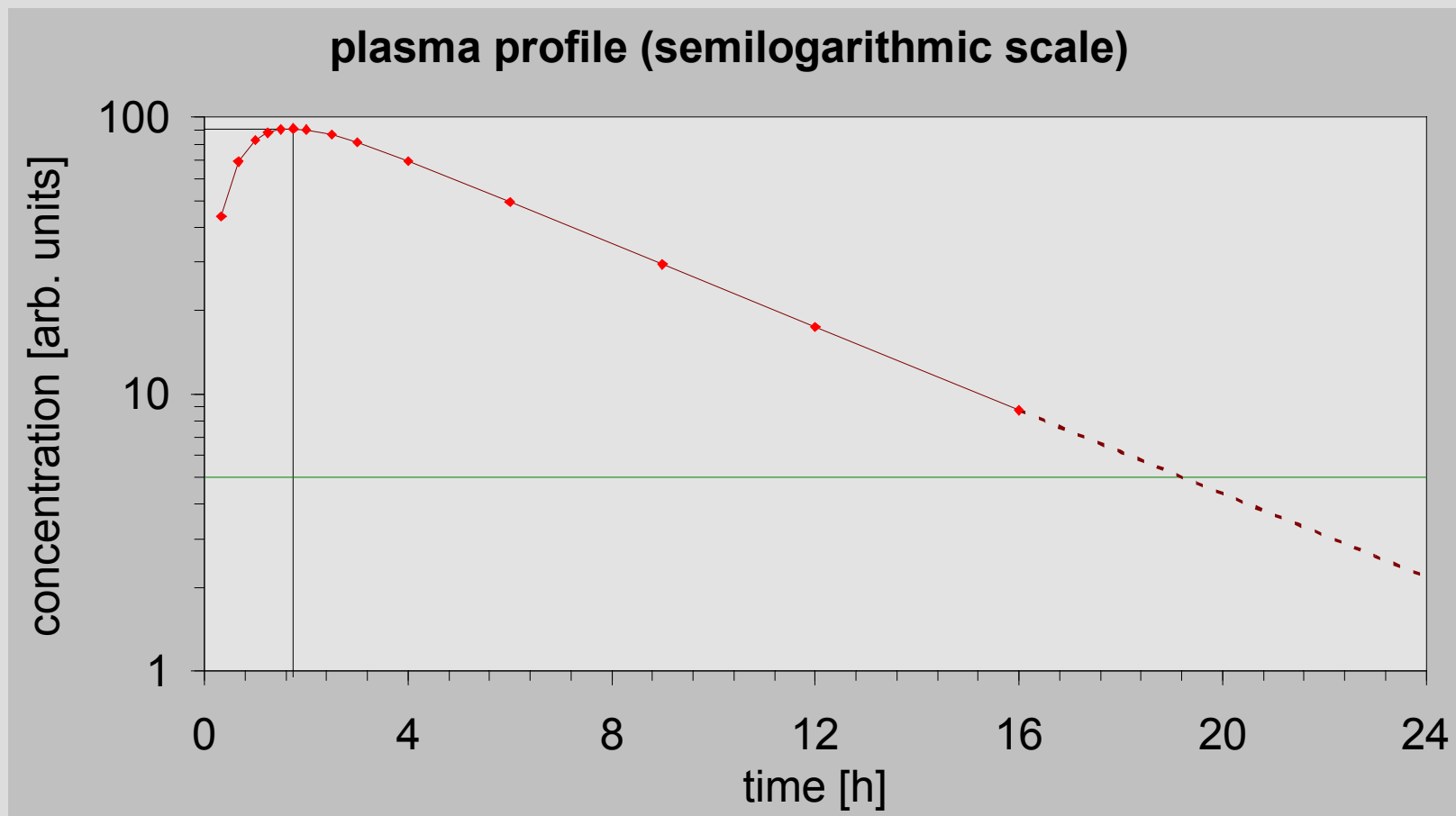   - $t_{1/2}$ Elimination half life time.

