

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

▪ Selection of CROs

• General Suitability of the CRO

- ♦ Location (Accessibility, 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 GxP (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-, Plasmaprobe, 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 Bundesministerin

BODMANN
10
REPUBLIC OF AUSTRIA
Ministerium für Gesundheit und Frauen

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 and adhered to (!).

• Financial Issues

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

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Bioavailability / Bioequivalence

▪ Selection of a Reference Product

- Pharmaceutical Equivalents, Pharmaceutical Alternatives (EU Definition).

- ◊ Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.
- ◊ Medicinal products are pharmaceutical alternatives 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?
 - ◊ Bioinequivalence 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

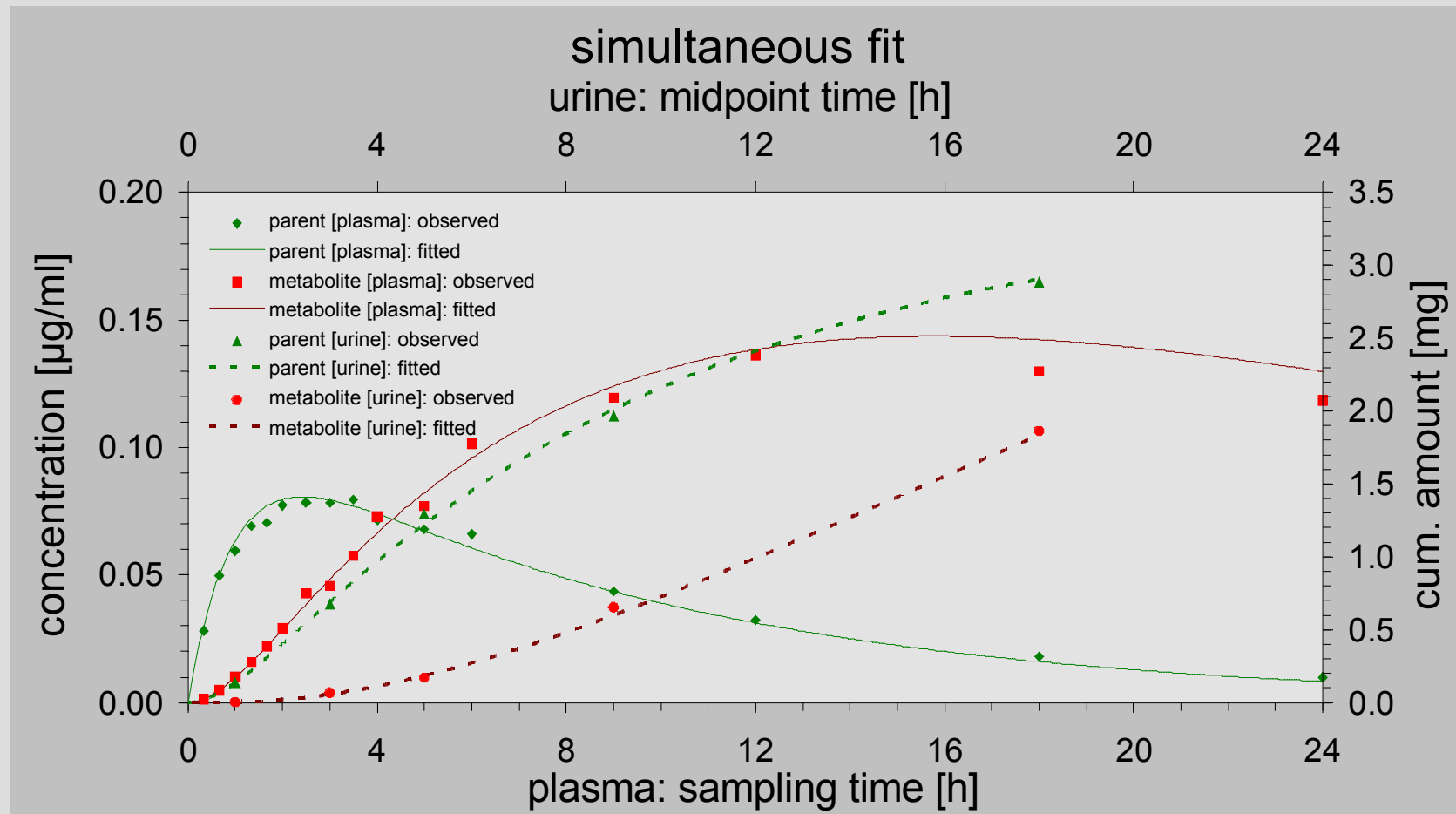
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Bioavailability / Bioequivalence

