Pharmacokinetic Analysis of BE Data
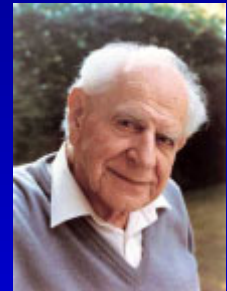
Helmut Schütz
BEBAC

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To bear in Remembrance...

Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve.   *Karl R. Popper*

Even though it's *applied* science we're dealin' with, it still is – *science!*

Leslie Z. Benet

NCA *vs.* PK Modeling

- Pharmacokinetic models
  - Useful for understanding the drug/formulation
    - Study design of BA/BE, *e.g.*,
      washout, accumulation / saturation to steady state
  - Drawbacks
    - Almost impossible to validate (fine-tuning of side conditions, weighting schemes, software, …)
    - Still a mixture of art and science
    - Impossible to recalculate any given dataset using different software – sometimes even different versions of the same software!
    - Not acceptable for *evaluation* of BE studies!

PK Modeling: AUC

- Based on integration of a PK model; *e.g.*, extravascular dose, one-compartment, no lag-time

$$C(t) = \frac{f \cdot D}{V} \frac{k_a}{k_a - k_{el}} \left(e^{k_{el}t} - e^{k_a t} \right)$$

$$AUC_{0-\infty} = \int_0^\infty C(t)dt = \frac{f \cdot D}{V} \frac{k_a}{k_a - k_{el}} \left(\frac{1}{k_{el}} - \frac{1}{k_a} \right) = \frac{f \cdot D}{V \cdot k_{el}} = \frac{f \cdot D}{CL}$$

NCA: Single Dose

- Noncompartmental methods do not rely on a PK (=compartmental) model

- Also known as SHAM (Shape, Height, Area, Moments)

  - Metrics (plasma, single dose)
    - Extent of absorption (EU…), total exposure (US): AUC (Area Under the Curve)
    - Rate of absorption (EU…), peak exposure (US): C_{max}
    - t_{max} (EU…)
    - Early exposure (US, CAN): $pAUC_{tmax}$; AUC truncated at population's (CAN: subject's) t_{max} of the reference
    - Others: C_{min}, Fluctuation, MRT, Occupancy time, t_{lag},…

NCA: AUC

- Since compartmental models not acceptable in BE, numeric approximation required
  - Linear trapezoidal rule[1]
  - Lin-log trapezoidal rule[1,2]
  - Lin-up/log-down trapezoidal rule
  - Cubic splines
  - Lagrange-polynomials
  - Simpson's rule

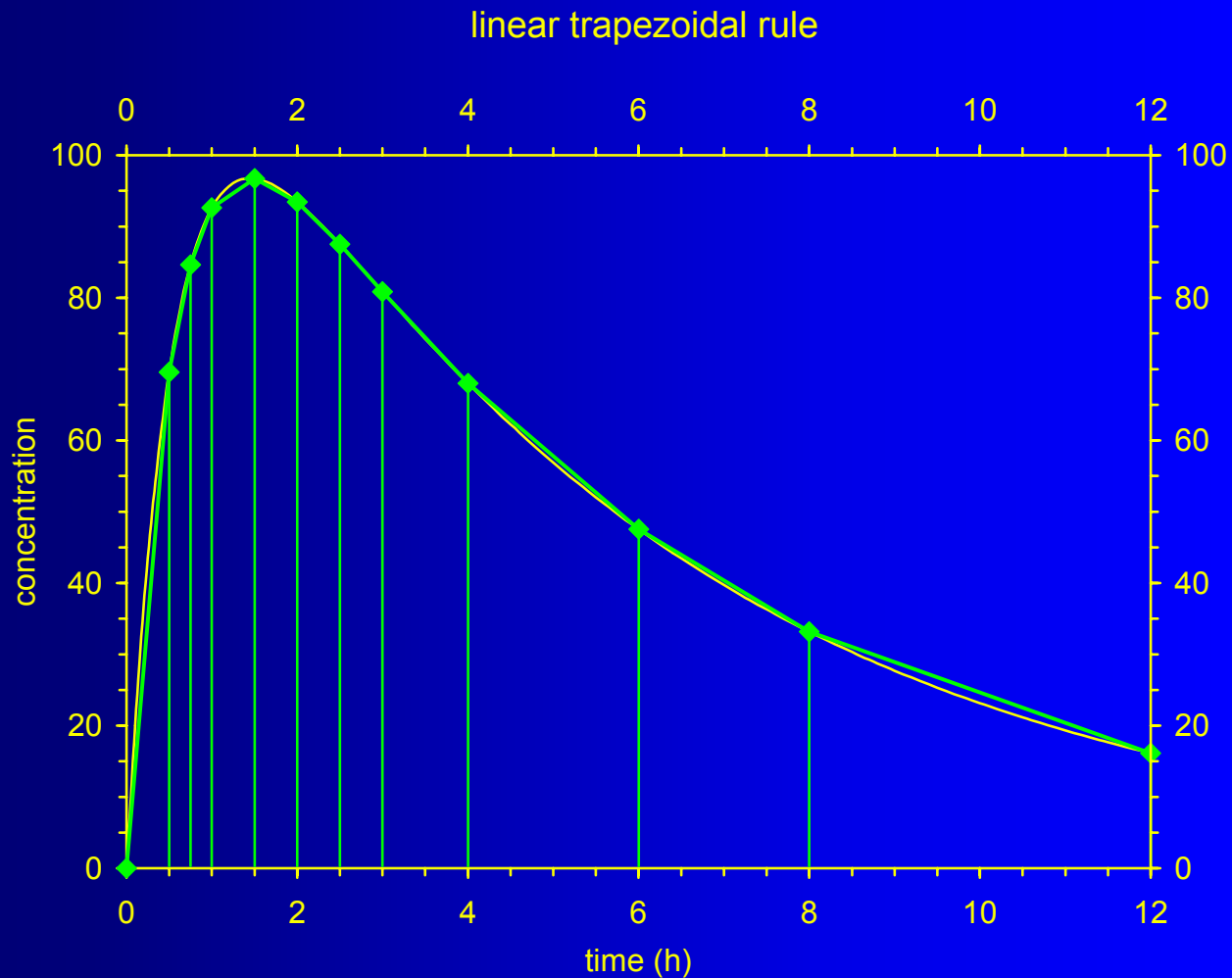[1] Russian GL; only these two acceptable?
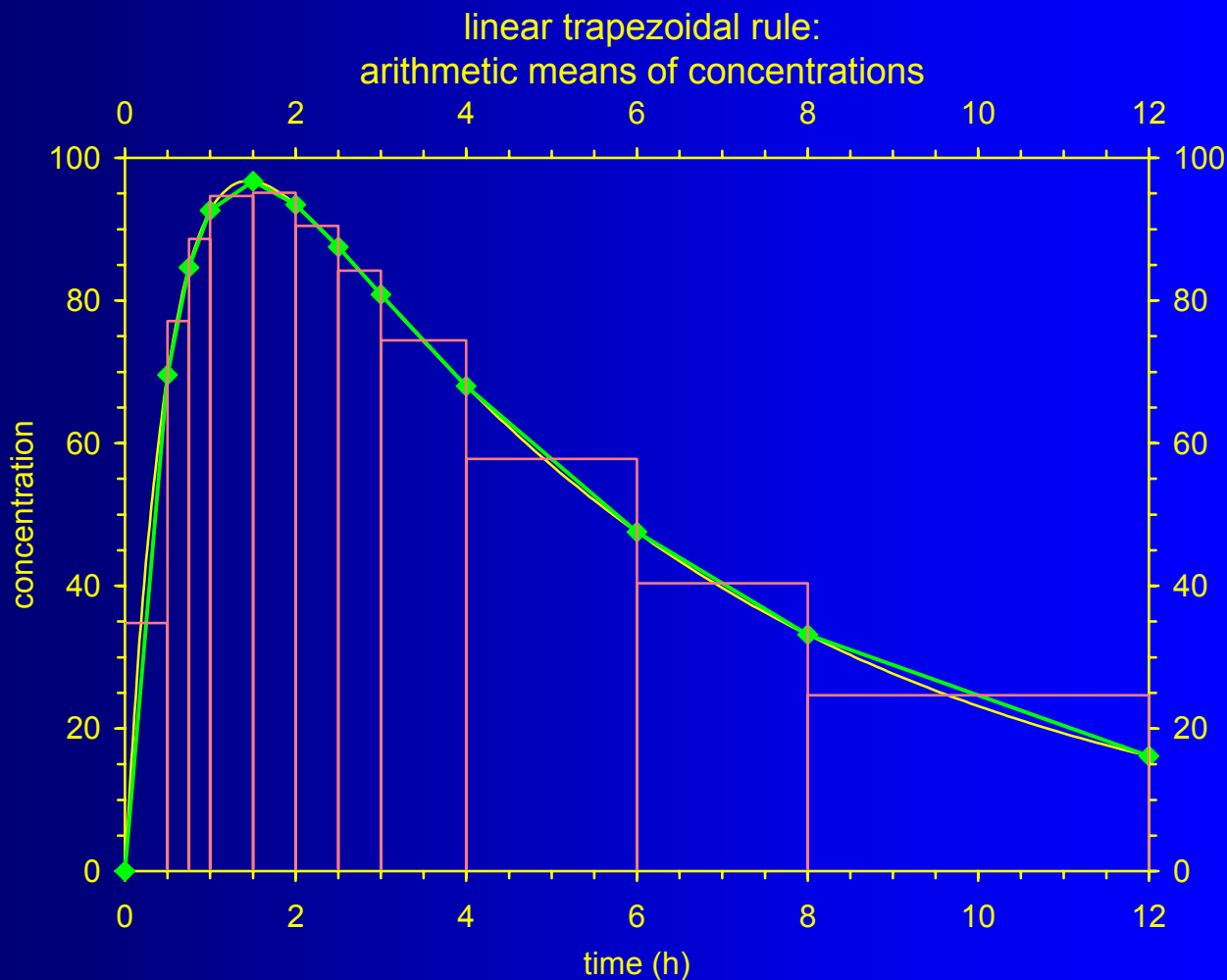
[2] WHO GL; only acceptable method?

NCA: AUC

- Linear trapezoidal rule
  - Linear interpolation between data points
  - Sections represented as trapezoids
  - Sides a, b = neighbouring concentrations
  - Time interval h
  - Area of trapezoid $A = \dfrac{a+b}{2}h$
  - Total

$$AUC_{0-t_n} \approx \sum_{i=1}^{i=n-1} \frac{C_i + C_{i+1}}{2}\left(t_{i+1} - t_i\right) \approx \frac{1}{2}\sum_{i=1}^{i=n-1}\left(C_i + C_{i+1}\right)\cdot\left(t_{i+1} - t_i\right)$$

NCA: AUC

linear trapezoidal rule

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NCA: AUC

linear trapezoidal rule:
arithmetic means of concentrations

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NCA: AUC

- Log-linear trapezoidal rule
  - Assumes exponential elimination
  - Log-linear interpolation between data points
  - Only valid for iv administration; sections in absorption phase underestimated if applied to ev
  - If $C = 0$ or subsequent concentrations are equal, section calculated by linear trapezoidal
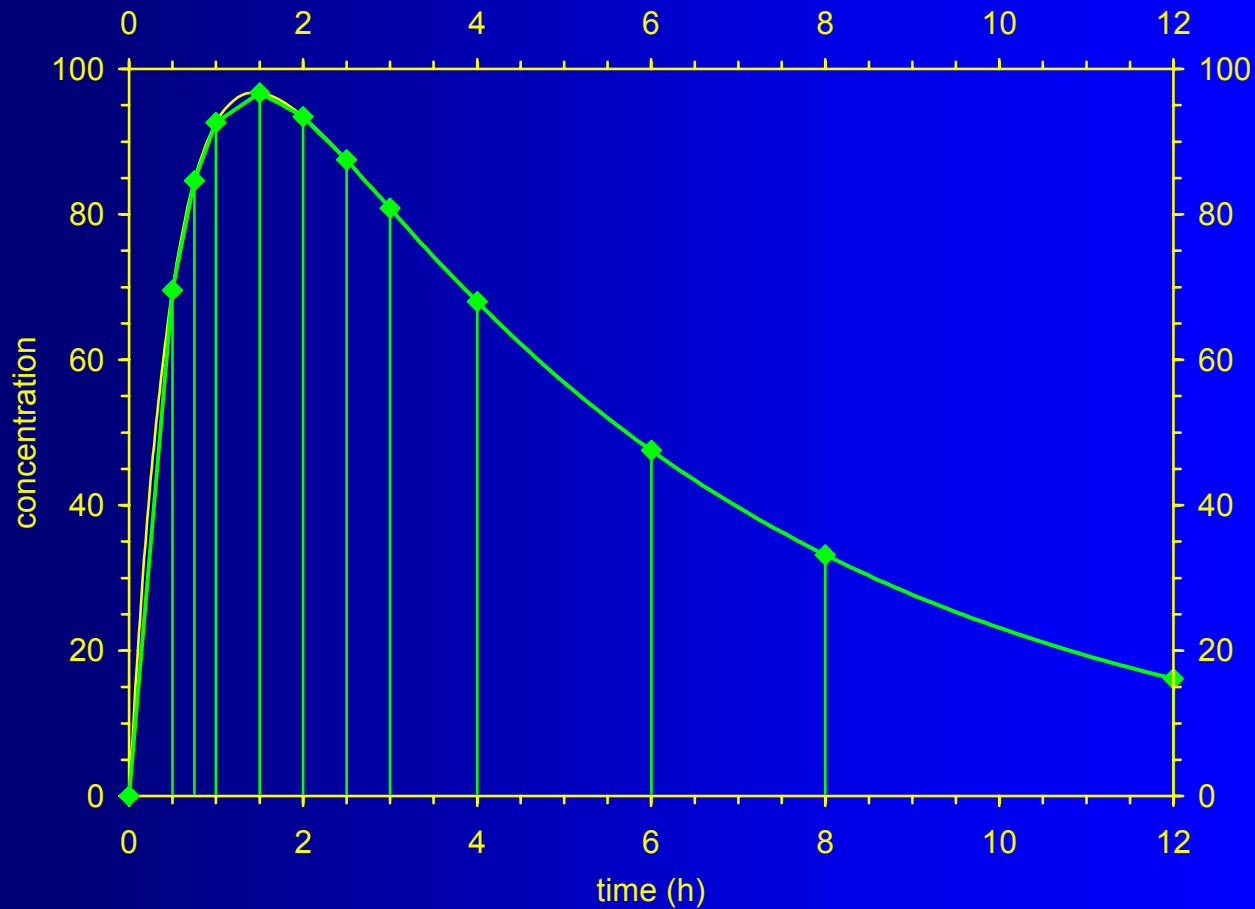 - Total

$$AUC_{0-t_n} \approx \sum_{i=1}^{i=n-1} \frac{C_{i+1} - C_i}{\ln \frac{C_{i+1}}{C_i}} \left(t_{i+1} - t_i \right)$$