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

plasma profile (linear scale)

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

plasma profile (semilogarithmic scale)

concentration [arb. units]

time [h]

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

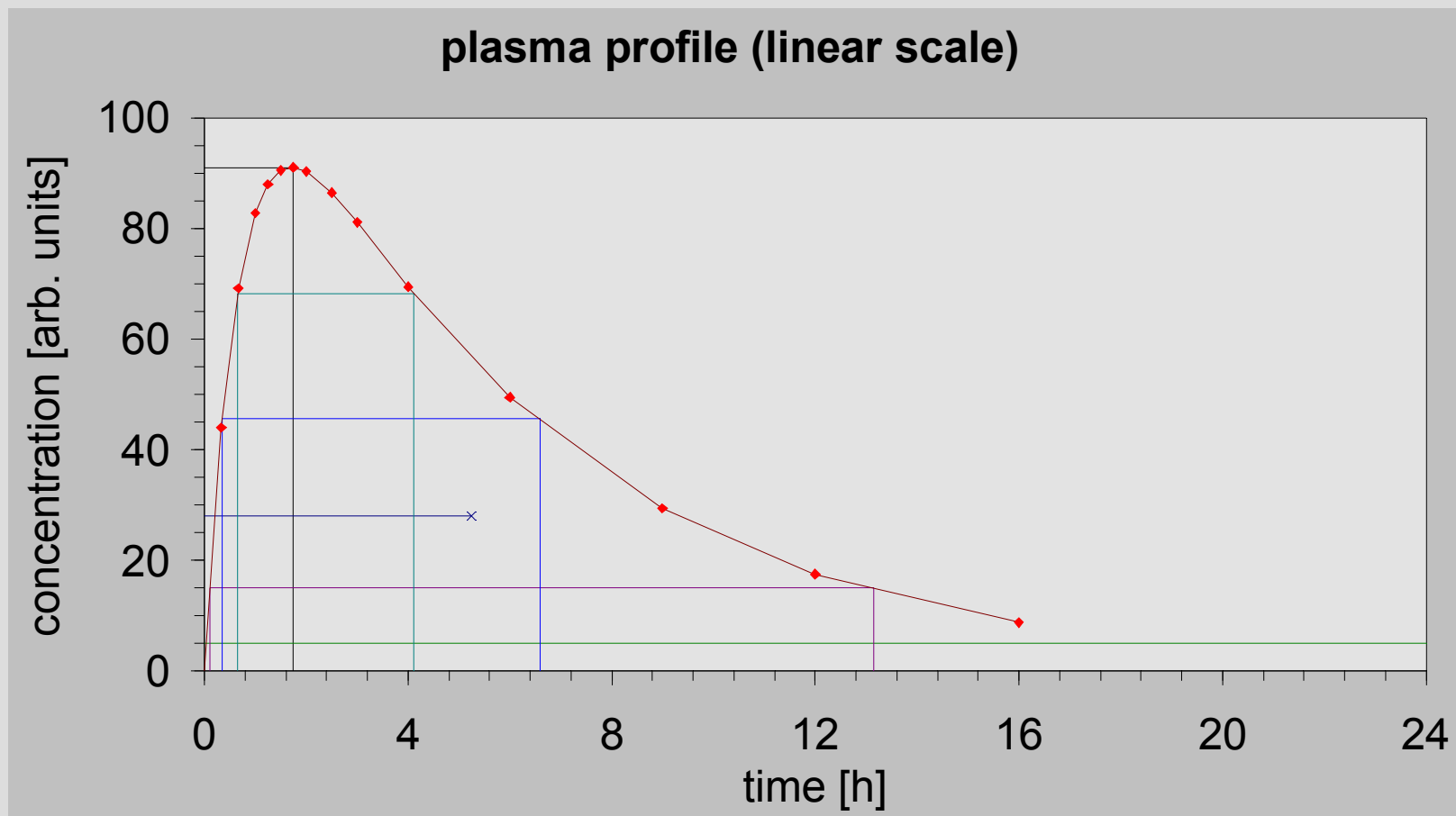 - Shape of Profile (single dose)

    - MRT_t Mean of Residence Times (average time a drug molecule spends in the circulation).

    - HVD   Half Value Duration; time interval where concentration $\geq$ 50 % of C_{max}.

    - $t_{75\%}$ Plateau time; time interval where concentration $\geq$ 75 % of C_{max}.

    - Occupancy   Time interval where concentration $\geq$ some limit (*e.g.*, MIC for antibiotics).

