Noncompartmental Analysis (NCA) in PK, PK-based Design

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Main Topics

- NCA *vs.* PK Modeling
- PK metrics derived by NCA
- Methods (single dose *vs.* steady state)
- Common problems
- Pitfalls

NCA *vs.* PK Modeling

- Noncompartmental methods do not rely on a pharmacokinetic model
  - Metrics (plasma)
    - 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 (EU BE Draft 2008, US): AUC_{tmax}; partial AUC truncated at population t_{max} of the reference
    - Others: C_{min}, Fluctuation, MRT, Occupancy time, t_{lag},…

NCA *vs.* PK Modeling

- Noncompartmental methods (cont'd)
  - Metrics (urine)
    - Extent of absorption (EU…), total exposure (US): Ae (cumulative amount excreted):
    - Rate of absorption (EU…), peak exposure (US): ΔAe_{max}
    - $t\Delta Ae_{max}$ (?)

NCA *vs.* PK Modeling

- Pharmacokinetic models
  - Useful for understanding the drug/formulation
    - If limited samples are available (phase II, paediatrics)
    - Study design of BA/BE!
  - 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 pieces of software (sometimes even different versions of the same software)
    - Not acceptable for evaluation of BA/BE studies

NCA

- Single dose
  - Calculation of Moments of Curve (AUC_t, MRT_t)
    - Linear trapezoidal rule, loglinear trapezoidal rule, or combination (lin-up, log-down).
  - Calculation of half life ($t_{½}$) from elimination rate (λ_z)
    - (Unweighted) log-linear regression
  - If necessary (US…) extrapolation from time point of last quantified concentration to infinity

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

  - C_{max} / t_{max} directly from profile

NCA

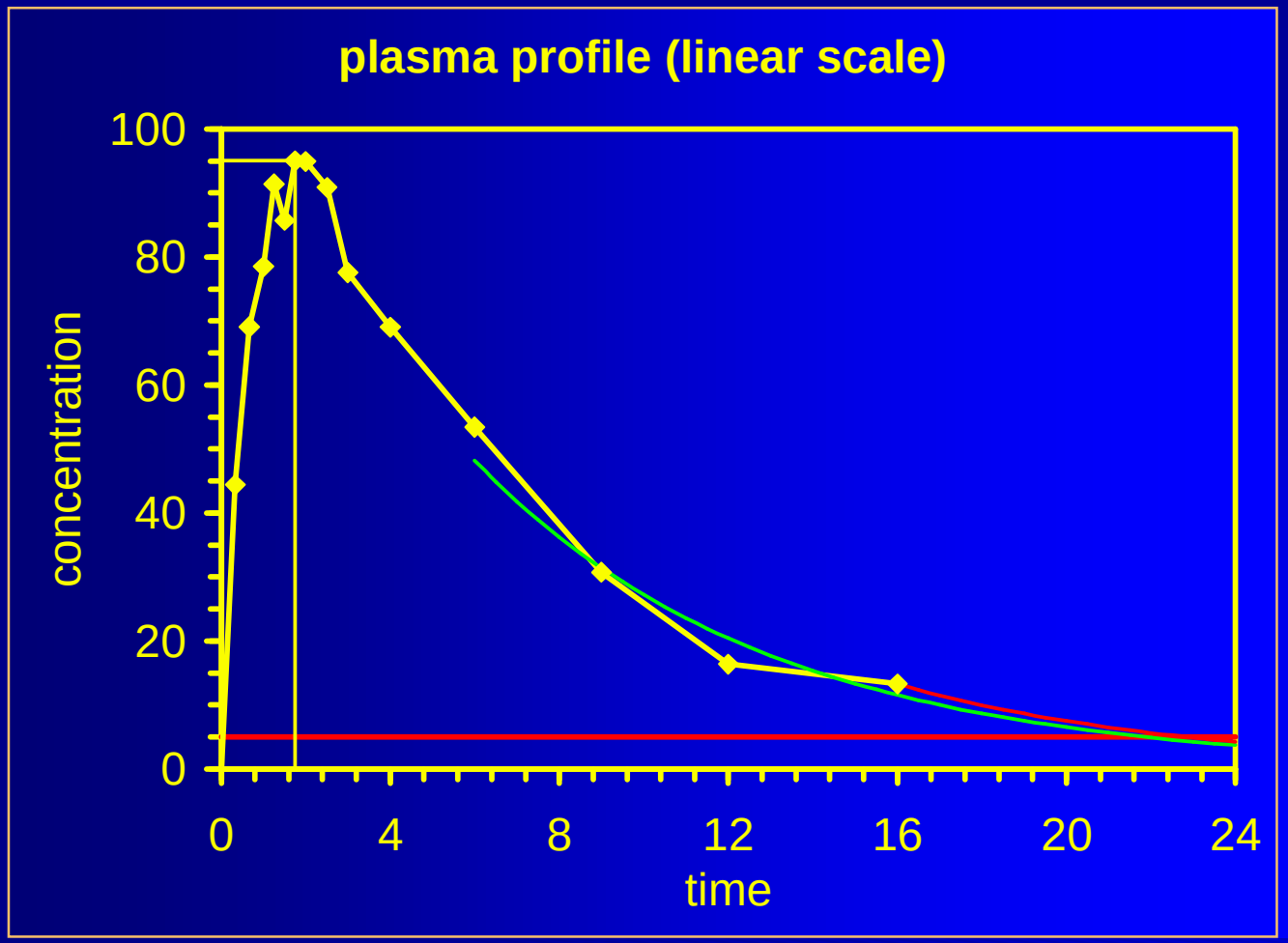
- Single dose
  - Method of estimation of λ_z stated in protocol!
    - One-compartment model: TTT-method *)
      (Two times t_{max} to t_z)
    - Maximum adjusted R^2 (WinNonlin, Kinetica)