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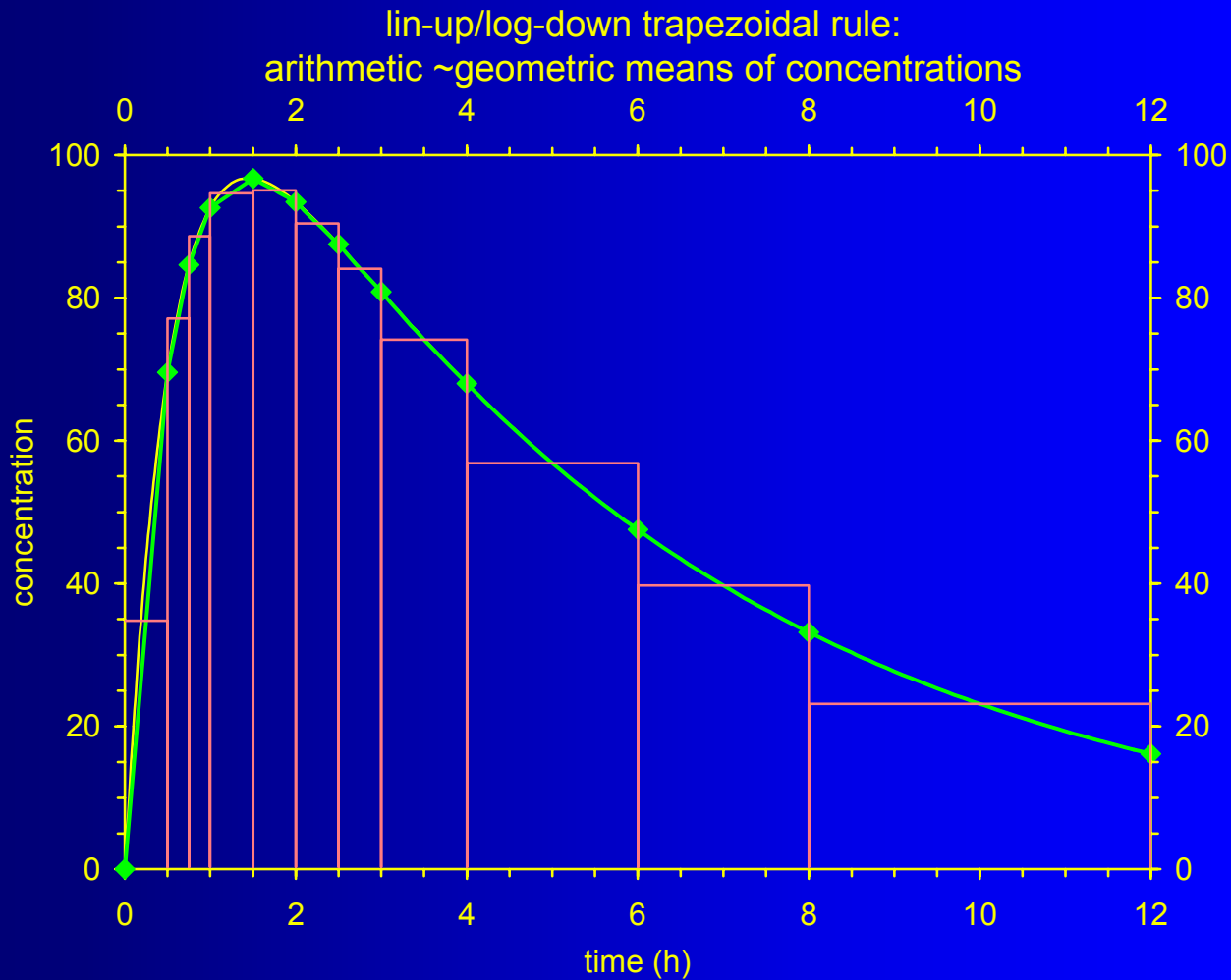**Leuven, 5–6 June, 2013**

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NCA: AUC

- Lin-up/log-down trapezoidal rule
  - Hybrid of linear and log-linear
  - Sections with *increasing or equal* concentrations ($C_{i+1} \geq C_i$) calculated by linear trapezoidal rule
  - Sections with *decreasing* concentrations ($C_{i+1} < C_i$) calculated by log-linear trapezoidal rule
  - Avoids bias in both absorption and distribution/ elimination phases
  - Suitable for iv and ev
  - Suitable for multiphasic profiles

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NCA: AUC

lin-up/log-down trapezoidal rule

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NCA: AUC

lin-up/log-down trapezoidal rule:
arithmetic ~geometric means of concentrations

Example 1

AUCi (R) 707.6, AUCi (T) 670.9, T/R 94.8%, bias -0.20%

Model
AUC_R 697.8
AUC_T 662.9
T/R   95.00%

linear trapezoidal
T/R   94.85%

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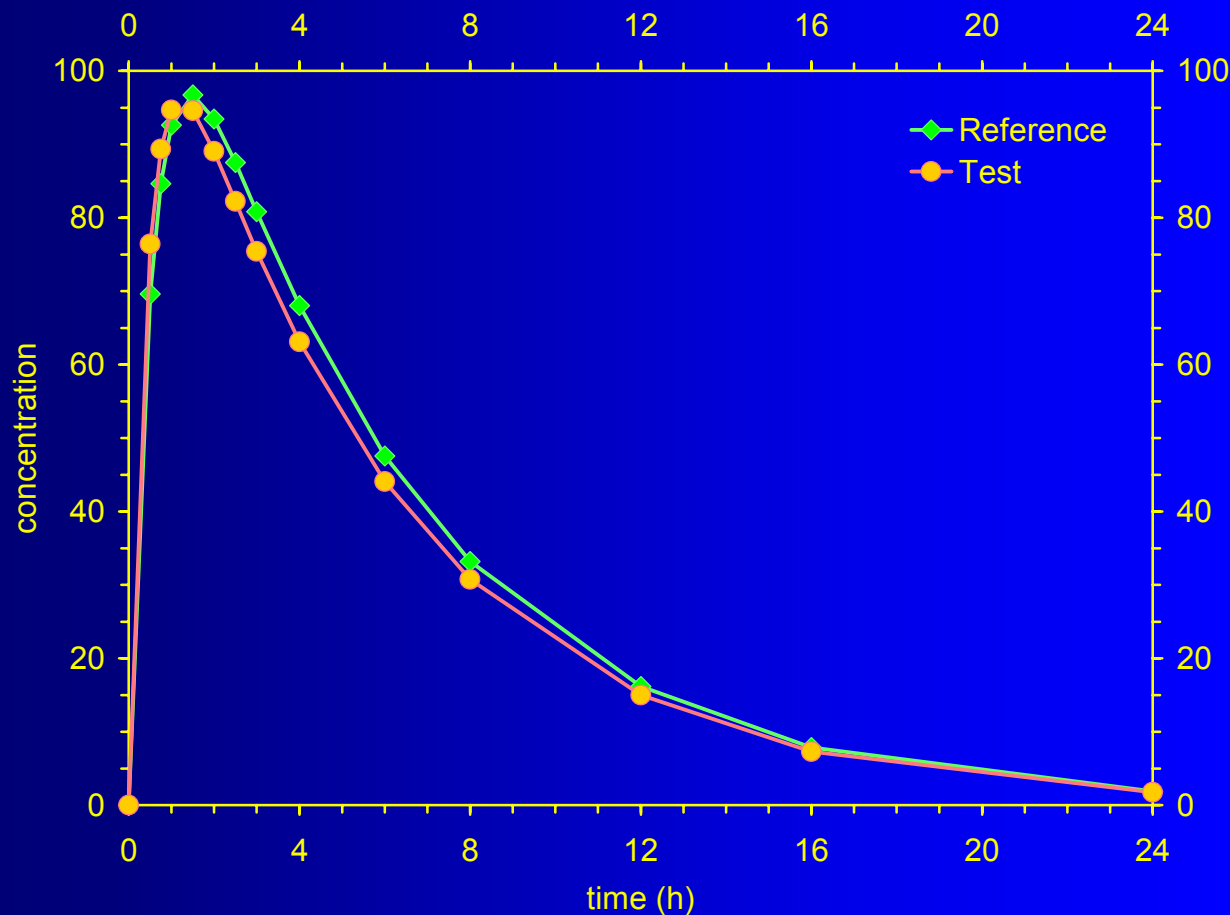
Example 1

Model

AUC_R 697.8
AUC_T 662.9
T/R   95.00%

lin-up/log-down
T/R   94.89%

AUCi (R) 693.7, AUCi (T) 658.0, T/R 94.9%, bias -0.16%

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Example 2

AUCi (R) 725.1, AUCi (T) 670.9, T/R 92.5%, bias -2.60%
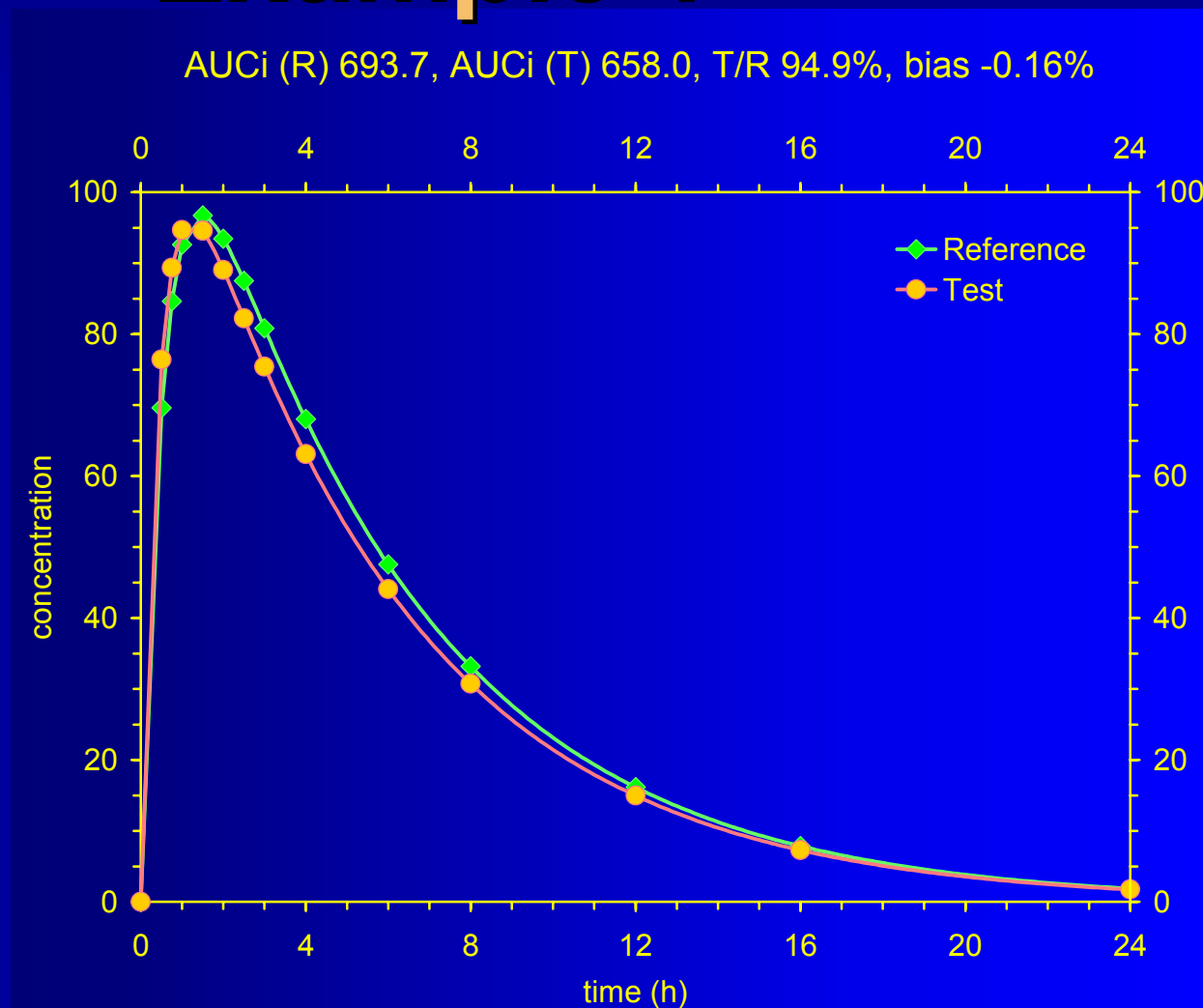
Model

AUC_R 697.8

AUC_T 662.9

T/R   95.00%

linear trapezoidal

12 h (R) missing
T/R   92.53%

Spaghetti & other pasta

linear trapezoidal

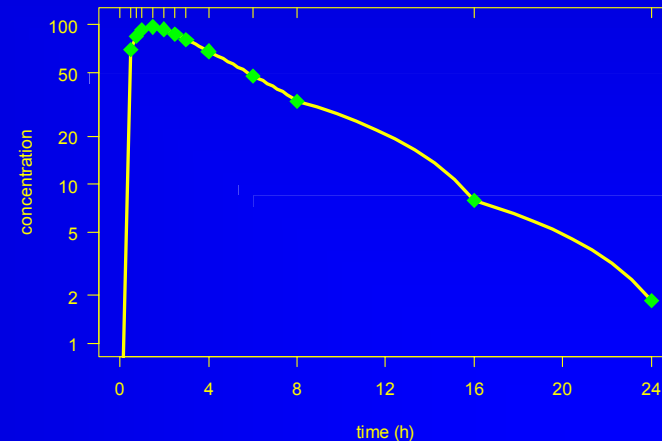Does the *semi-log plot* reflect the calcu-lation of AUC?
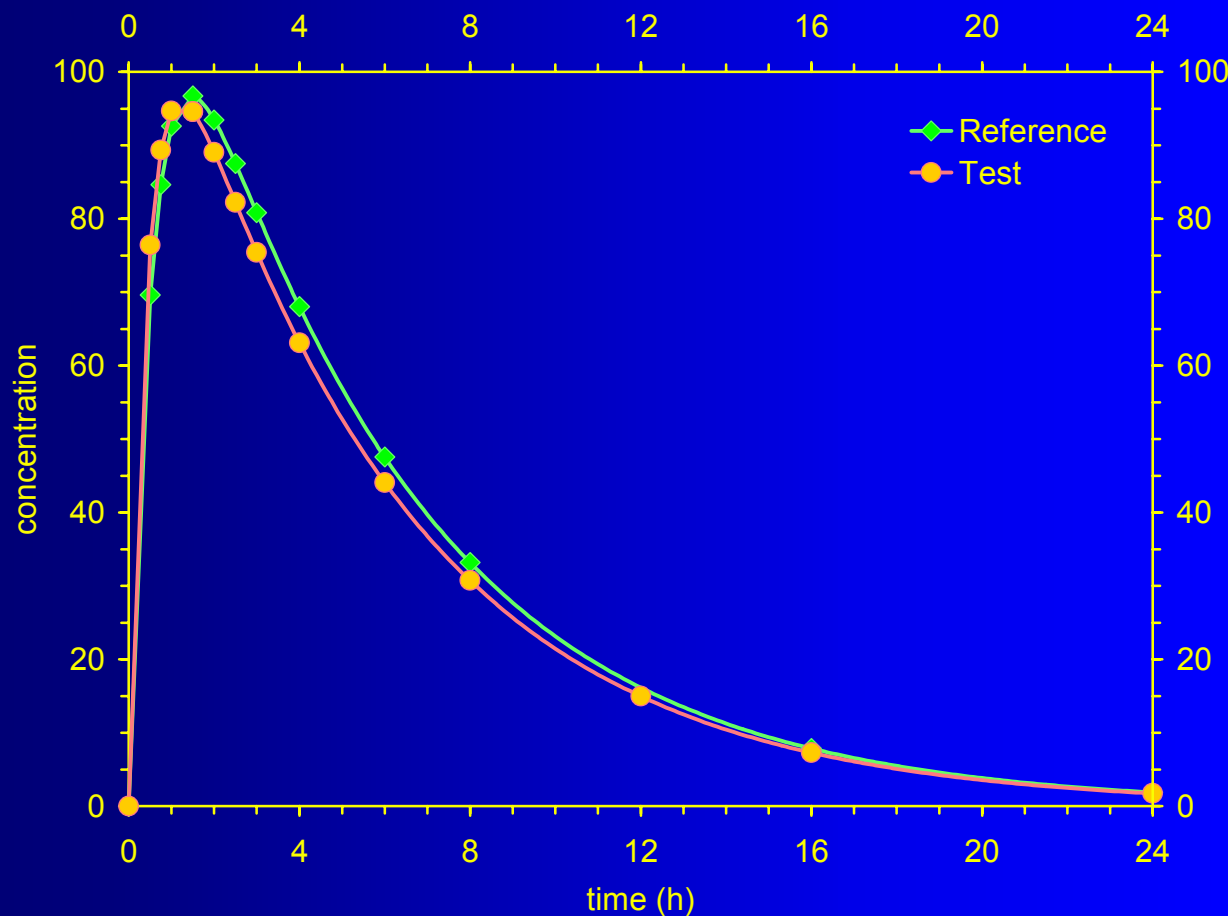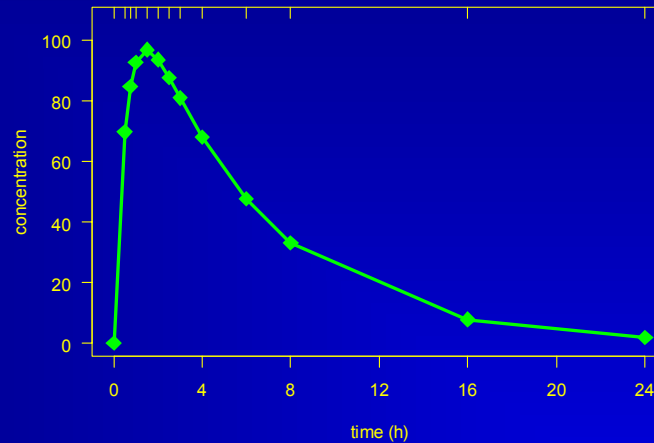
Weired?