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

  - Shape of Profile (single dose)
    - C_{max}/AUC_t Area-corrected C_{max}.
    - t_{lag} Lag-time.
    - t_{max}-t_{lag} t_{max} corrected for lag-time (*e.g.*, delayed release formulations).
    - AUC_{tmax} 'Early Exposure' (FDA; AUC truncated at median t_{max} of the reference).

Bioavailability / Bioequivalence

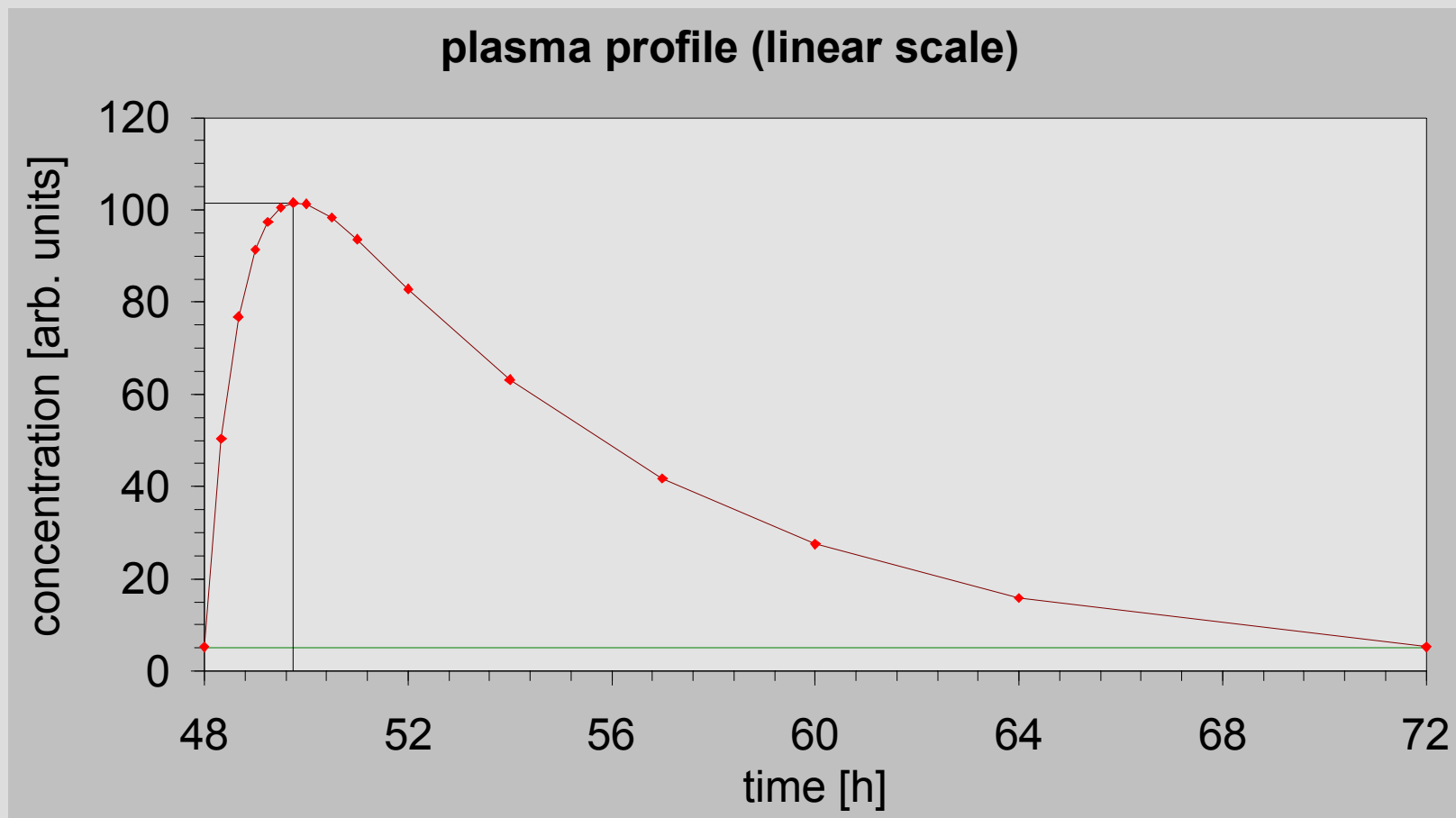- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

plasma profile (linear scale)