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

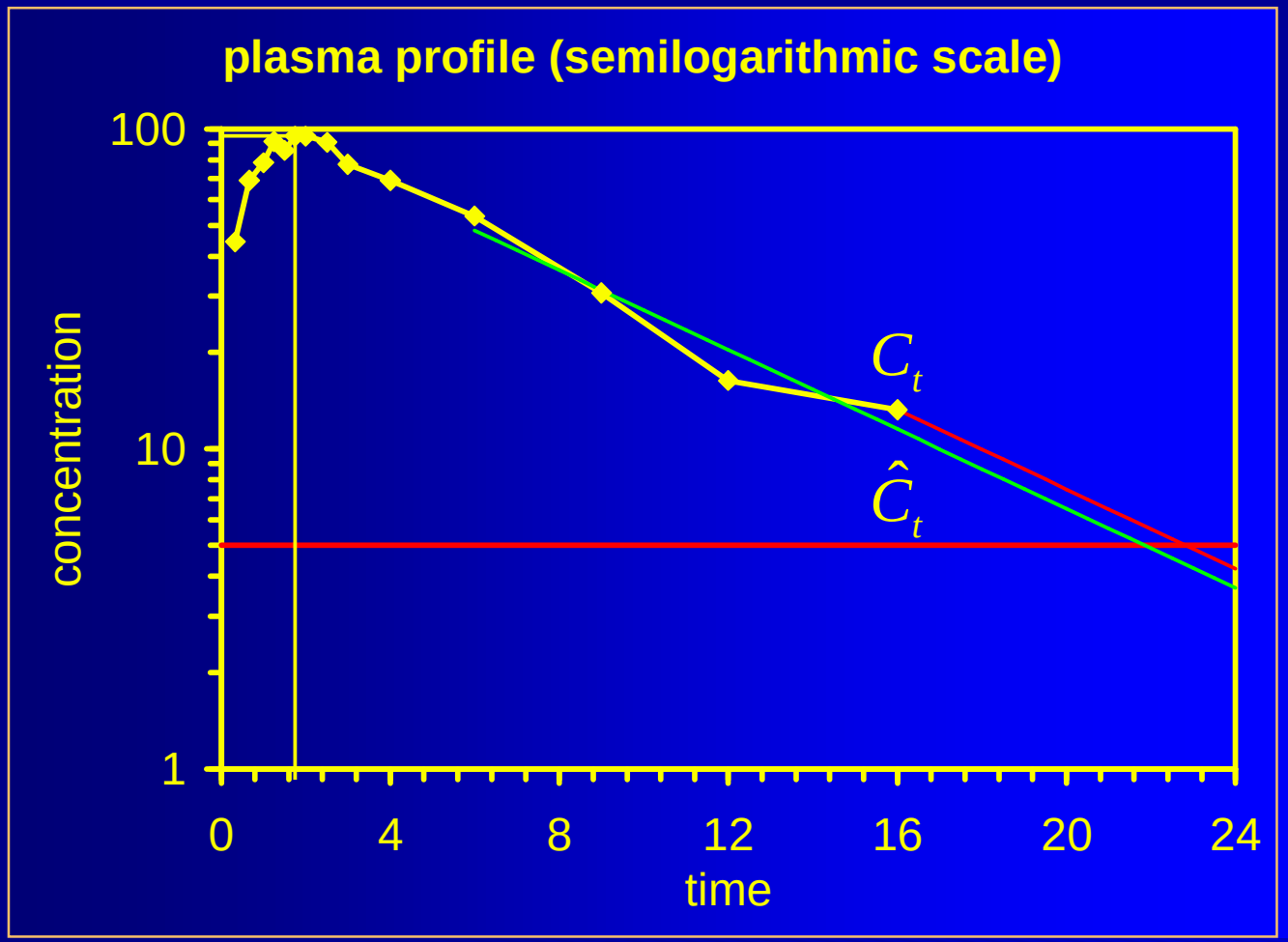
    - Multi-compartment models: starting point = last inflection
    - Minimum AIC $AIC = n \cdot [\ln(2 \cdot \pi) + 1] + n \cdot \ln(RSS/n) + 2 \cdot p$
    - Visual inspection of fit mandatory!