- **Metrics (AUC, C_{\max}/t_{\max} , Shape of Profile)**
 - EMEA
 - ◆ Two medicinal products are bioequivalent if they are pharmaceutically 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 shape of and the area under the plasma concentration *versus* time curves are mostly used to assess extent and rate of absorption.

Bioavailability / Bioequivalence

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



Bioavailability / Bioequivalence

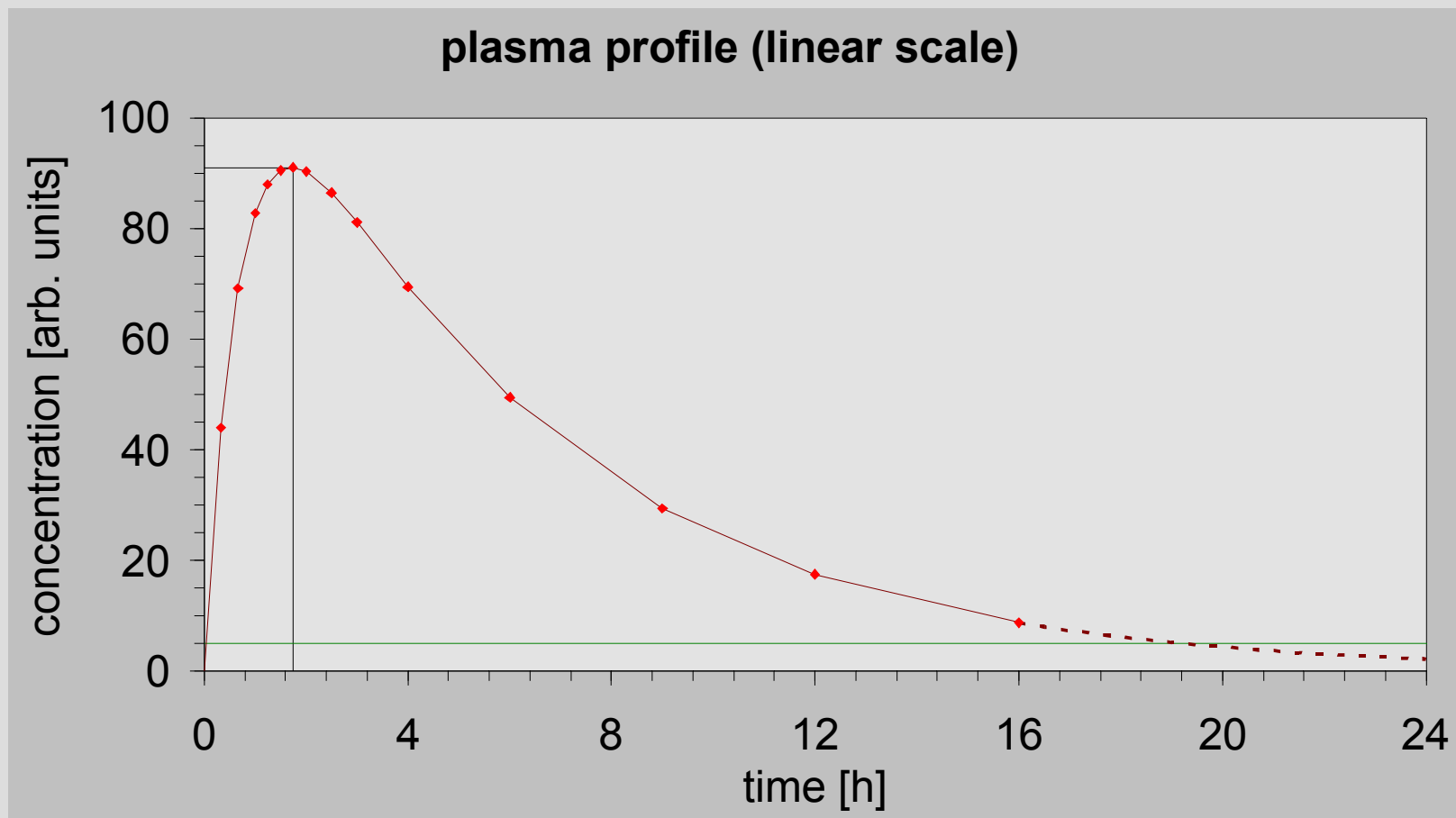
- **Metrics (AUC, C_{\max}/t_{\max} , Shape of Profile)**
 - Calculation of PK parameters by Noncompartmental Analysis (NCA) only; no PK modelling!
 - Calculation of Moments of Curve (AUC, MRT)
 - ◊ Linear trapezoidal rule, or
 - ◊ Log-linear trapezoidal rule (lin-up, log-down).
 - Estimation of elimination 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 administration 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.