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

  - 'Classical Metrics' (multiple dose)
    - AUC_τ Area Under the Curve during a dosage interval in steady state (note: *if linear PK, then single dose AUC_∞ = steady state AUC_τ*).
    - C_{max} Highest observed concentration.
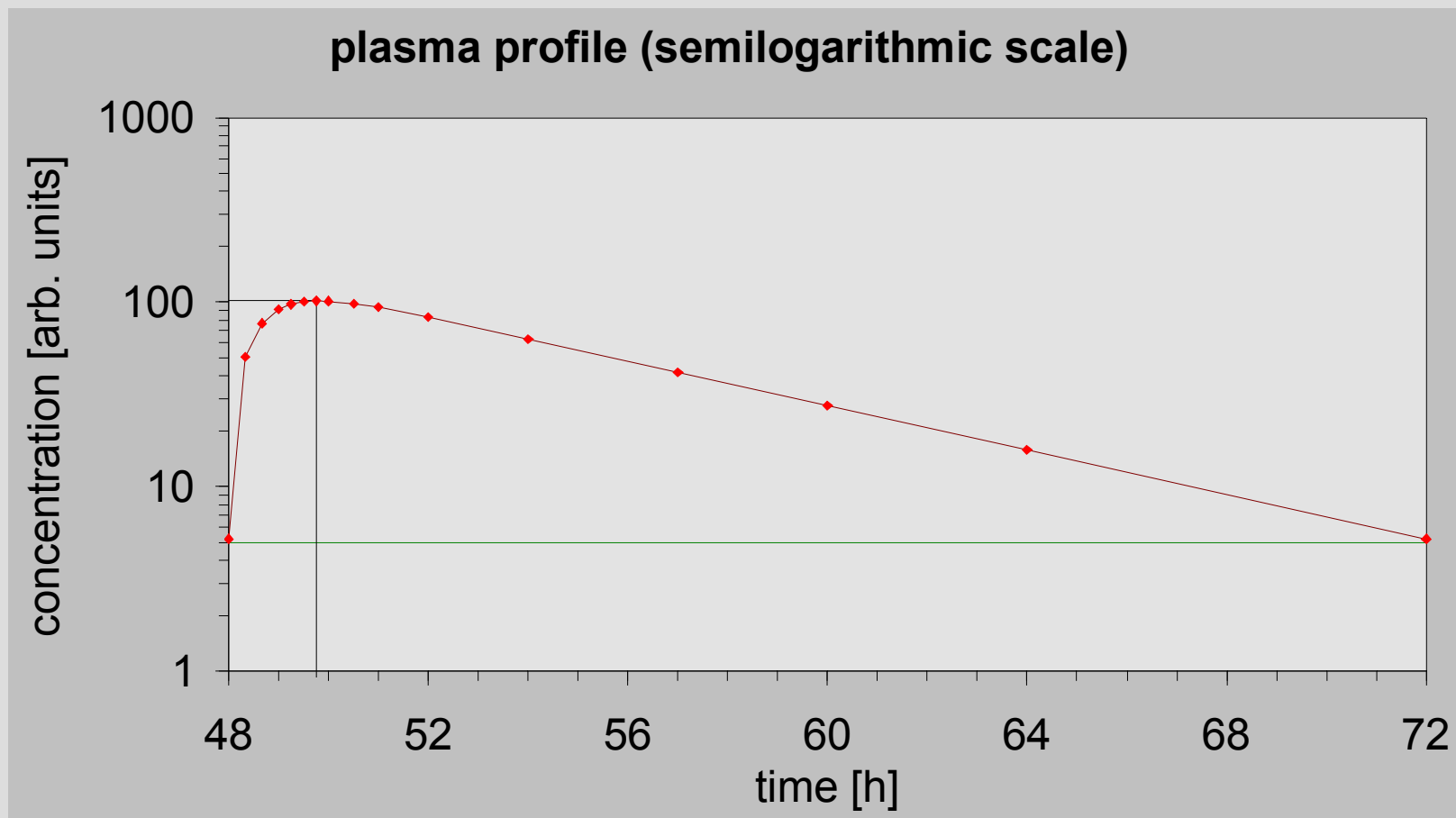   - C_{min} Minimal observed concentration.