Overestimates AUC in the distribution/ elimination phase…
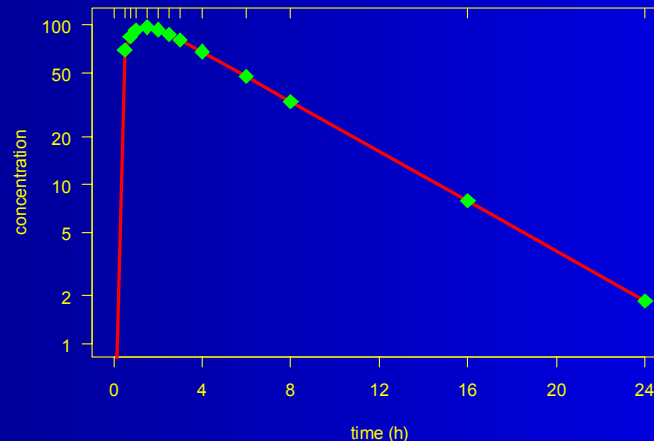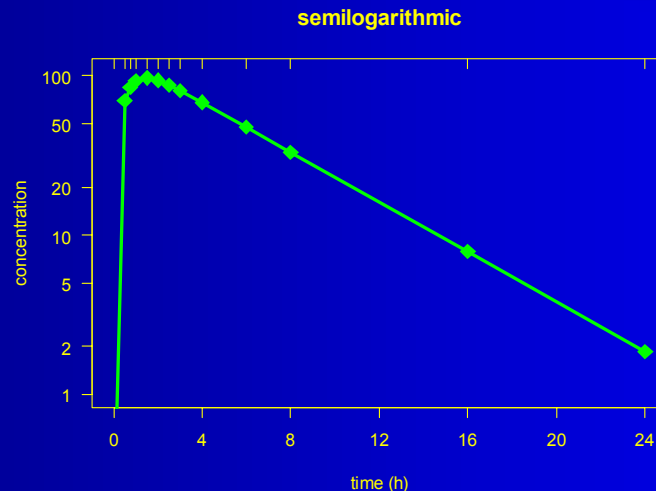
Spaghetti & other pasta

lin-up/log-down

Does the
linear plot
reflect the calcu-
lation of AUC?
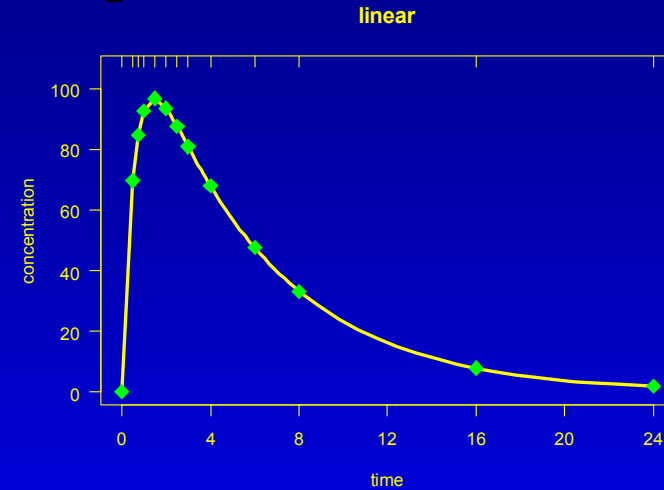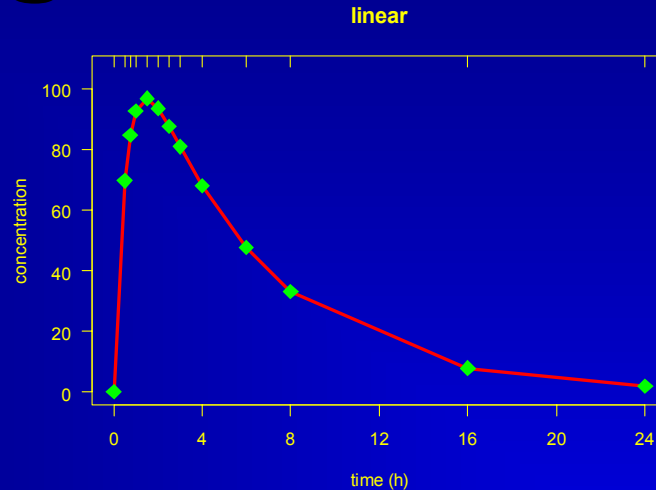
Maybe we should
change the way we
draw spaghetti
plots…

Recommendations

- Don't exclude a subject if only – a few – data points are missing (loss of power)
  - *Only* if linear rule is required for any reason: data imputation
    - Linear within increasing/equal values ($C_{i+1} \geq C_{i-1}$)

$$\hat{C}_i = C_{i-1} + \left| \frac{t_i - t_{i-1}}{t_{i+1} - t_{i-1}} \right| \left(C_{i+1} - C_{i-1} \right)$$

    - Log-linear within decreasing values ($C_{i+1} < C_{i-1}$)

$$\hat{C}_i = e^{\ln C_{i-1} + \left| \frac{t_i - t_{i-1}}{t_{i+1} - t_{i-1}} \right| \ln \left(C_{i-1}/C_{i+1} \right)}$$

Recommendations

- Don't exclude a subject … (cont'd)
    - Although I had never problems with this procedure in 500+ BE studies (stated in the protocol, according to SOP, and by validated software) data imputation may be unfamiliar to assessors
    - Lin-up/log-down trapezoidal not affected by missing values and unbiased estimates are obtained

NCA: AUC Extrapolation

- $AUC_{0-\infty}$

  - Unweighted log-linear regression of ≥ 3 data points in the elimination phase

  - Extrapolation from AUC_{0-t} (regardless the method)

$$AUC_{\infty} = AUC_{t} + \frac{C_t}{\hat{\lambda}_z}$$ or better $$AUC_{\infty} = AUC_{t} + \frac{\hat{C}_t}{\hat{\lambda}_z}$$

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NCA: AUC Extrapolation

- **Single dose only!**
  - Method of estimation of λ_z stated in protocol!
    - One-compartment model: 'TTT'–method[*]
      (Two times t_{max} to t_z)
    - Maximum adjusted R^2 (Phoenix/WinNonlin, Kinetica)

      $$R^2_{adj} = 1 - \frac{(1 - R^2) \cdot (n - 1)}{n - 2}$$

      WinNonlin $\leq$5.3: C_{max} included
      Phoenix/WNL $\geq$6.0: C_{max} excluded

    - Multi-compartment models: starting point = last inflection
    - Minimum AIC: $AIC = n \cdot \left[\ln(2 \cdot \pi) + 1\right] + n \cdot \ln(RSS/n) + 2 \cdot p$
    - Visual inspection of fit mandatory!

    [*] **Scheerans C, Derendorf H, and C Kloft**
    Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs
    Biopharm Drug Dispos 29, 145–57 (2008)

NCA: AUC Extrapolation

● $AUC_{0-\infty}$

■ EMA (and all countires except US and Russia):
No primary PK metric; but demonstrates that AUC_{0-t}
is a reliable estimate of extent of absorption
(*i.e.*, extrapolated area $\leq$ 20% of $AUC_{0-\infty}$)

■ FDA: Primary PK metric (*additionally* to AUC_{0-t})

■ What if extrapolated $AUC_{0-t} >$ 20% of $AUC_{0-\infty}$ in some subjects?

■ EMA: Subjects should not be excluded, but requires discussion if observed in > 20% of cases

■ Russia: Use $AUC_{0-\infty}$ *instead* of AUC_{0-t} as primary metric of the study

NCA: AUC Extrapolation

plasma profile (linear scale)

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NCA: AUC Extrapolation

plasma profile (semilogarithmic scale)

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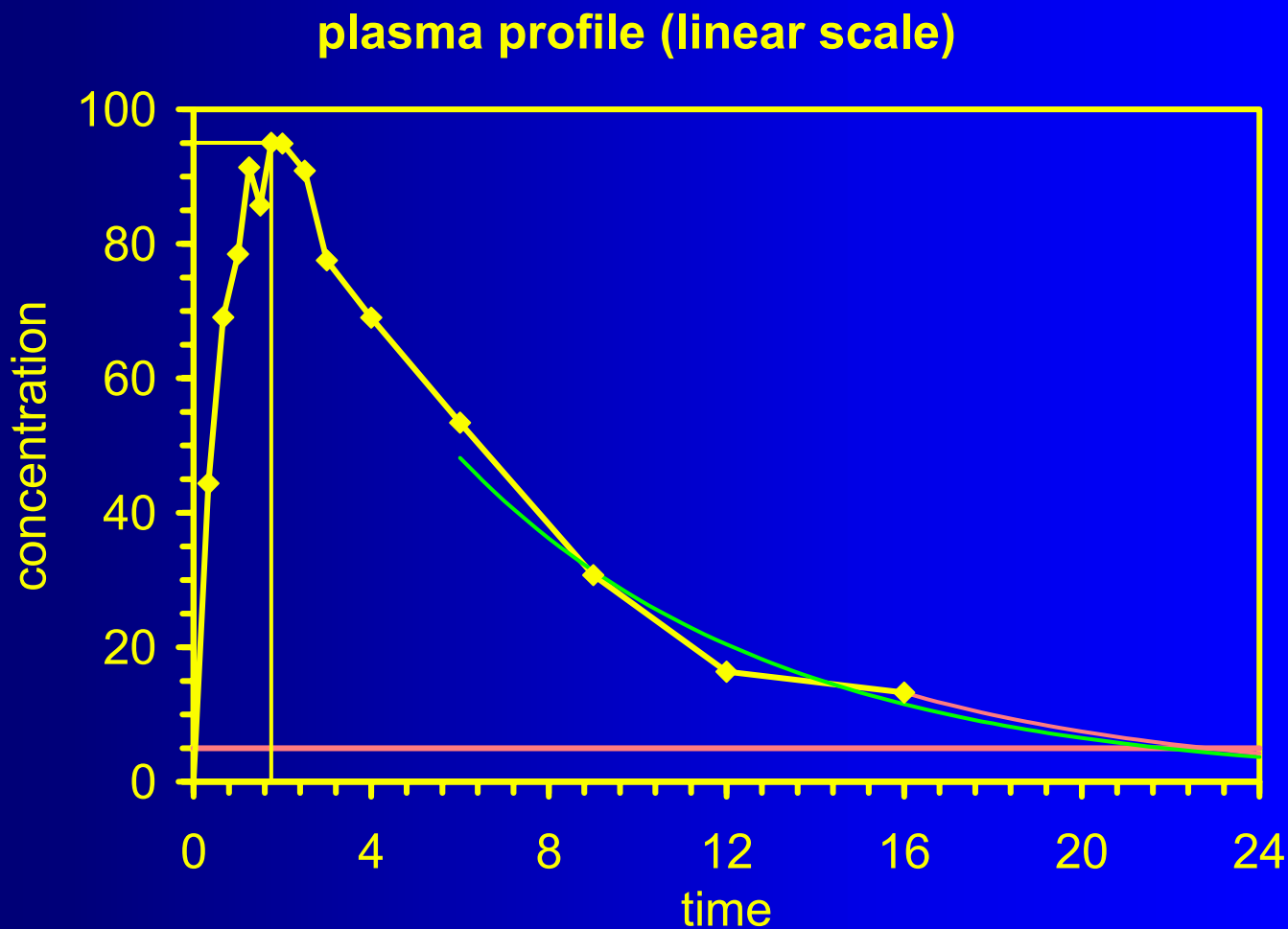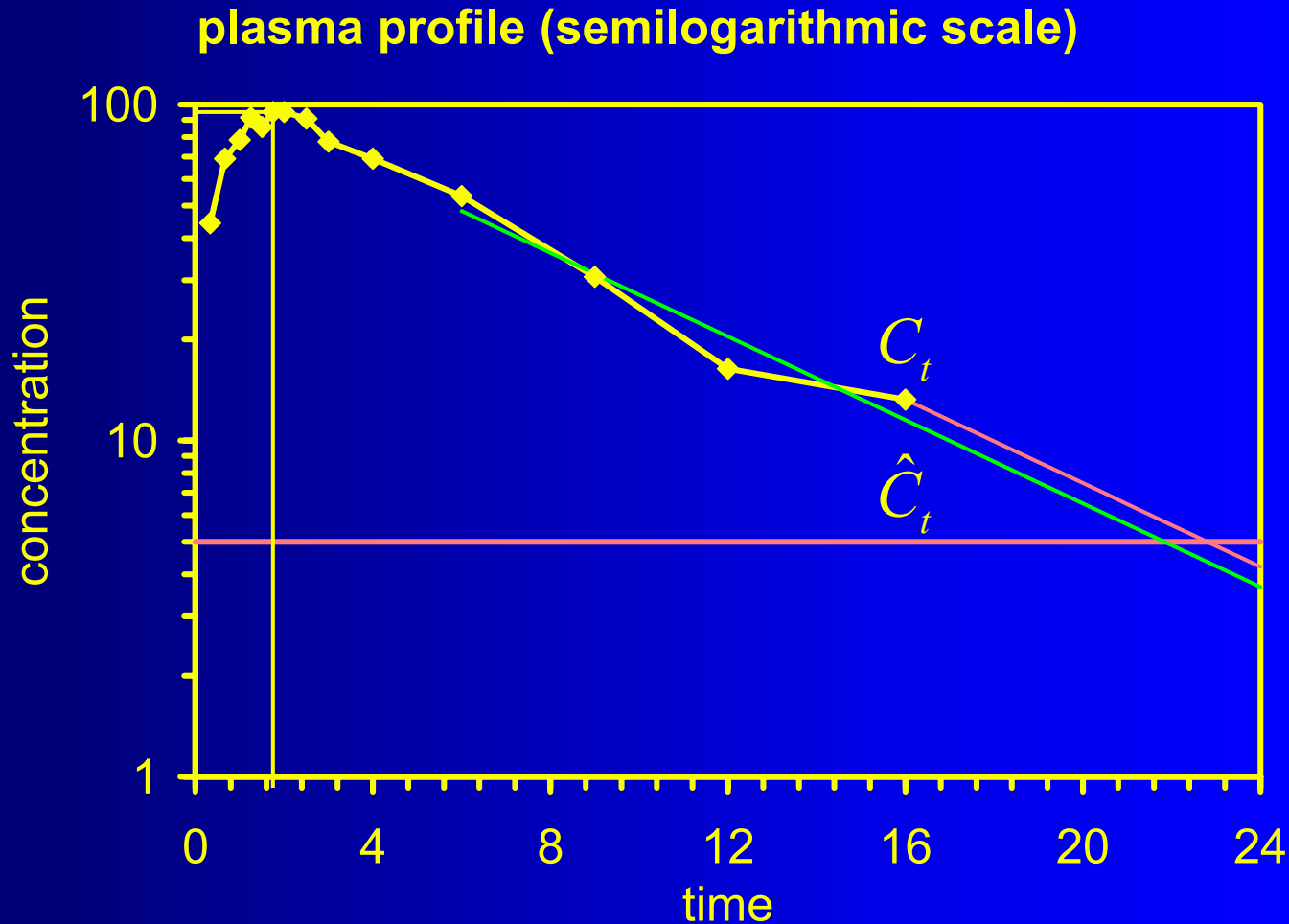
NCA: other PK Metrics