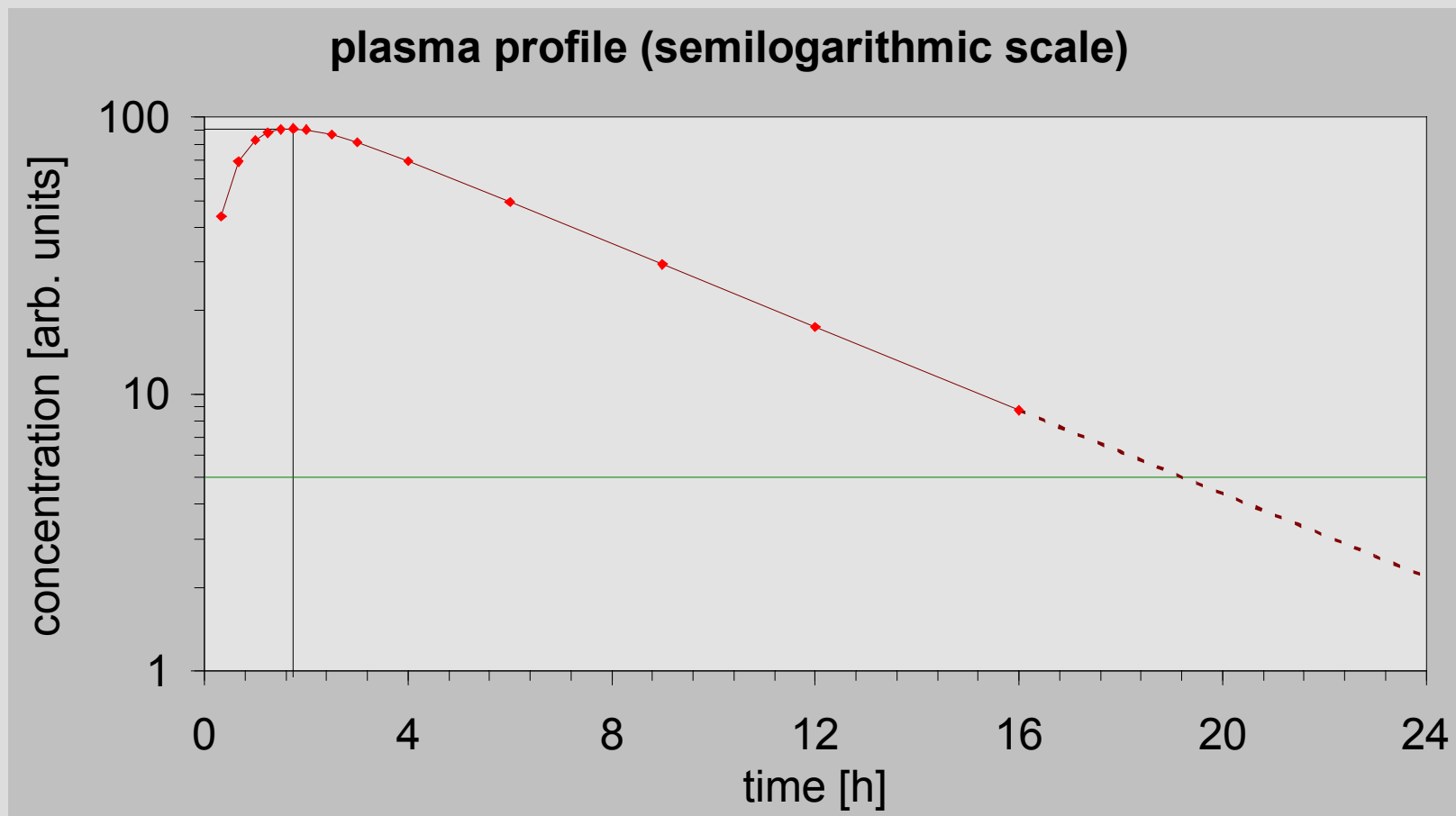
Bioavailability / Bioequivalence

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



Bioavailability / Bioequivalence

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



Bioavailability / Bioequivalence

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

- Shape of Profile (single dose)