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

plasma profile (linear scale)

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

plasma profile (semilogarithmic scale)

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

  - Shape of Profile (multiple dose)

    - Fluctuation   Aka %PTF (Peak-to-Trough Fluctuation); $(C_{max} - C_{min})/C_{av}$ (note: $C_{av} = AUC_{\tau}/\tau$).

    - Swing $(C_{max} - C_{min})/C_{min}$.

    - HVD   Half Value Duration; time interval where concentration $\geq$ 50 % of C_{max}.

    - $t_{75\%}$ Plateau time; time interval where concentration $\geq$ 75 % of C_{max}.

    - Occupancy   Time interval where concentration $\geq$ some limit (*e.g.*, MIC for antibiotics).
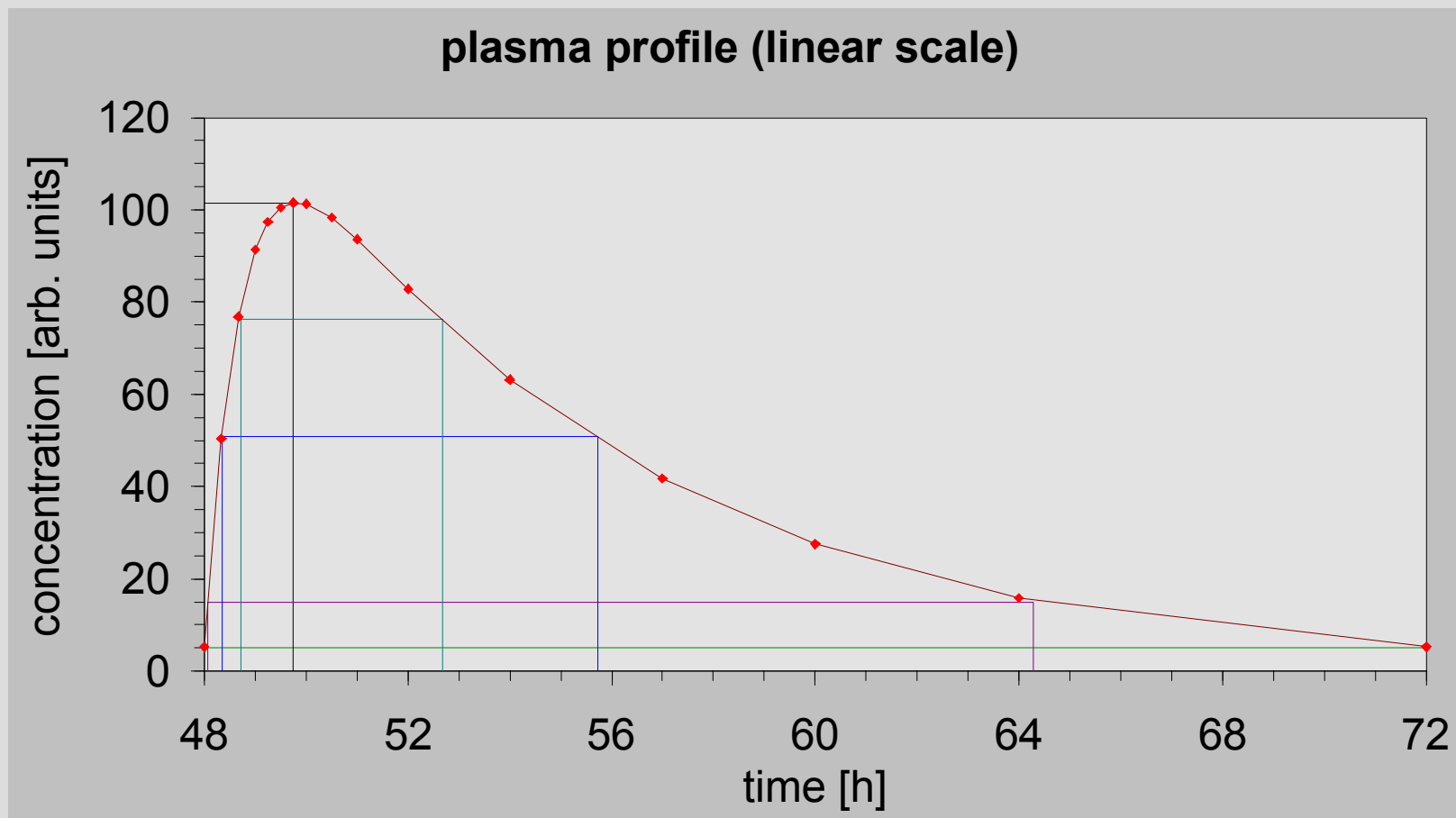
Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

  - Shape of Profile (multiple dose)
    - C_{max}/AUC_{τ} Area-corrected C_{max}.
    - t_{lag} Lag-time.
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    - AUC_{tmax} 'Early Exposure' (FDA; AUC truncated at median t_{max} of the reference).