*) **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, 145–157 (2008)

NCA


plasma profile (linear scale)
concentration
100
80
60
40
20
0
0
4
8
12
16
20
24
time

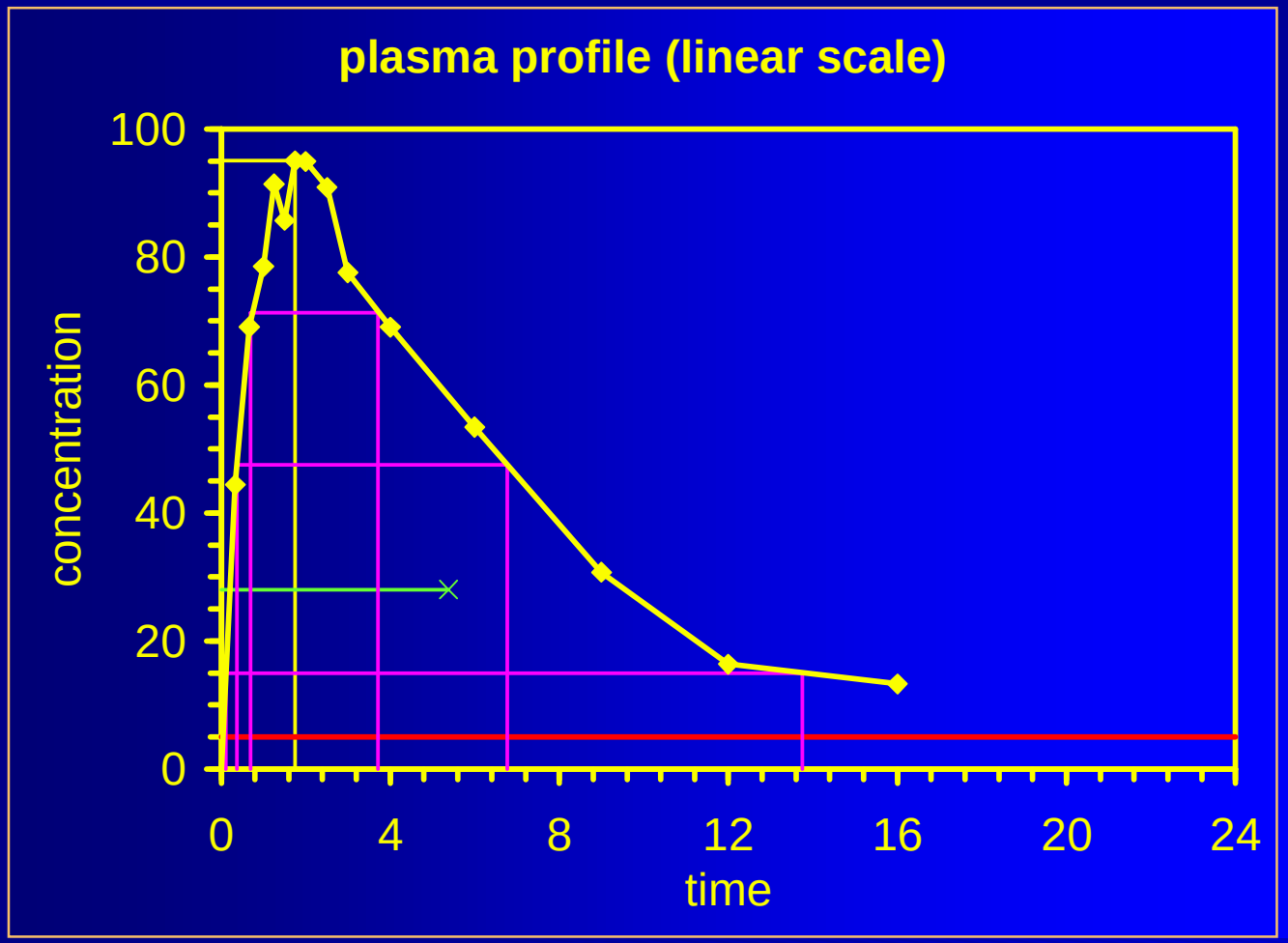
NCA


plasma profile (semilogarithmic scale)
100
10
1
concentration
C_t
$\hat{C}_t$
0
4
8
12
16
20
24
time