- Single dose
  - C_{max} and t_{max} directly from profile
  - Metrics describing the shape of the profile
    - Early exposure (US, CAN): AUC_{tmax} = $pAUC$ truncated at population (CAN: subject's) t_{max} of the reference
    - Biphasic MR formulations: $pAUCs$ truncated at a prespeci-fied cut-off time point
      - FDA: Product specific guidances (methylphenidate, zolpidem)
      - EMA: All products
        Questions & Answers: positions on specific questions addressed to the pharmacokinetics working party
        EMA/618604/2008 Rev. 4 (16 February 2012)
        http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002963.pdf

NCA: other PK Metrics

- Single dose
  - Metrics describing the shape of the profile
    - C_{max}/AUC
    - $t_{75\%}$ (Plateau time: interval where $C(t) \geq 75\%$ of C_{max})*
    - HVD (Half value duration: time interval where $C(t) \geq 50\%$ of C_{max})
    - Occupancy time, $t \geq MIC$ (time interval where $C(t)$ is above some limiting concentration)

* Russia: mandatory for sustained release formulations

NCA: Urine

- Noncompartmental methods (cont'd)
  - Extent of absorption (EU…), total exposure (US): Ae_t (cumulative amount excreted); rarely extrapolated to $t = \infty$
  - Rate of absorption, peak exposure (US): ΔAe_{max}, $t\Delta Ae_{max}$
  - EMA: C_{max}, t_{max} from plasma!

NCA (Methods)

- Multiple dose

  - Calculation of AUC_τ (dosage interval τ); $AUC_{ss,24h}$ if more than *o.a.d.* and chrono-pharmacological variation)

  - No extrapolation!

  - $C_{ss,max}$ and $C_{ss,min}$ directly from profile

  - Peak-Trough-Fluctuation: $(C_{ss,max} - C_{ss,min}) / C_{ss,av}$, where $C_{ss,av} = AUC_\tau / \tau$

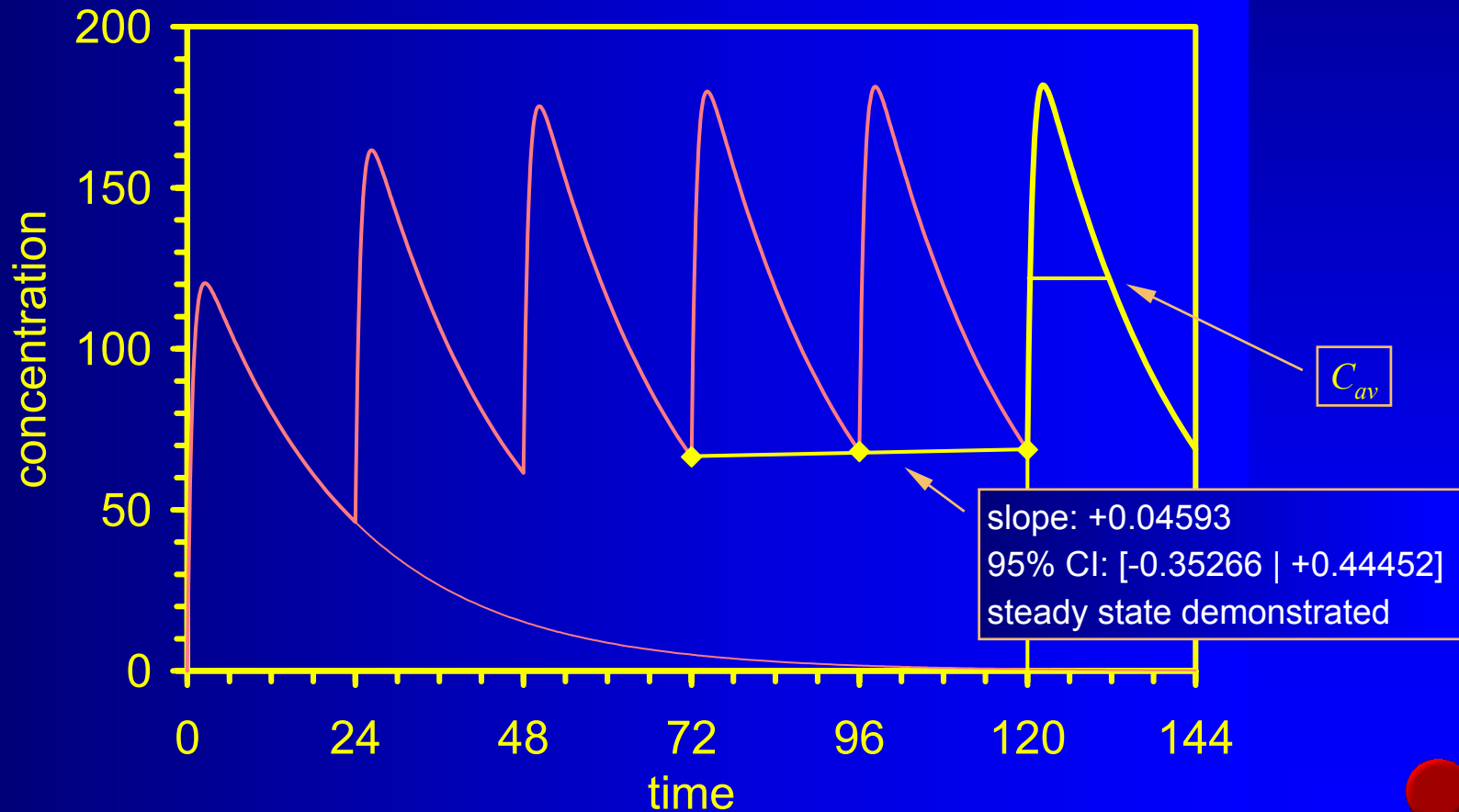 - Swing: $(C_{ss,max} - C_{ss,min}) / C_{ss,min}$

NCA (Methods)

- Multiple dose
  - Assessment whether steady state is reached (in a linear PK system: $AUC_\tau = AUC_\infty$)
    - No recommendations in GLs (except EU/US Veterinary)
    - Not required according to comments to EMA's BE-GL
    - MANOVA-model (sometimes in CAN, rarely used)
    - t-test of last two pre-dose concentrations
    - Hotelling's T^2
    - Linear regression of last three pre-dose concentrations, individually for each subject/treatment
  - Only the last method allows the exclusion of subjects being not in stead state. Other methods give only a yes|no result!

NCA (Methods)

plasma profile (linear scale)

C_{av}

slope: +0.04593
95% CI: [-0.35266 | +0.44452]
steady state demonstrated

concentration vs. time

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NCA (Problems)

- C_{min}

  - Defined by EMA as the concentration (C_{trough}) *at the end* of the dosing interval τ
  - Not implemented in PK software: C_{min} global minimum concentration. Requires adaption.
  - More variable than C_{max} (if little accumulation close to LLOQ)
  - EMA requires pre-dose sampling at $\leq$–5 min and sampling at τ ±10 min
  - Common in *o.a.d.* MD studies last sample at 23:55 in period 1 and at 24:00 in period 2…

NCA (Problems)

- Missing last samples may lead to *'Apples-and-Oranges' statistics* (biased treatment effect)
- If a reliable estimate of λ_z is possible ($\geq$3 data points), we can use an estimate
  - $\pm$ shift of C_z according to λ_z*

$$\hat{C}_{ss,min} = C_z e^{-\hat{\lambda}_z (\tau - t_z)} \quad (1)$$

  - or independent from measured C_z

$$\hat{C}_{ss,min} = e^{\left(\hat{C}_0 - \hat{\lambda}_z \cdot (t_0 + \tau) \right)} \quad (2)$$
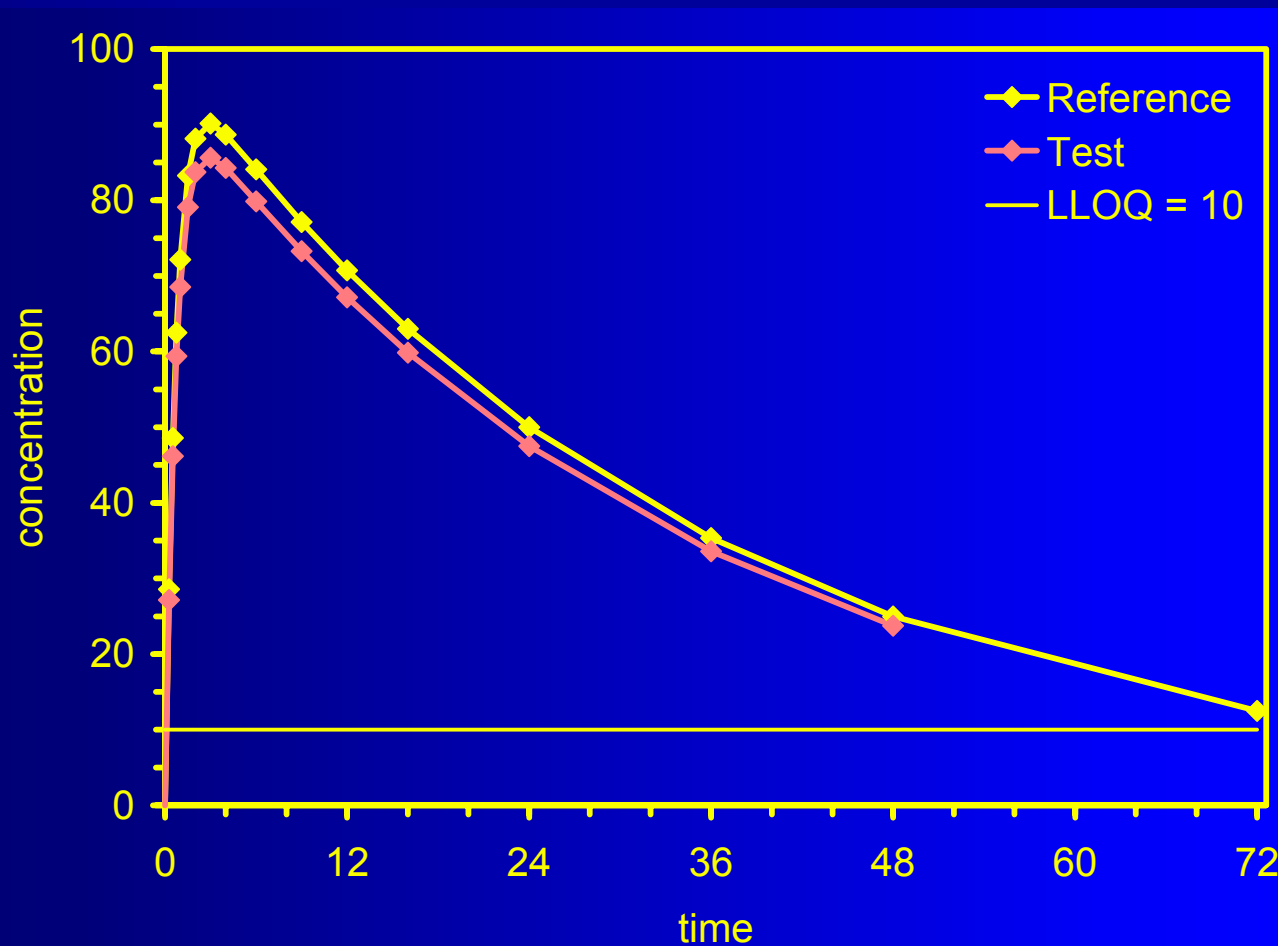
* **Gabrielsson J and D Weiner**
Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts and Applications
Swedish Pharmaceutical Press, Stockholm, p163 (4th ed. 2006)

NCA (Problems)

- Missing values I

    - Procedure for imputation must be stated in the protocol; recommended:

        - in the absorption phase ($t < t_{max}$) by linear Interpolation of adjacent values

        - in the distribution/elimination phase ($t \geq t_{max}$) by log/linear Interpolation of adjacent values

        - imputed value must not be used in estimating λ_z!

    - Don't rely on softwares' defaults!