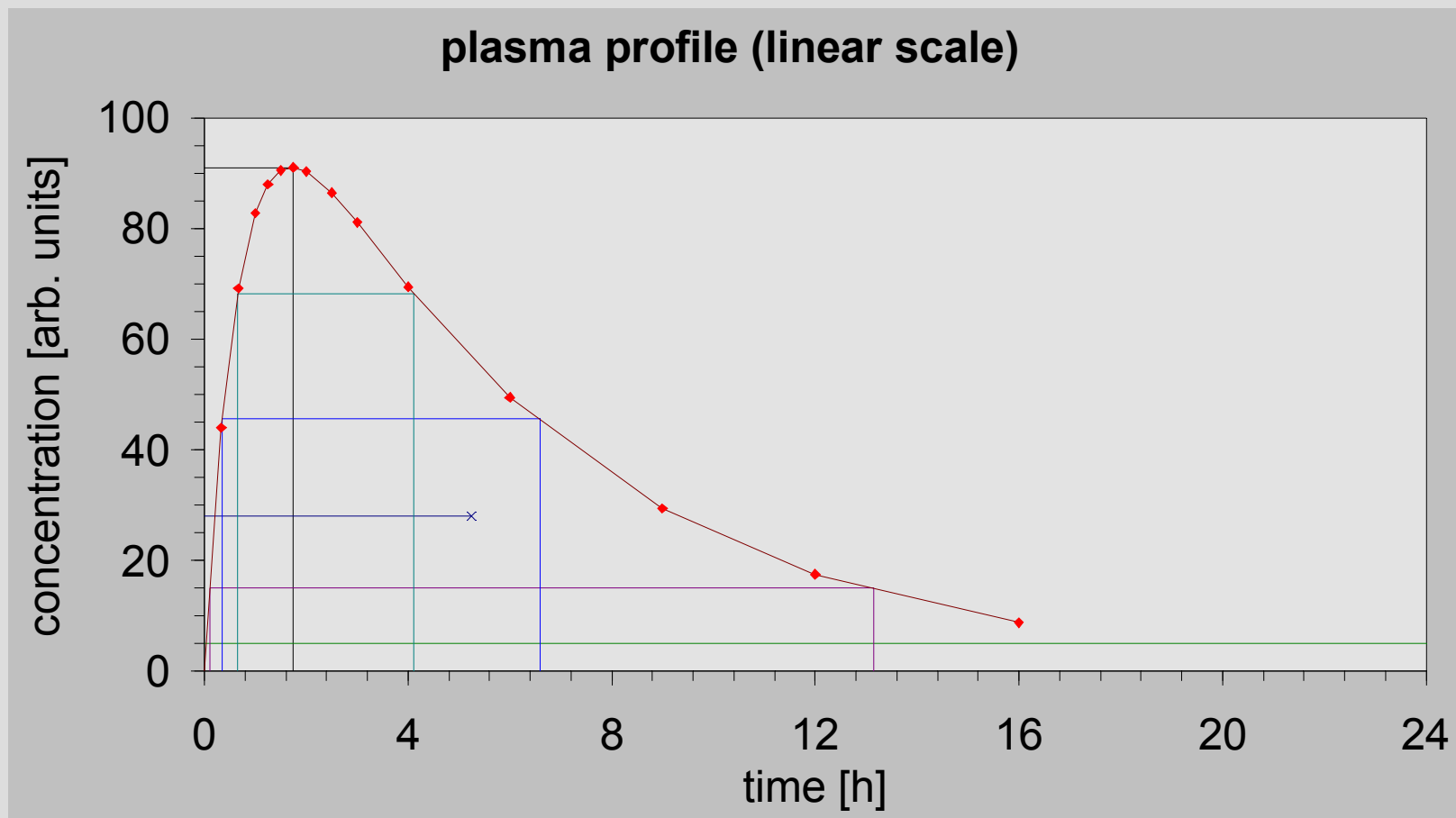
- MRT_t Mean of Residence Times (average time a drug molecule spends in the circulation).
- HVD Half Value Duration; time interval where concentration $\geq 50\%$ of C_{\max} .
- $t_{75\%}$ Plateau time; time interval where concentration $\geq 75\%$ of C_{\max} .
- Occupancy Time interval where concentration \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.
 - ♦ $t_{\max} - t_{\text{lag}}$ t_{\max} corrected for lag-time (e.g., delayed release formulations).
 - ♦ $AUC_{t_{\max}}$ 'Early Exposure' (FDA; AUC truncated at median t_{\max} of the reference).