NCA

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

NCA


plasma profile (linear scale)
concentration
100
80
60
40
20
0
0
4
8
12
16
20
24
time

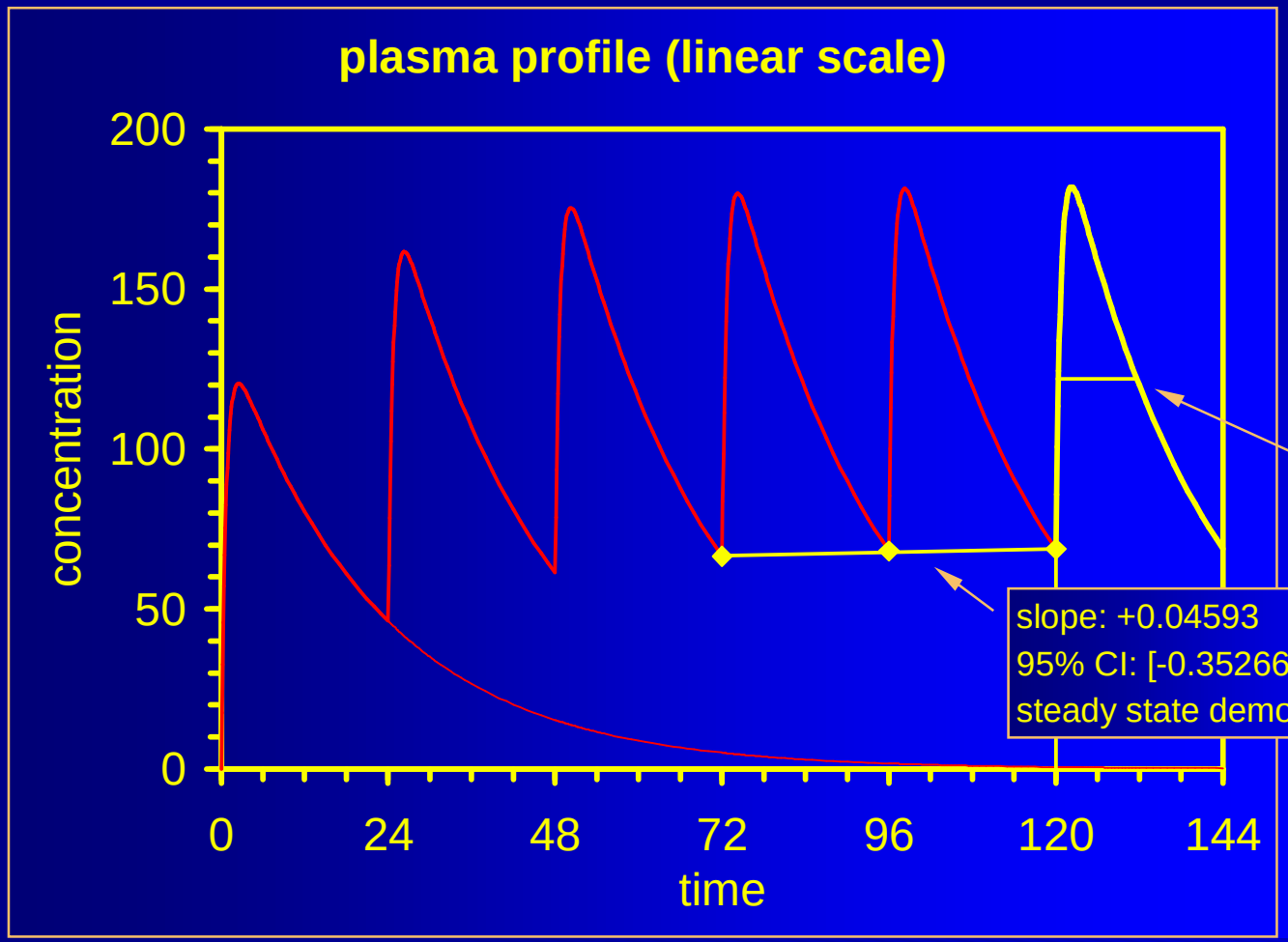
NCA

- Multiple dose
  - Calculation of AUC_{τ} (τ: dosage interval); $AUC_{ss,24h}$ if more than *o.a.d.* and chronopharmaco-logical variation)
  - No extrapolation!
  - $C_{ss,max}$ / $C_{ss,min}$ directly from profile
  - Peak-Trough-Fluctuation: $(C_{ss,max} - C_{ss,min}) / C_{ss,av}$, where $C_{ss,av} = AUC_{\tau} / \tau$
  - Swing: $(C_{ss,max} - C_{ss,min}) / C_{ss,min}$