        - Phoenix/WinNonlin interpolates linear – unless the lin-up/log-down trapezoidal method is used

        - Kinetica interpolates lin/log within descending values

NCA (Problems)

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NCA (Problems)

- Missing values II
  - Last value of T missing (*e.g.*, vial broken)
    - AUC_{tlast} (48) T = 2407
      AUC_{tlast} (72) R = 2984
        T/R = 80.67% biased!
    - Using AUC to t where $C \geq$ LLOQ for both formulations (48)
      AUC_{48} T = 2534
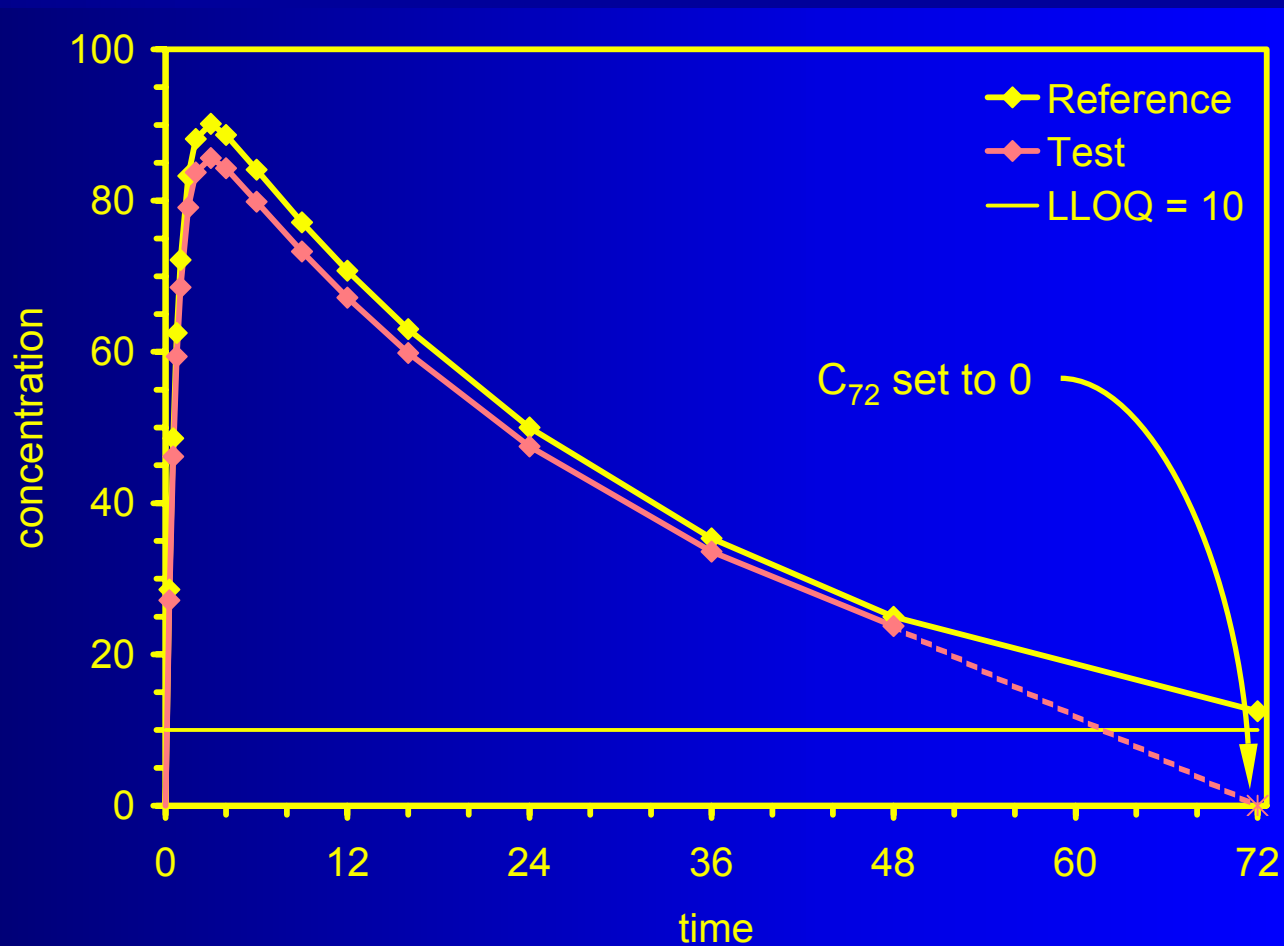 AUC_{48} R = 2407
        T/R = 95% ✓
      - ➢ Not available in software
      - ➢ Regulatory acceptance?

time	Reference		Test	
	conc	AUC_{0-t}	conc	AUC_{0-t}
0	BLQ	0	BLQ	0
0.25	28.57	4	27.14	3
0.50	48.57	13	46.14	13
0.75	62.50	27	59.38	26
1.00	72.15	44	68.55	42
1.5	83.26	83	79.10	79
2	88.14	126	83.73	119
3	90.14	215	85.63	204
4	88.70	304	84.26	289
6	84.07	477	79.86	453
9	77.11	719	73.25	683
12	70.71	940	67.18	893
16	63.00	1208	59.85	1147
24	50.00	1660	47.50	1577
36	35.36	2172	33.59	2063
48	25.00	**2534**	23.75	**2407**
72	12.50	**2984**	Missing	NA

NCA (Problems)

NCA (Problems)

- Missing values II
  - Last value of T missing (*e.g.*, vial broken)
    - Setting the first concentration in the profile where $C < $ LLOQ to zero. AUC_{all}, 'invented' by Pharsight
      AUC_{all} (72) T = 2692
      AUC_{all} (72) R = 2984
   T/R = 90.22% biased!
      - Available in Phoenix / WinNonlin, Kinetica
      - Regulatory acceptance?

time	Reference conc	Reference AUC_{0-t}	Test conc	Test AUC_{0-t}
0	BLQ	0	BLQ	0
0.25	28.57	4	27.14	3
0.50	48.57	13	46.14	13
0.75	62.50	27	59.38	26
1.00	72.15	44	68.55	42
1.5	83.26	83	79.10	79
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16	63.00	1208	59.85	1147
24	50.00	1660	47.50	1577
36	35.36	2172	33.59	2063
48	25.00	2534	23.75	2407
72	12.50	**2984**	= *0	**2692**

NCA (Problems)
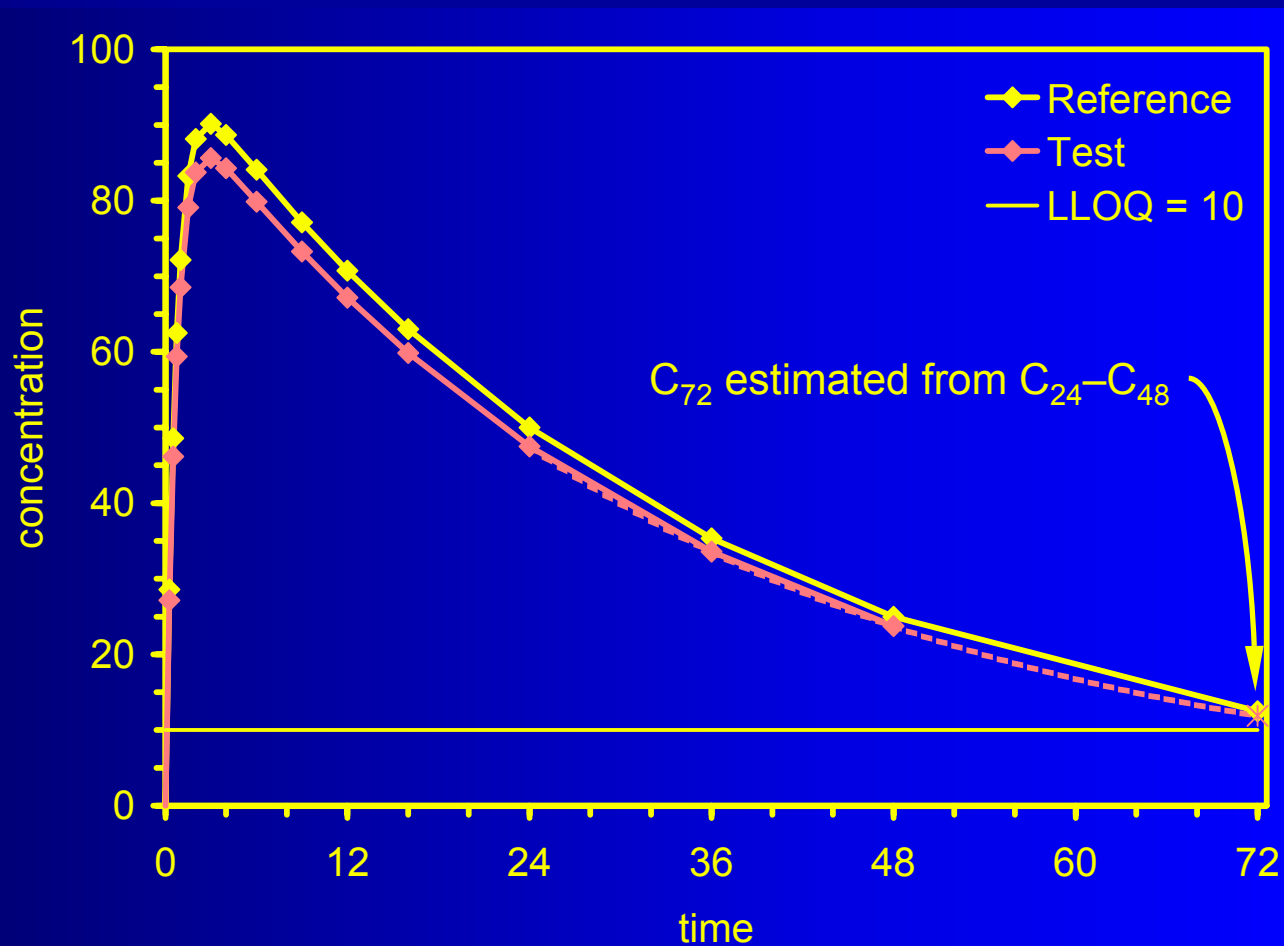
NCA (Problems)

- Missing values II
  - Last value of T missing (*e.g.*, vial broken)
    - Estimating the missing value from elimination phase.

      AUC_{72*} T = 2835

      AUC_{72} R = 2984

      T/R = 95% ✓
      - ➤ Not available in software
      - ➤ Regulatory acceptance ±

time	Reference		Test	
	conc	AUC_{0-t}	conc	AUC_{0-t}
0	BLQ	0	BLQ	0
0.25	28.57	4	27.14	3
0.50	48.57	13	46.14	13
0.75	62.50	27	59.38	26
1.00	72.15	44	68.55	42
1.5	83.26	83	79.10	79
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24	50.00	1660	47.50	1577
36	35.36	2172	33.59	2063
48	25.00	2534	23.75	2407
72	12.50	**2984**	*11.88	***2835**

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NCA (Problems)

- Missing values II
  - Values below the lower limit of quantitation (LLOQ)
    - Example as before, but LLOQ = 12.5 (instead 10)
    AUC_{72}: T = ?, R = 2984
      T/R = ?
    AUC_{48}: T = 2407, R = 2534
      T/R = 95% ✓
    AUC_{all}: T = 2692, R = 2984
      T/R = 90.22% biased!
    AUC_{72*}: T = ?, R = 2984
      T/R = ?

time	Reference		Test	
	conc	AUC_{0-t}	conc	AUC_{0-t}
24	50.00	1660	47.50	1577
36	35.36	2172	33.59	2063
48	25.00	**2534**	23.75	2407
72	12.50	**2984**	BLQ	NA

time	Reference		Test	
	conc	AUC_{0-t}	conc	AUC_{0-t}
24	50.00	1660	47.50	1577
36	35.36	2172	33.59	2063
48	25.00	2534	23.75	2407
72	12.50	**2984**	= *0	**2692**

time	Reference		Test	
	conc	AUC_{0-t}	conc	AUC_{0-t}
24	50.00	1660	47.50	1577
36	35.36	2172	33.59	2063
48	25.00	2534	23.75	2407
72	12.50	**2984**	*11.88	NA

NCA (Problems)

What would *you* do?

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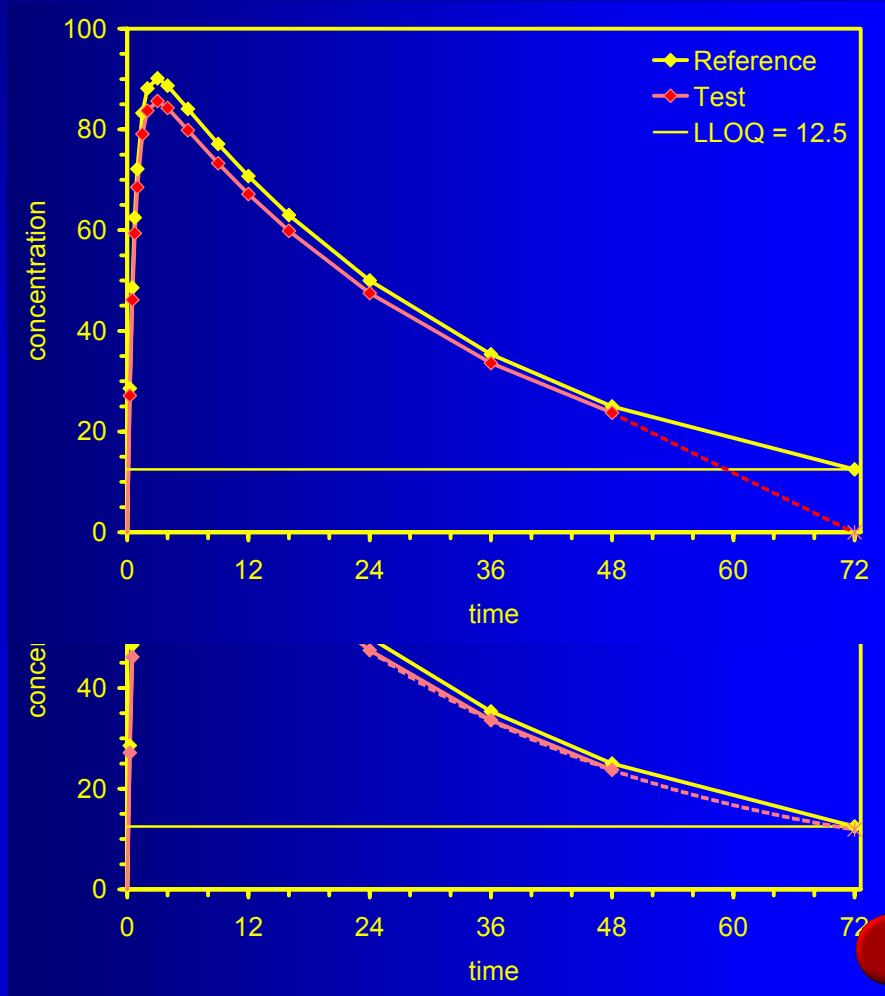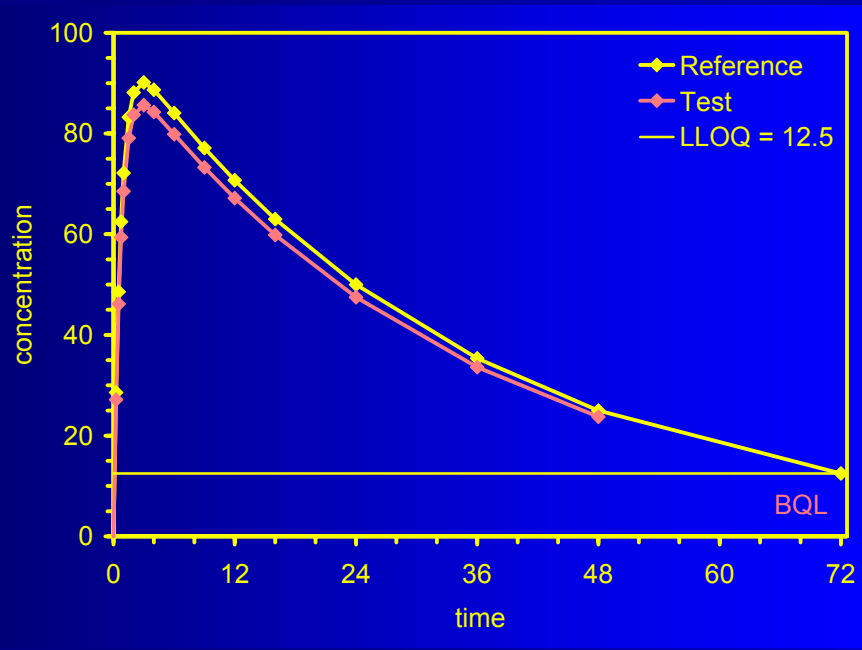
Sampling at C_{max}