Bioavailability / Bioequivalence

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

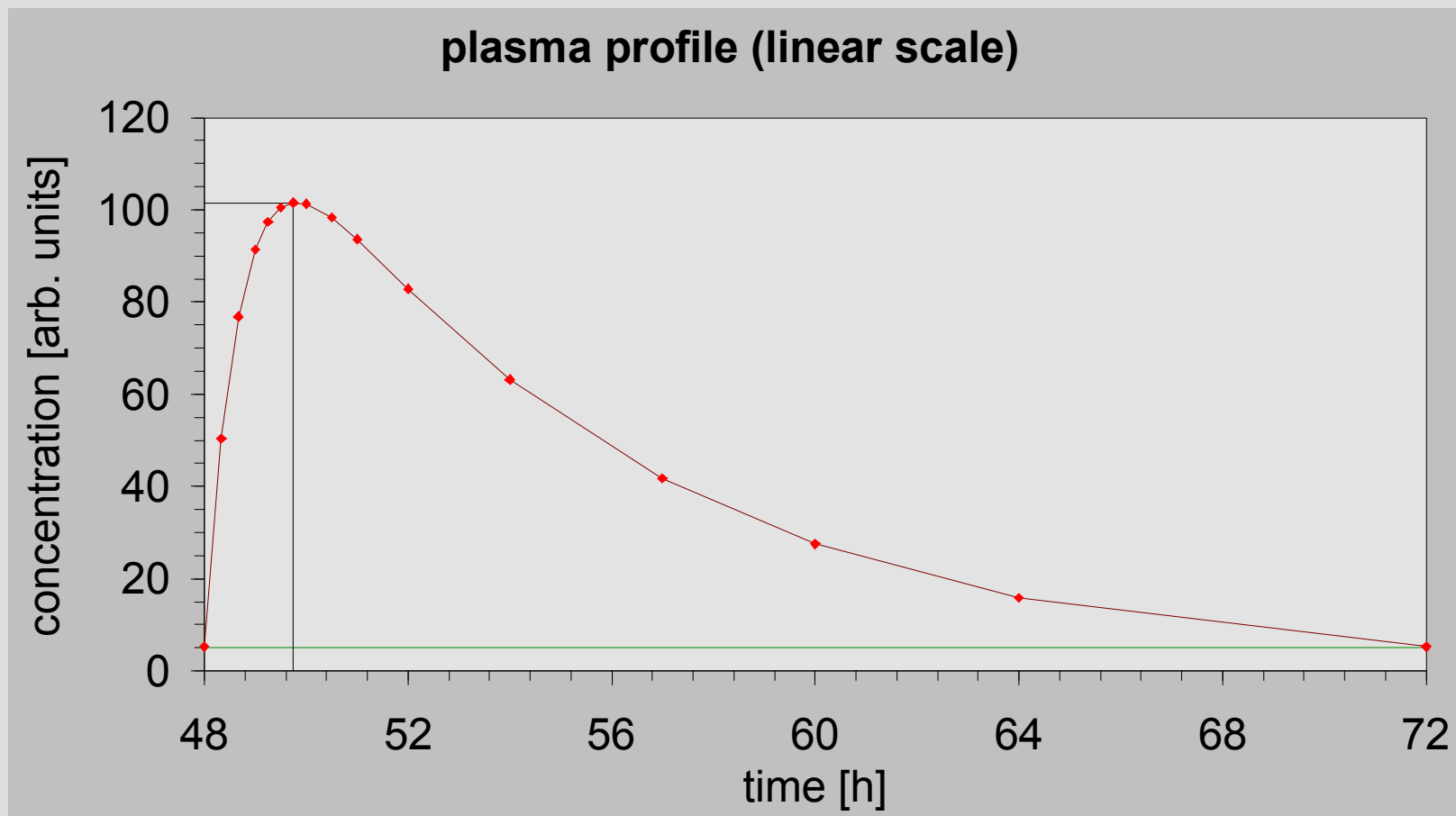


Bioavailability / Bioequivalence

- **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.