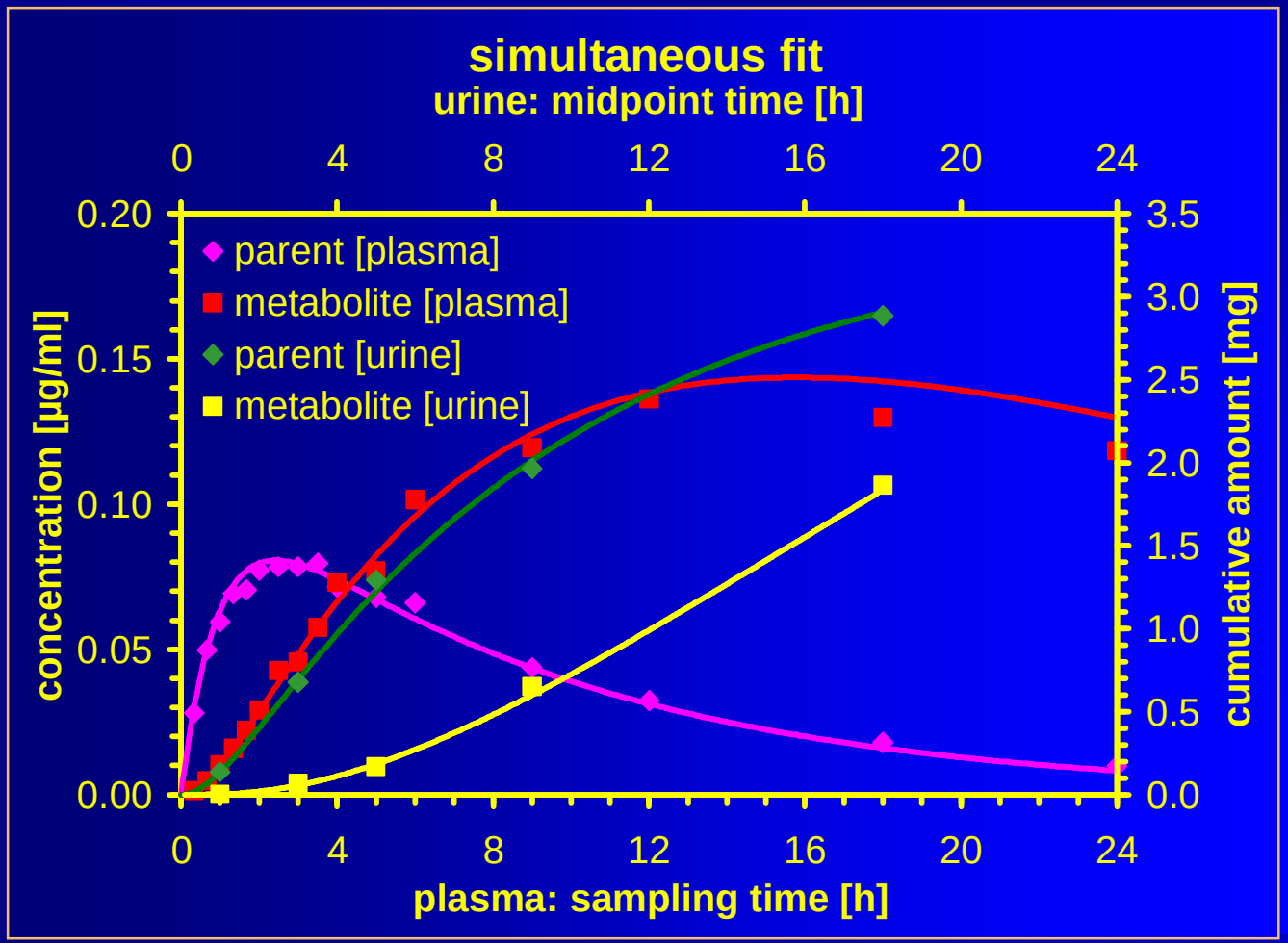
NCA

- Multiple dose
  - Assessment whether steady state is reached (in a linear PK system: $AUC_{\tau} = AUC_{\infty}$)
    - No recommendations in guidelines
    - MANOVA-model (sometimes mentioned in Canada, 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!