- With *any* [*sic*] given sampling scheme the *'true'* C_{max} is missed
  - It is extremely unlikely that we sample *exactly* at the true C_{max} for any given subject
  - High inter- and/or intra-subject variability (single point metric)
  - Variability higher than $AUC's$
  - In many studies the win/loose metric!
  - Try to decrease variability
    - Increase sample size (more subjects)
    - Increase sampling *within* each subject (*maybe* better)

Sampling at C_{max}

- Theoretical values (from PK simulation)
  C_{max}: 41.9/53.5 (81.2%), t_{max}: 6.11/4.02 (Δ 2.09)

  - # samples [2–12h]
    - n = 4
      - C_{max} 78.3%
      - t_{max} Δ 4
    - n = 5
      - C_{max} 78.3%
      - t_{max} Δ 4
    - n = 6
      - C_{max} 79.8%
      - t_{max} Δ 1
    - n = 7
      - C_{max} 81.2%
      - t_{max} Δ 2

Legend: R theoretical, T theoretical, R sampled, T sampled
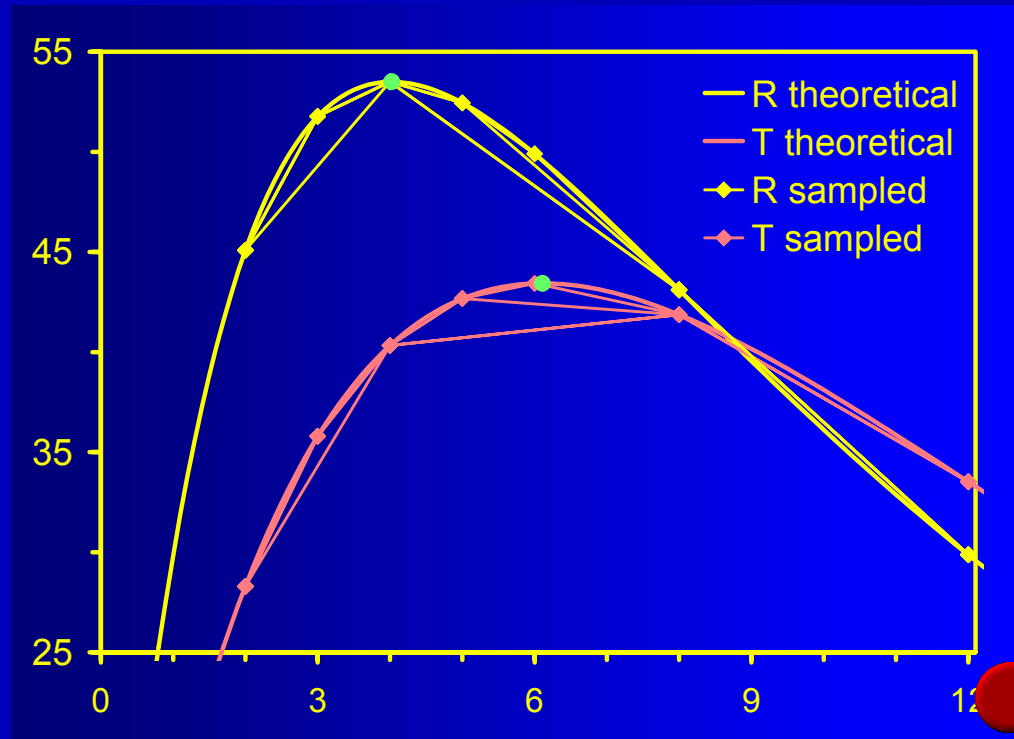
Sampling at C_{max}

- Quote from the literature:

C_{max} *was observed within two to five hours after oral administration…*

  - Elimination is drug specific,

  - but what about absorption?
    - Formulation specific!
    - Dependent on the sampling schedule (in a strict sense study-specific)

Sampling at C_{max}

2–5 hrs

- arithmetic mean
- geometric mean
- median

$k_a = [0.182 \mid 0.260]$

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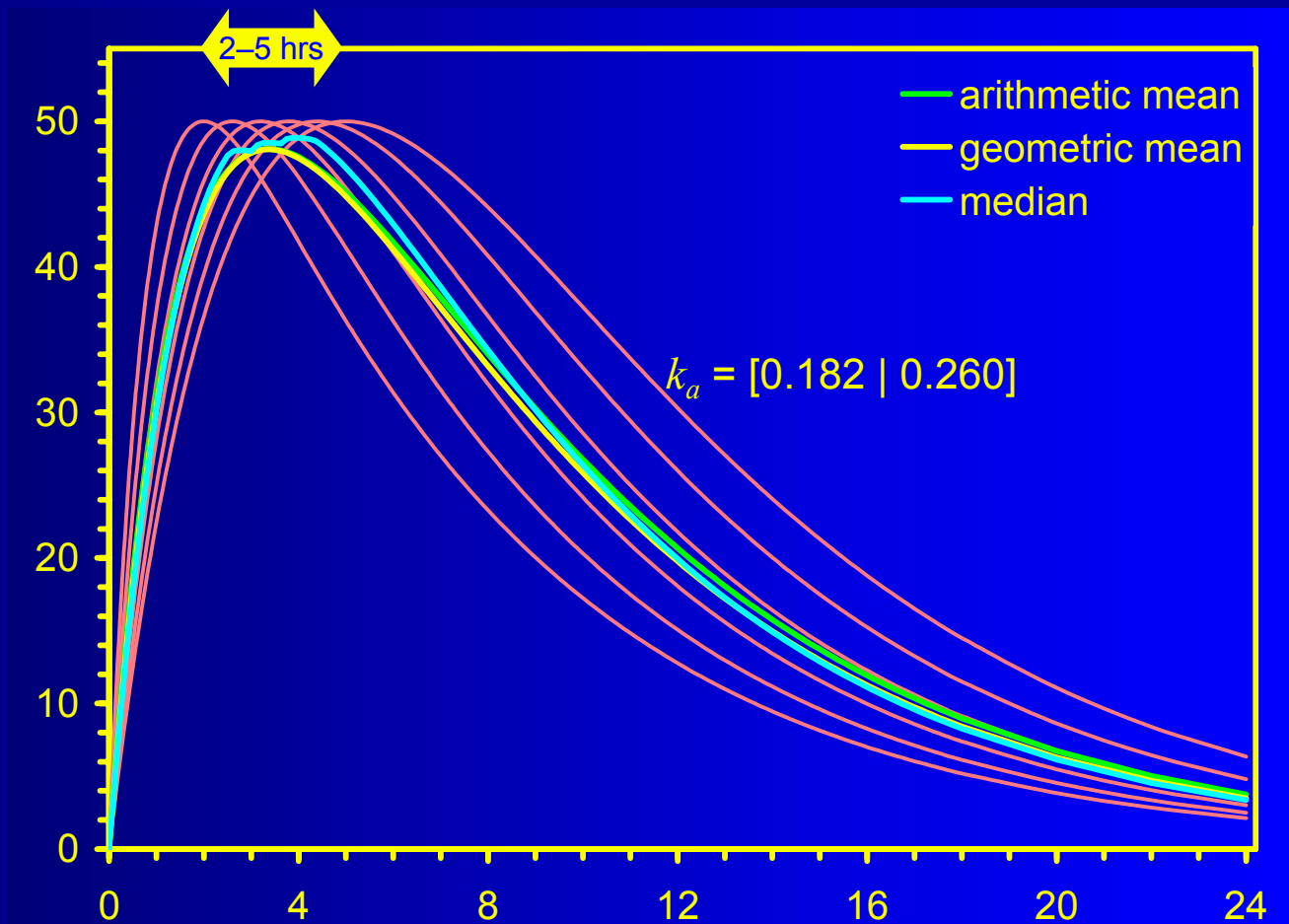
Sampling at C_{max}
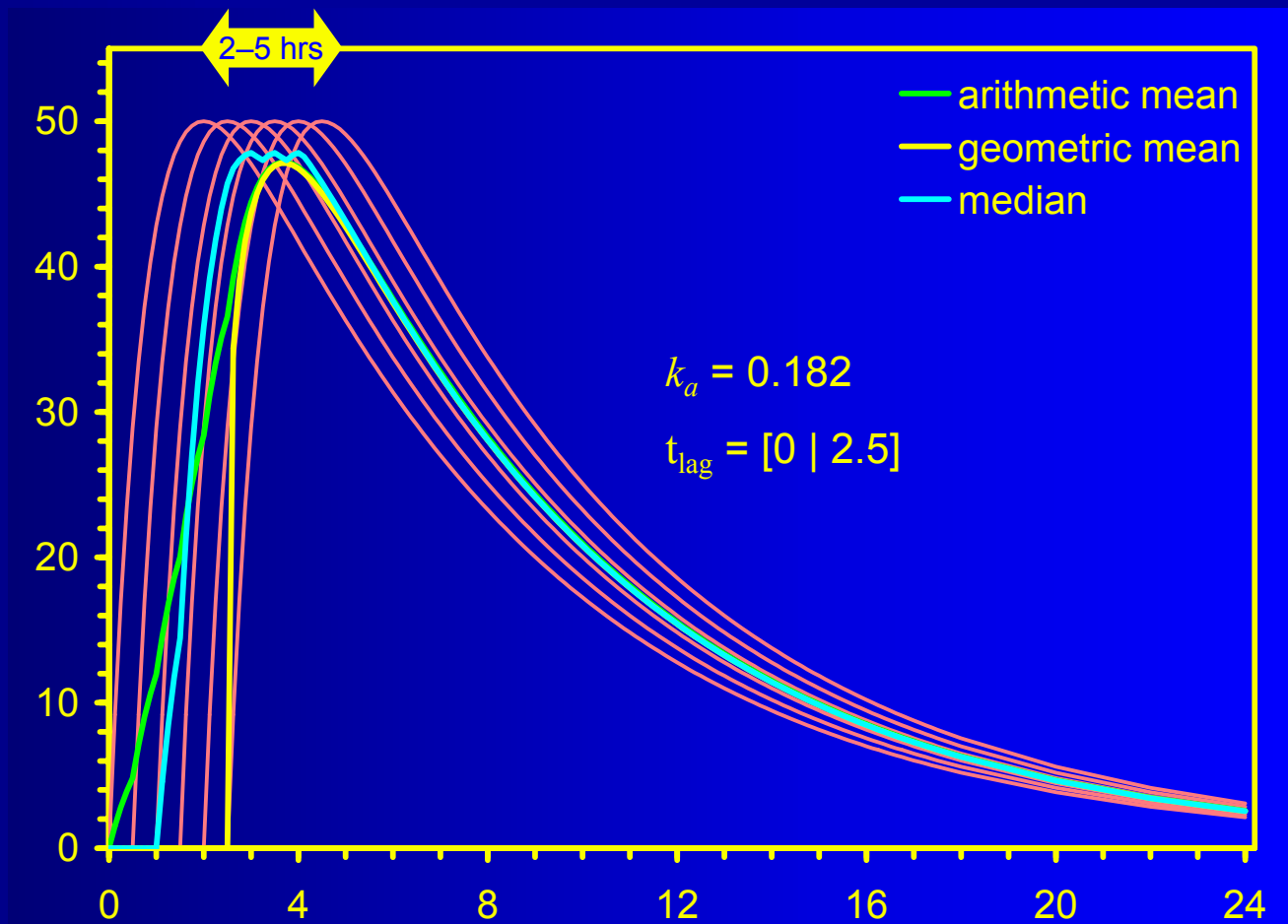
Another Problem

- EMA GL on BE (2010)
  - Section 4.1.8 Reasons for exclusion 1)
    - A subject with lack of any measurable concentrations or only very low plasma concentrations for reference medicinal product. A subject is considered to have very low plasma concentrations if its AUC is less than 5% of reference medicinal product geometric mean AUC (which should be calculated without inclusion of data from the outlying subject). The exclusion of data […] will only be accepted in exceptional cases and may question the validity of the trial.

    Remark: Only possible after unblinding!

Another Problem

- EMA GL on BE (2010)
  - Section 4.1.8 Resons for exclusion 1) cont'd
    - The above can, for immediate release formulations, be the result of subject non-compliance […] and should as far as possible be avoided by mouth check of subjects after intake of study medication to ensure the subjects have swallowed the study medication […]. The samples from subjects excluded from the statistical analysis should still be assayed and the results listed.

Another Problem

- Gastro-resistant (enteric coated) preparations
  - Gastric emptying of single unit dosage forms non-disintegrating in the stomach is prolonged and highly erratic. The consequences of this effect on the enteric coating of delayed release formulations are largely unpredictable.
    - Sampling period should be designed such that measurable concentrations are obtained, taking into consideration not only the half-life of the drug but the possible occurrence of this effect as well. This should reduce the risk of obtaining incomplete concentration-time profiles due to delay to the most possible extent. These effects are highly dependent on individual behaviour.

Another Problem

- Gastro-resistant (enteric coated) preparations
  - Therefore, but only under the conditions that sampling times are designed to identify very delayed absorption and that the incidence of this outlier behaviour is observed with a comparable frequency in both, test and reference products, these incomplete profiles can be excluded from statistical analysis provided that it has been considered in the study protocol.
    EMEA, CHMP (EWP-PK)
    Questions & Answers: positions on specific questions addressed to the pharmacokinetics working party
    EMA/618604/2008 Rev. 4 (16 February 2012)
    http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002963.pdf

    What is *'comparable'*? For a study in 24 subjects, we get a significant difference for 5/0 (Fisher's exact test: p 0.0496).

t_{lag} – a 'nasty' PK Metric

- Only relevant for delayed release (gastric resistant) formulations
- Highly variable – mainly not due to the formulation but the intrinsic variability in gastric emptying
- Less variability for multiparticulate formulations than for monolithic ones, but still problematic
- Sampling schedule difficult to design
- Assessment (descriptive *vs.* nonparametric)?

t_{lag} – a 'nasty' PK Metric

- Little is published about calculation; five methods assessed[*]

- Commercial software (Phoenix/WinNonlin, Kinetica) treat t_{lag} as the time point prior to the first measurable (non-zero) concentration

- Other methods require programming skills; some of them might be judged by assessors already borderline PK models (?!)

[*] **Csizmadia F and L Endrenyi**
Model-Independent Estimation of Lag Times with First-Order Absorption and Disposition
J Pharmaceut Sci 87(5), 608–12 (1998)

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t_{lag} – a 'nasty' PK Metric

- Is t_{lag} *really* clinically relevant – even for formulations where rapid onset of effects is of importance?