Bioavailability / Bioequivalence

- **Metrics (AUC, C_{max}/t_{max}, Shape of Profile)**

plasma profile (linear scale)

Bioavailability / Bioequivalence

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Bioavailability / Bioequivalence

- **Acceptance Ranges (0.80 – 1.25 and beyond)**

  - FDA

    - AUC, C_{max} 0.80 – 1.25, no exceptions (!)

Bioavailability / Bioequivalence

- **Acceptance Ranges (0.80 – 1.25 and beyond)**

  - Turkey

    - AUC, C_{max} 0.80 – 1.25, also for Narrow Therapeutic Index Drugs (NTIDs); only for Highly Variable Drugs (HVDs) the acceptance interval may be wider (0.75 – 1.33).

  Turkish Ministry of Health, Division of Drug Regulatory Affairs;
  Directive # 21942: BA/BE studies of pharmaceutical products. (May 1994)

Bioavailability / Bioequivalence

- **Acceptance Ranges (0.80 – 1.25 and beyond)**

  - EMEA
    - AUC   0.80 – 1.25, in specific cases of NTIDs the accep-tance interval <u>may need to be tightened</u> (*e.g.*, 0.9 – 1.11), in rare cases <u>a wider acceptance range may be acceptable (based on sound clinical justification</u>).

  European Agency for the Evaluation of Medicinal Products / Committee for Proprietary Medicinal Products;
  CPMP/EWP/QWP/1401/98: CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence (July 2001)

Bioavailability / Bioequivalence

- **Acceptance Ranges (0.80 – 1.25 and beyond)**

    - EMEA

        - C_{max} 0.80 – 1.25, in specific cases of NTIDs the accep-
          tance interval <u>may need to be tightened</u>; in certain
          cases a wider interval may be acceptable. The
          interval must be <u>prospectively defined</u>
          (*e.g.*, 0.75 – 1.33) and <u>justified addressing in
          particular any safety or efficacy concerns</u> for
          patients switched between formulations.

Bioavailability / Bioequivalence

- **Acceptance Ranges (0.80 – 1.25 and beyond)**

  - EMEA

    - t_{max} Non-parametric 90 % confidence interval

      should lie within a clinically determined range;
      only if:

      → clinically relevant claim for rapid release
      (*e.g.*, analgetics), or
      → action or signs related to adverse effects
      (*e.g.*, IR nifedipine).

    - all others   Considerations analogous to those for AUC,

      C_{max} or t_{max} apply, taking into consideration the

      use of log-transformed or untransformed data.

Bioavailability / Bioequivalence

- **Acceptance Ranges (0.80 – 1.25 and beyond)**

  - EMEA

    Although a wider acceptance range (at least for

    C_{max}) was pioneered in Europe (currently practice

    in the EU, Turkey, Australia, Japan, Switzerland,

    New Zealand, Malaysia, Taiwan, Argentina,

    South Africa; suggested by WHO) EMEA's EWP

    is considering a more restrictive approach.

Bioavailability / Bioequivalence

- **Acceptance Ranges (0.80 – 1.25 and beyond)**

  - EMEA

    There have been rumours at *BioInternational '05*,

    that a 'QA' Document to the NfG is in preparation

    by the EWP and can be expected for mid-2006.

    - 0.80–1.25   No exceptions (not even for HVDs, no
      clinical justification acceptable).
    - HVDs   No multiple dose studies to reduce variability.
    - Outliers   Nonparametric statistical methods not
      acceptable.

Bioavailability / Bioequivalence

- **Acceptance Ranges (0.80 – 1.25 and beyond)**

  - EMEA

    is also considering to issue two distinct guidance documents for bioavailability and bioequivalence studies, which will replace the current NfG (BA-NfG will focus more on the formulation, whereas the BE-NfG on BA as a the surrogate for safety/efficacy).