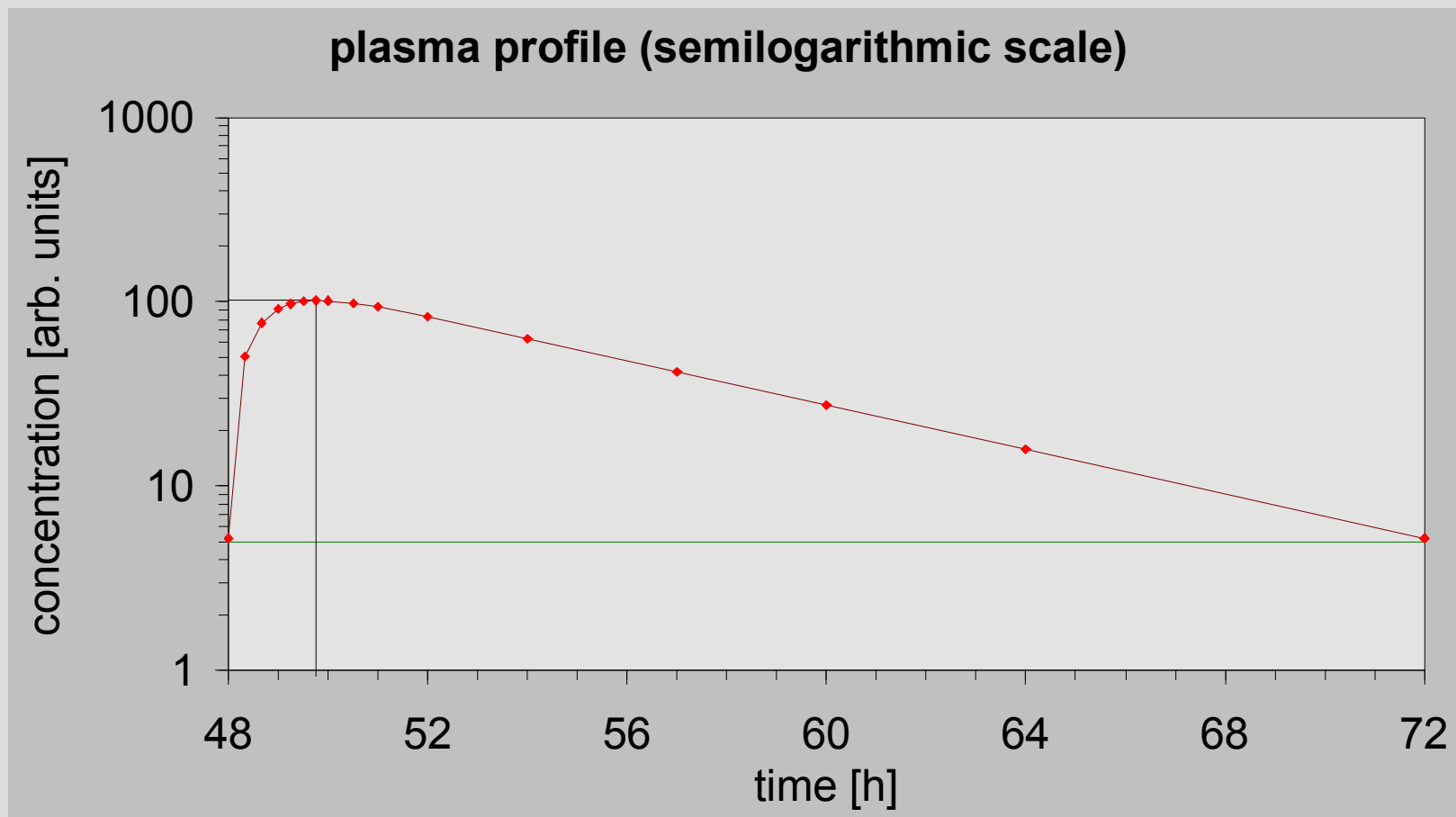
Bioavailability / Bioequivalence

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



Bioavailability / Bioequivalence

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



Bioavailability / Bioequivalence

■ Metrics (AUC, C_{\max} / t_{\max} , Shape of Profile)

• Shape of Profile (multiple dose)