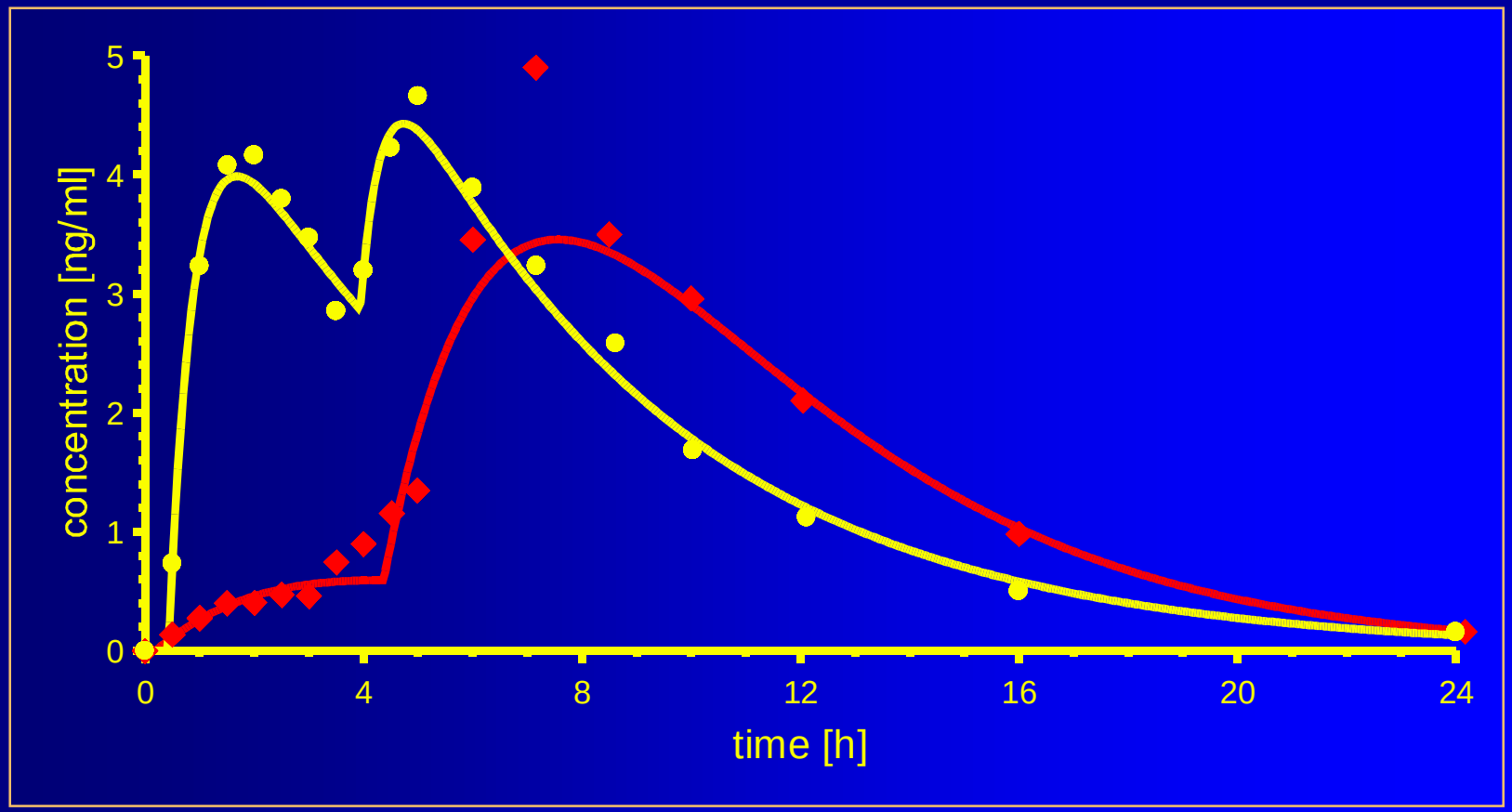
NCA


plasma profile (linear scale)
concentration
200
150
100
50
0
0
24
48
72
96
120
144
time
C_{av}
slope: +0.04593
95% CI: [-0.35266 | +0.44452]
steady state demonstrated

PK Modeling


simultaneous fit
urine: midpoint time [h]
0
4
8
12
16
20
24
0.20
0.15
0.10
0.05
0.00
concentration [µg/ml]
parent [plasma]
metabolite [plasma]
parent [urine]
metabolite [urine]
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
cumulative amount [mg]
plasma: sampling time [h]