- If two formulations follow identical pharmaco-kinetics *except t_{lag}*, this difference is reflected in t_{max} as well (both in SD and MD)

t_{lag} *vs.* t_{max}

- Single dose
  - DR, flip flop PK; V 10, D 100, F 100%, k 0.09902 h^{-1}
    t_{lag} 1 h (R), 4 h (T)
    t_{max} 11.1 h (R), 14.1 h (T)
    C_{max} 3.68 (R&T)
    C_{τ} 2.335 (R), 2.733 (T)
    $AUC_{0-\tau}$ 67.0 (R) 59.4 (T)
    $AUC_{0-\infty}$ 101.0 (R&T)
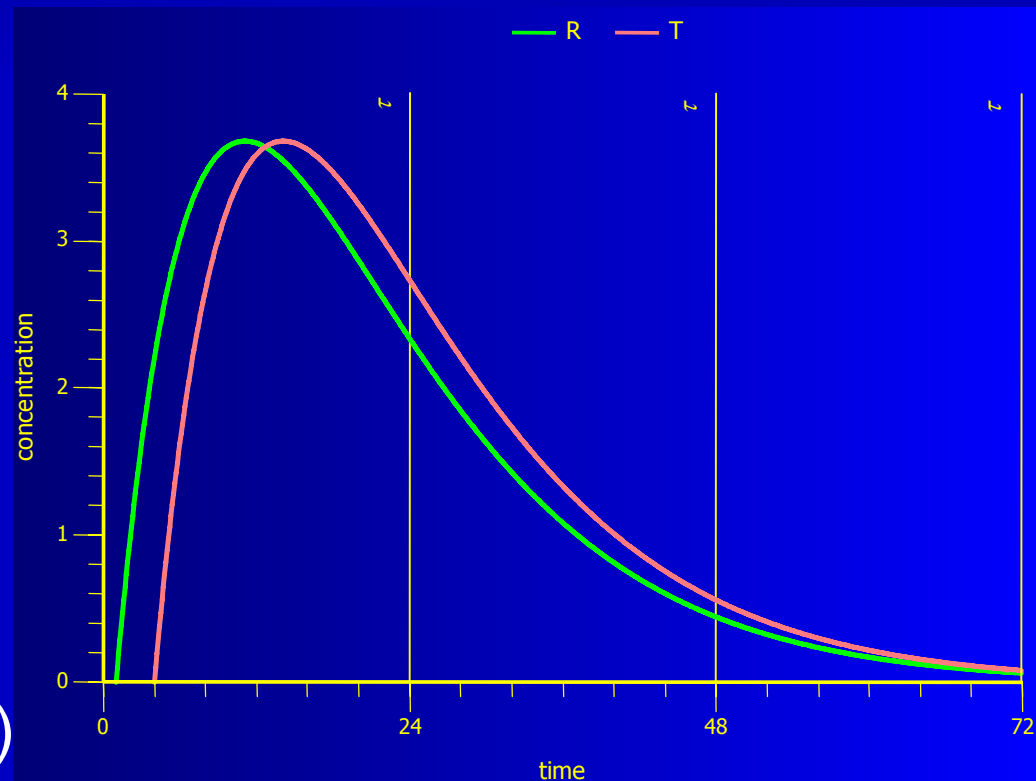
t_{lag} *vs.* t_{max}

- Simulation of steady state (τ 24 h; 6 d $\approx$ 20$\times t_{1/2}$)
 - Formulations differ in t_{lag} only!
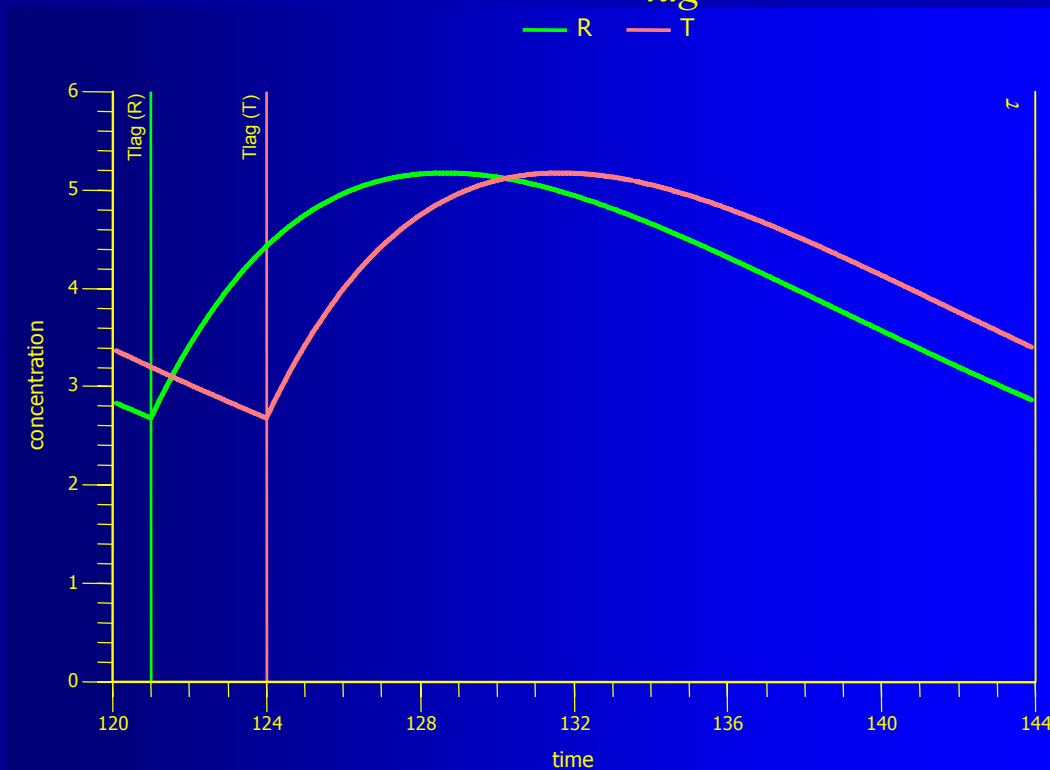
- t_{lag} is discriminatory:

T	4
R	1
T − R	+3

- Might be difficult to measure; frequent sampling required
- Nonparametric statistics (EMA!)

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t_{lag} *vs.* t_{max}

- Simulation of steady state (τ 24 h; 6 d $\approx$ 20×$t_{\frac{1}{2}}$)
  - Formulations differ in t_{lag} only! Surrogate possible?
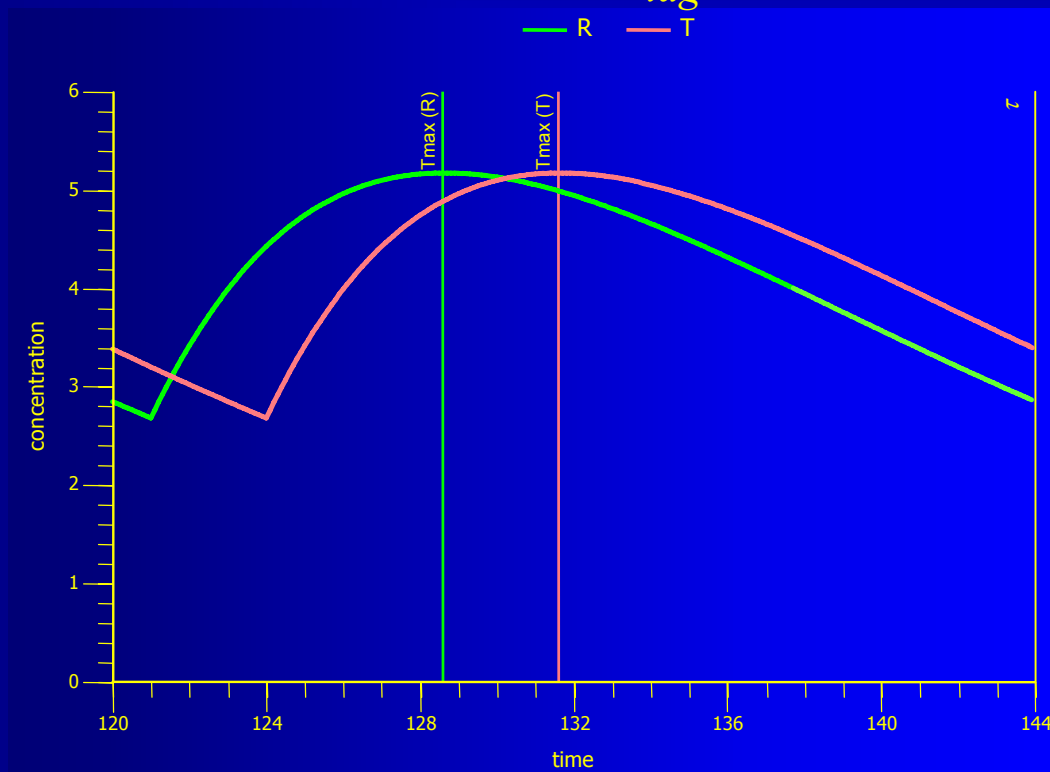

- t_{max} is discriminatory as well:
  T   14.1
  R   11.1
  T – R +3
- Maybe better; frequent sampling in the area of C_{max} common
- Nonparametric statistics (EMA!)

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Case Study (PPI 1)

- Attempt to deal with high variability

Powered to 90% according to CV from previous studies; 140 (!) subjects and to 80% for expected dropout rate. Sampling every 30 min up to 14 hours (7,785 total)

First time C_{max}

$t_{\frac{1}{2}}$ 12 h

t_{max} 15 h, C_{max} 3.5×LLOQ

t_{lag} 6 h

time (h)
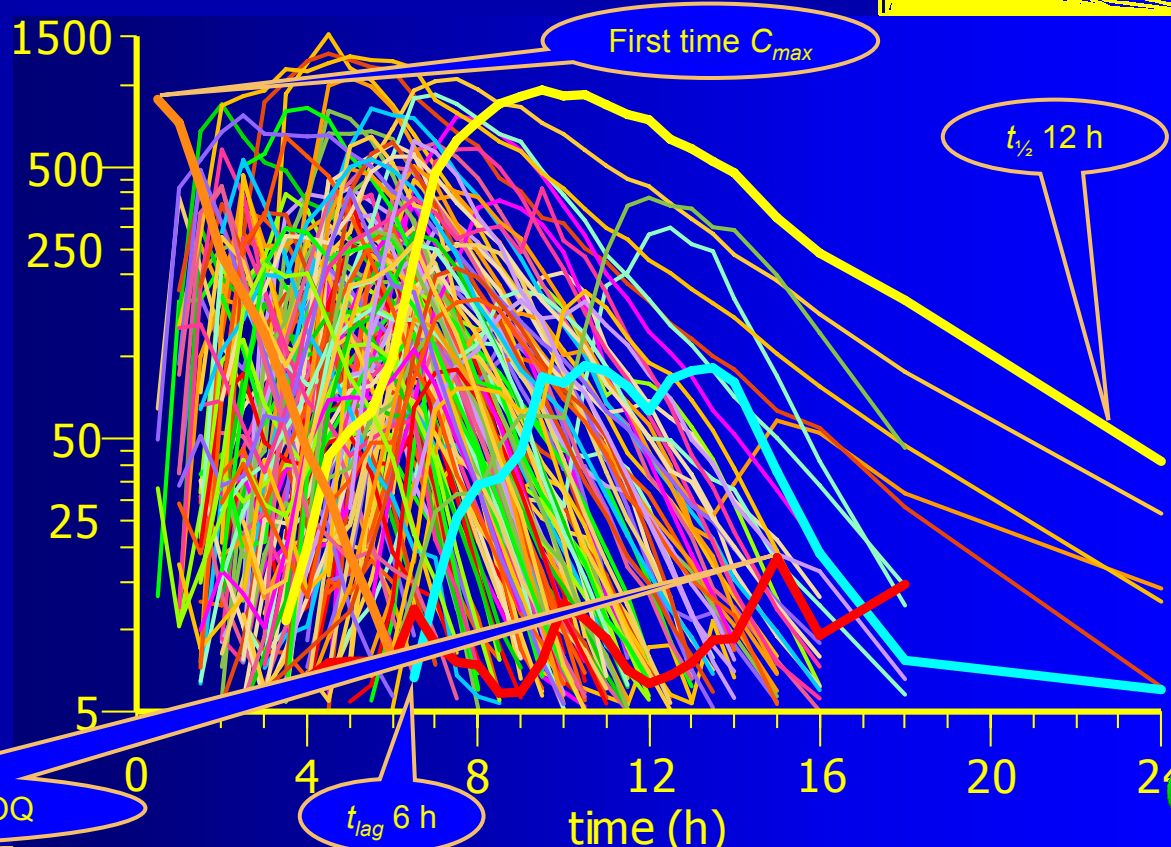
Case Study (PPI 2)

- ## Submission in China

  AUC_t 87.60, 95.53%
  C_{max} 75.39, 91.84%
  t_{max} +0.500, +1.333
  significantly delayed
  (CI does not contain zero)

- ## Company's defending argument:highly variable GI-transit manifested in t_{lag}
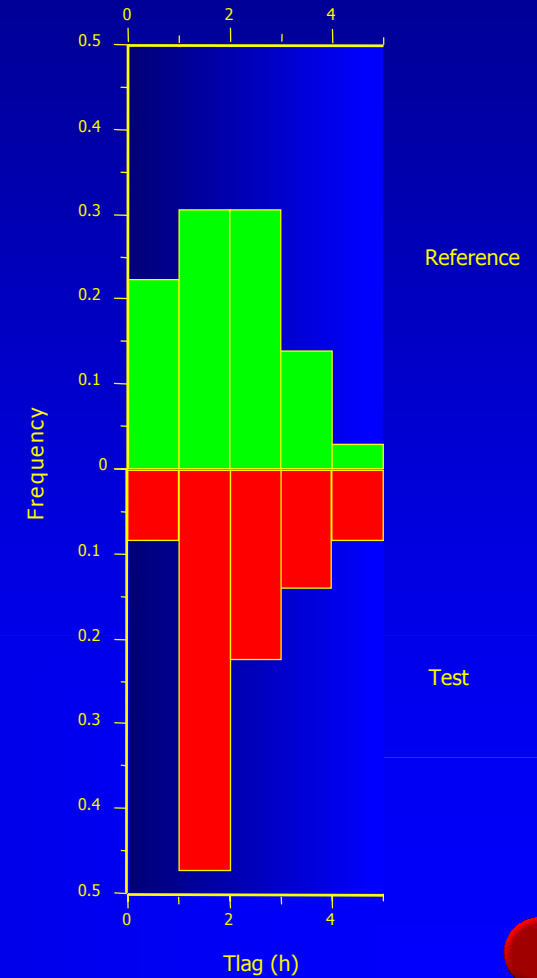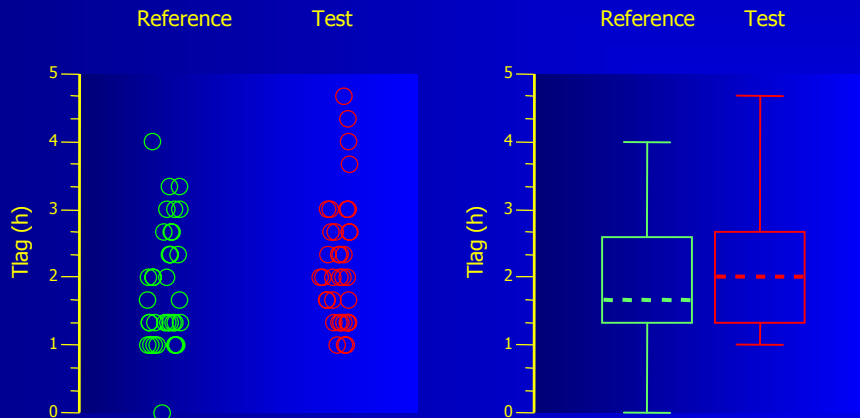
- ## Let's see…