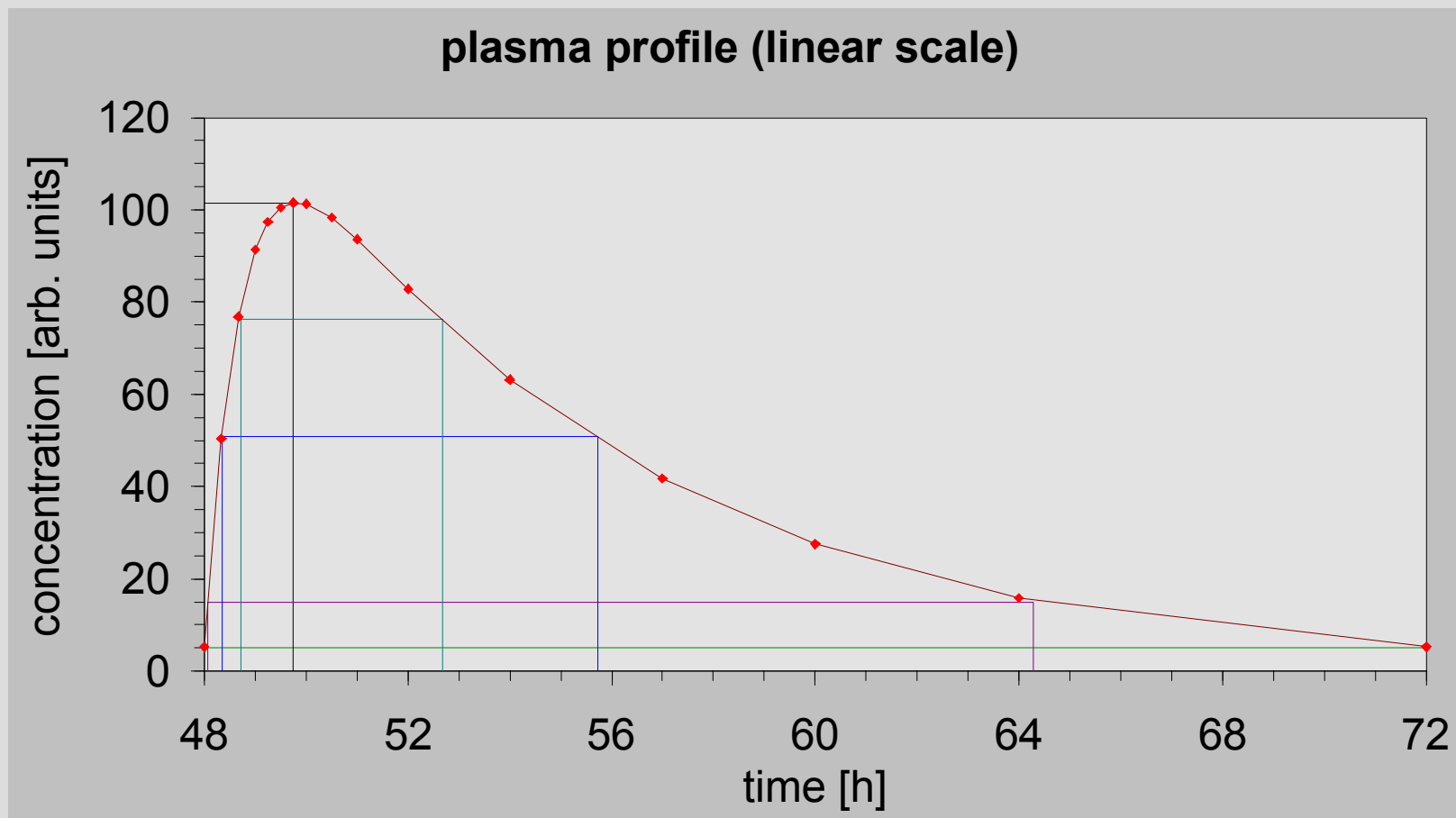
- Fluctuation Aka %PTF (Peak-to-Trough Fluctuation);
 $(C_{\max} - C_{\min})/C_{av}$ (note: $C_{av} = AUC_{\tau}/\tau$).
- Swing $(C_{\max} - C_{\min})/C_{\min}$.
- HVD Half Value Duration; time interval where
concentration $\geq 50\%$ of C_{\max} .
- $t_{75\%}$ Plateau time; time interval where
concentration $\geq 75\%$ 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)
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- **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 acceptance interval may need to be tightened (e.g., 0.9 – 1.11), in rare cases a wider acceptance range may be acceptable (based on sound clinical justification).

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 acceptance interval may need to be tightened; in certain cases a wider interval may be acceptable. The interval must be prospectively defined (e.g., 0.75 – 1.33) and justified addressing in particular any safety or efficacy concerns 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).