PK Modeling

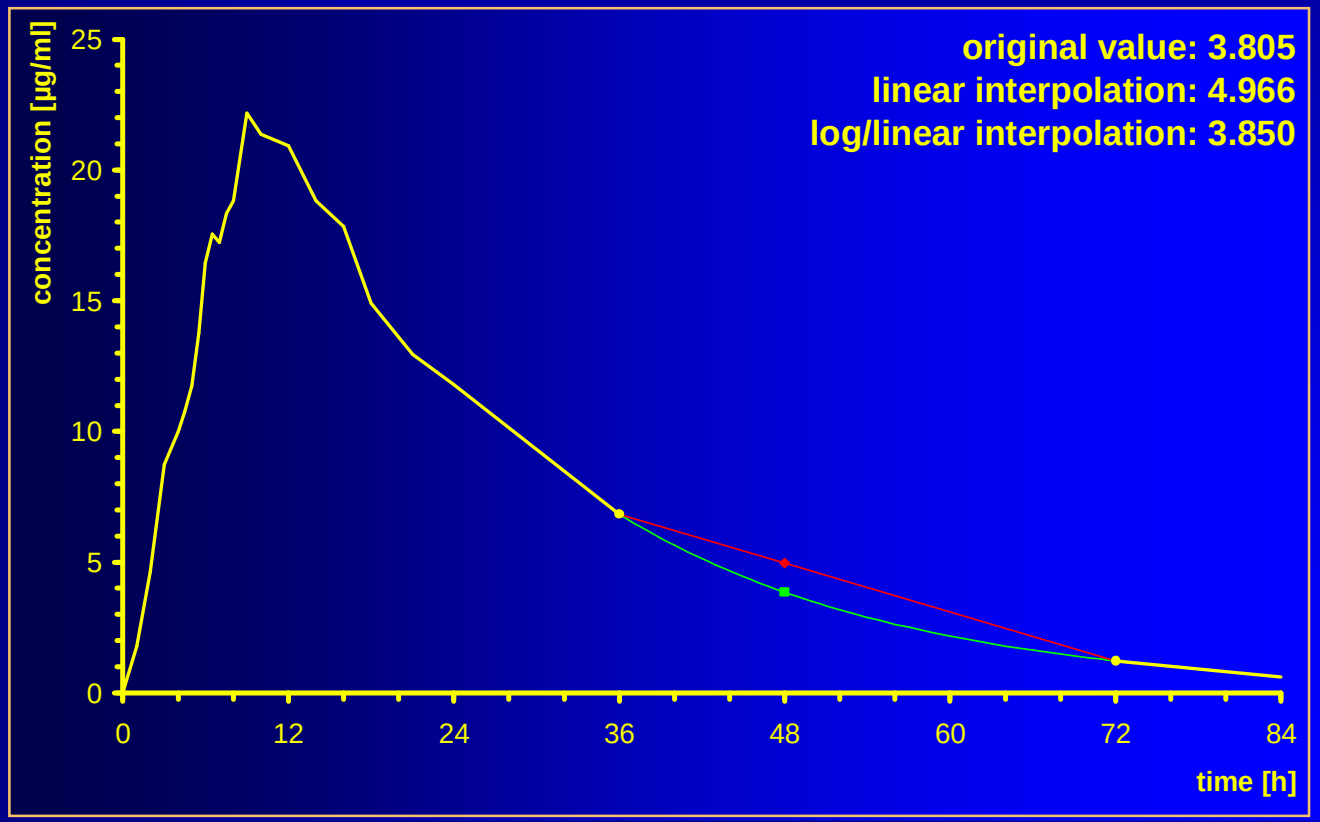


Some Problems…

- Missing values I
  - Procedure for Imputation must be stated in the Protocol; recommended:
    - in the Absorption Phase ($t < t_{max}$) by linear Interpolation of two adjacent values
    - in the Elimination Phase ($t \geq t_{max}$) by log/linear Interpolation of two adjacent values
    - estimated value must not be used in calculation of the terminal half life!