Reference

Test

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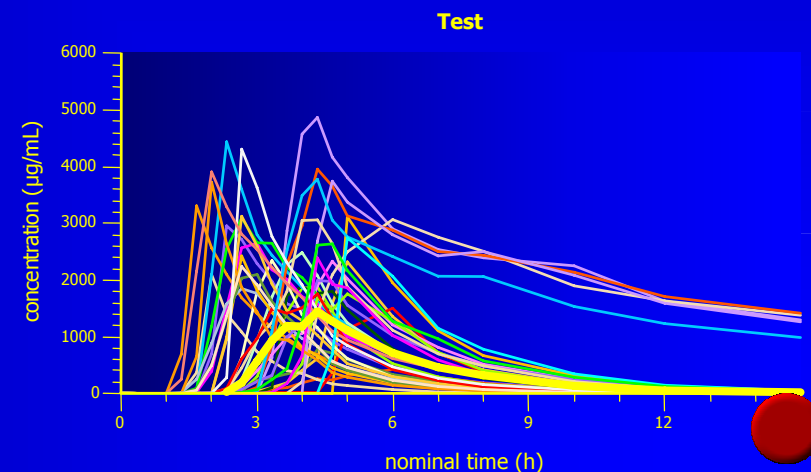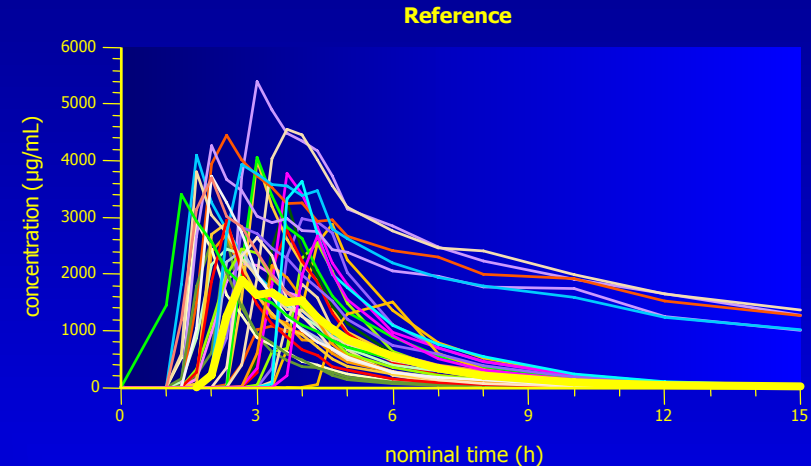
Case Study (PPI 2)

● Analysis

t_{lag} ±0.000, +0.667
not different (but borderline)

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Case Study (PPI 2)

● Analysis

$t_{max}-t_{lag}$ +0.167, +0.667
significantly delayed
(0 not within CI)

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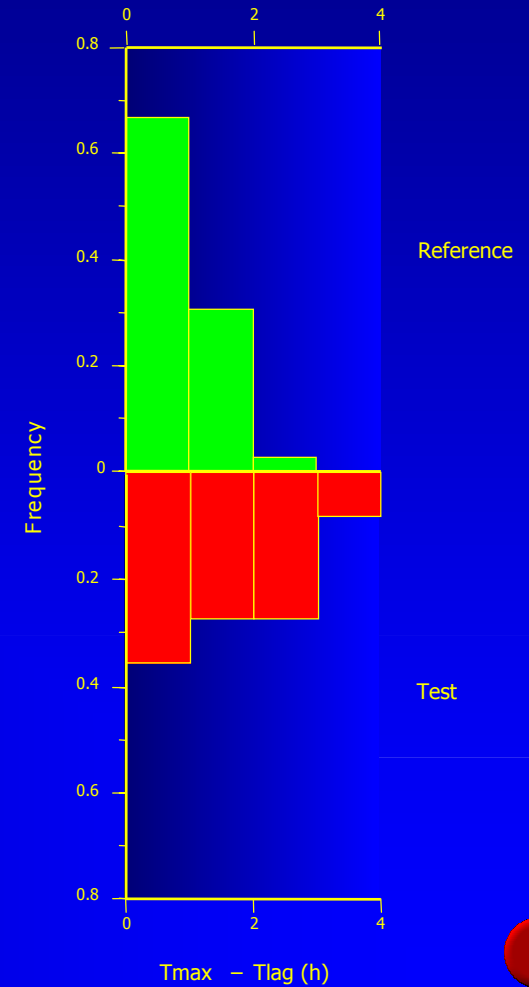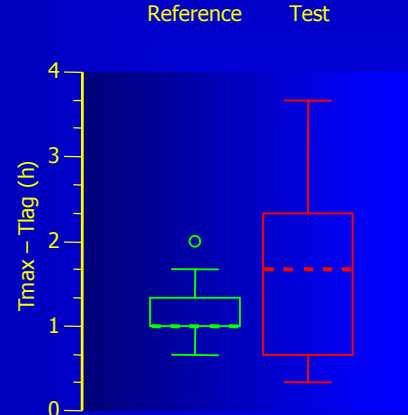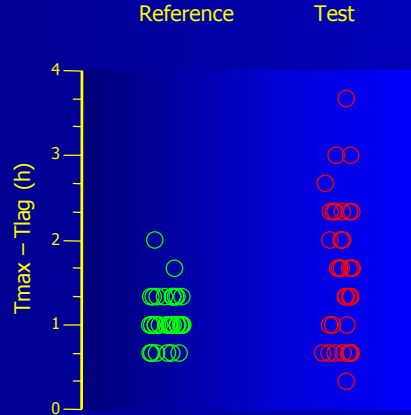
Case Study (PPI 2)

- Assessment
  - Although there was no sig-nificant difference in t_{lag}, the 'corrected' $t_{max}-t_{lag}$ was significantly delayed
  - Variability of the test formulation was higher
  - It seems that the com-pany's assumption does not hold – formulations differ
  - Clinical relevance?

Reference

concentration (µg/mL) vs shifted time (h)

Test

concentration (µg/mL) vs shifted time (h)

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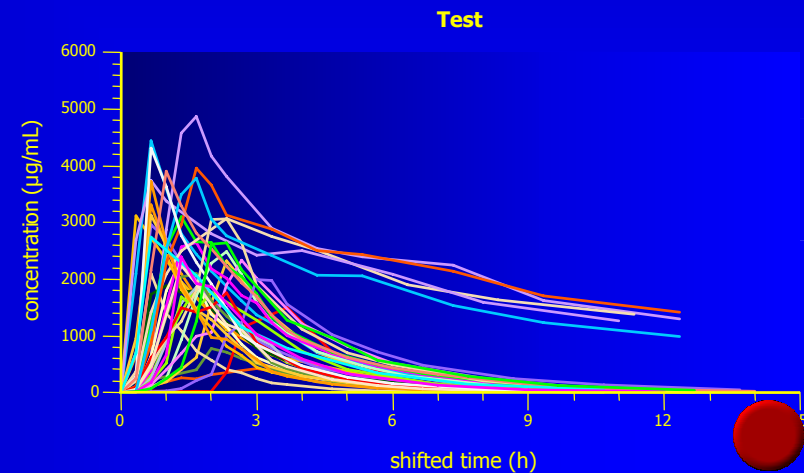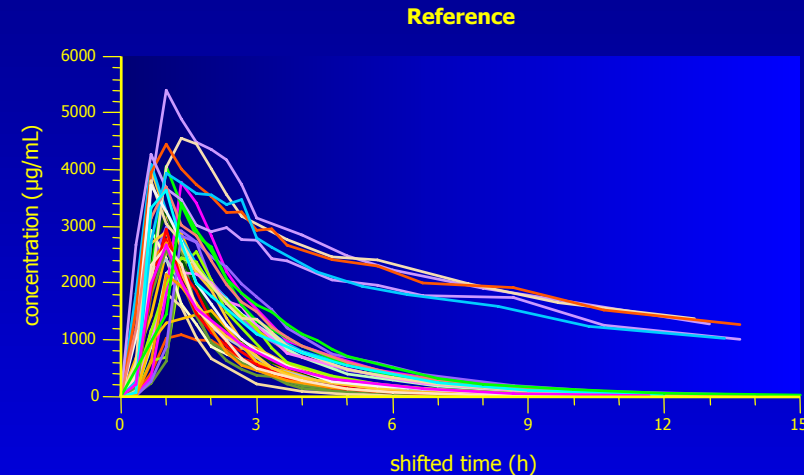
Half lives

- Drug specific, *but*…
  - The *apparent* elimination represents the *slowest* rate constant (controlled release, topicals, transdermals) – not necessarily elimination!
  - Avoid the term 'terminal elimination' – might not be true
  - Important in designing studies
    - To meet $AUC_t \geq 80\% \, AUC_\infty$ criterion
    - To plan sufficiently long wash-out (avoid carry–over)
    - To plan saturation phase for steady state

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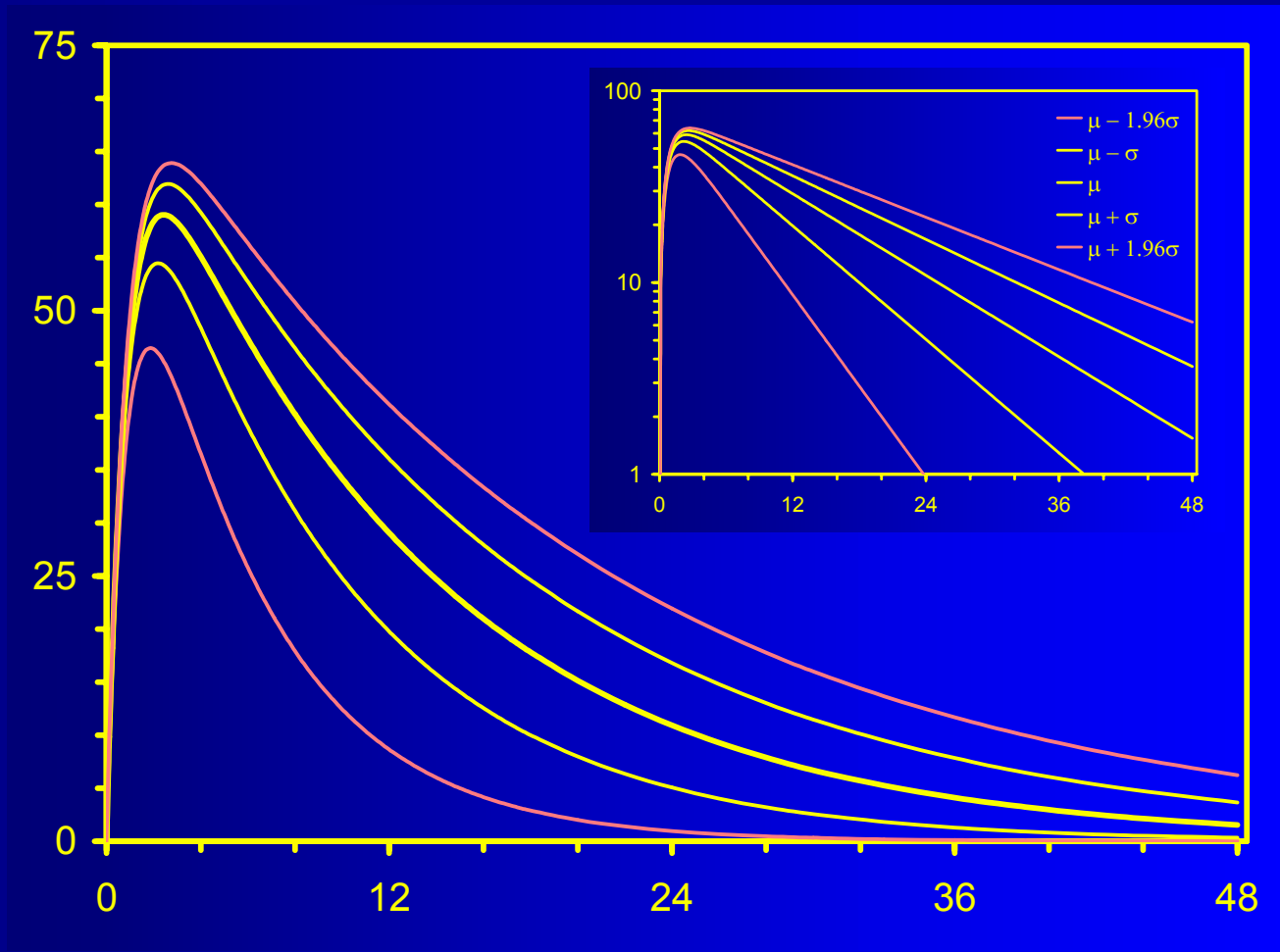**Leuven, 5–6 June, 2013**

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Half lives

- Dealing with literature data
  - What if only mean ±SD is given?
    - Assuming normal distribution:
      $\mu \pm \sigma$ covers 68.27% of values (15.87% of values are expected to lie outside of $\mu \pm \sigma$)
    - Example: 8.5 ± 2.4 hours, 36 subjects.
      0.1587 × 36 = 5.71 or in at least five subjects we may expect a half life of > 10.9 hours.
    - Plan for 95% coverage ($z_{0.95}$ = 1.96): $p_{0.95} = \mu \pm z_{0.95} \times \sigma$
      8.5 ± 1.96 × 2.4 = [3.80, 13.2] hours.
      We may expect a half life of >13.2 hours in ~one subject (0.05/2 × 36 = 0.90).

Half lives

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Thank You!
# Pharmacokinetic Analysis of BE Data
Open Questions?

Helmut Schütz
BEBAC
Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria
helmut.schuetz@bebac.at

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To bear in Remembrance...

The fundamental cause of trouble in the world today is that the stupid are cocksure
while the intelligent are full of doubt.   *Bertrand Russell*
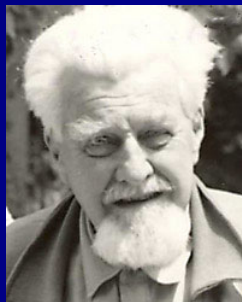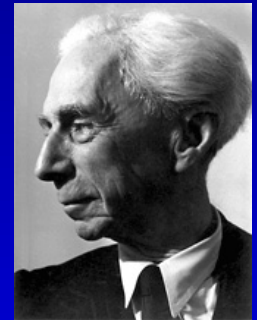
It is a good morning exercise for a research scientist to discard a pet hypothesis every day before breakfast.
It keeps him young.   *Konrad Lorenz*

If you shut your door to all errors
truth will be shut out.

Rabindranath Tagore