Some Problems…

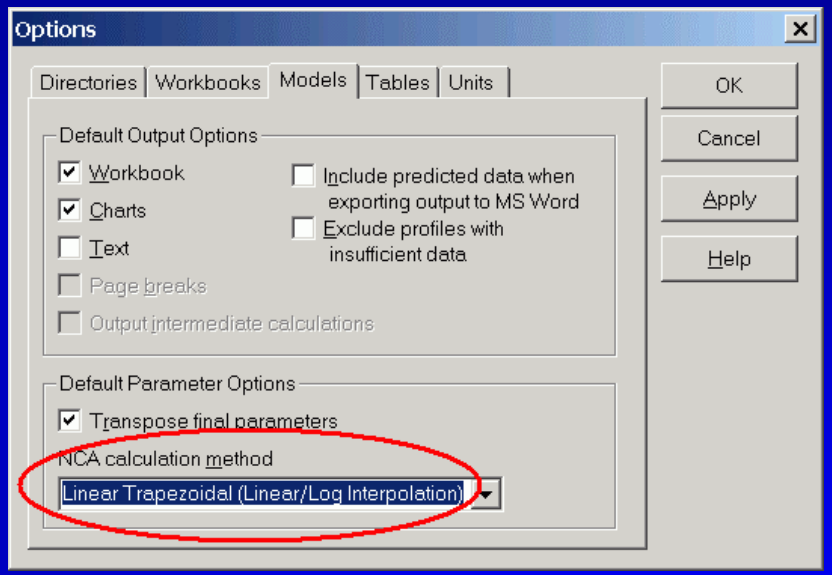
- Missing values I



Some Problems…

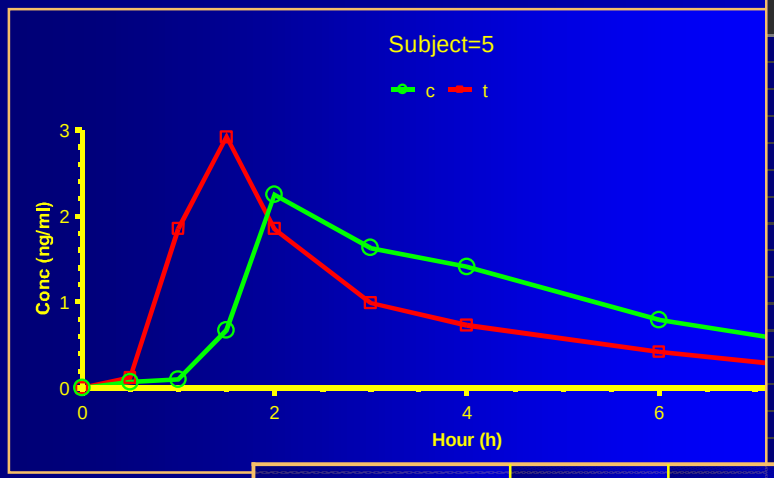
- Missing values I

  Recommended Procedure may not be the ‘default’ in your software (has to be actively set, *e.g.*, in WinNonlin 4+)

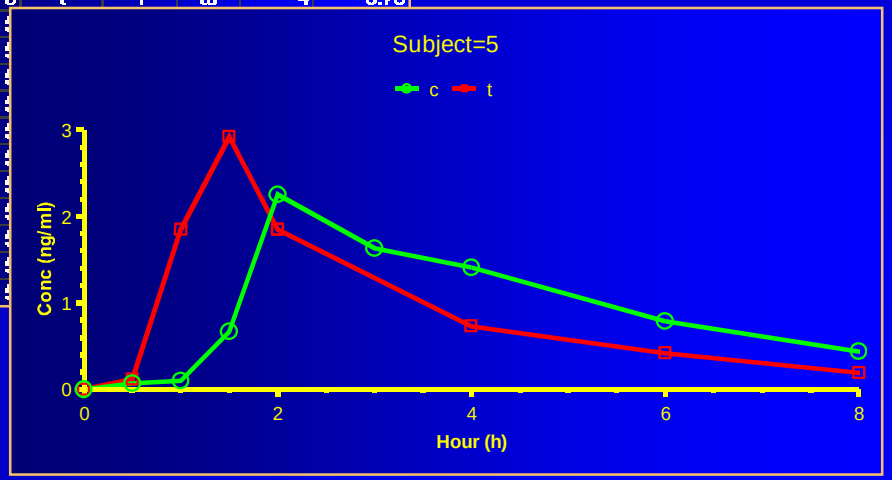


Some Problems…

- Missing values I
  - Do you ‘see’ a missing value at all?



Subject	Form	Period	Seq	Hour	Conc (ng/ml)
5	t	1	tc	0	0
5	t	1	tc	0.5	0.12
5	t	1	tc	1	1.85
5	t	1	tc	1.5	2.92
5	t	1	tc	2	1.85
5	t	1	tc	3	Missing
5	t	1	tc	4	0.73



	t/c [%]	bias [%]
original value	88.3%	–
linear interpol.	92.1%	+4.3%
log/linear interpol.	90.4%	+2.4%

Some Problems…

- Missing values II
  - At the end of the profile
    - Example:

      $t_{½abs}$ = 0.5, $t_{½el}$ = 24

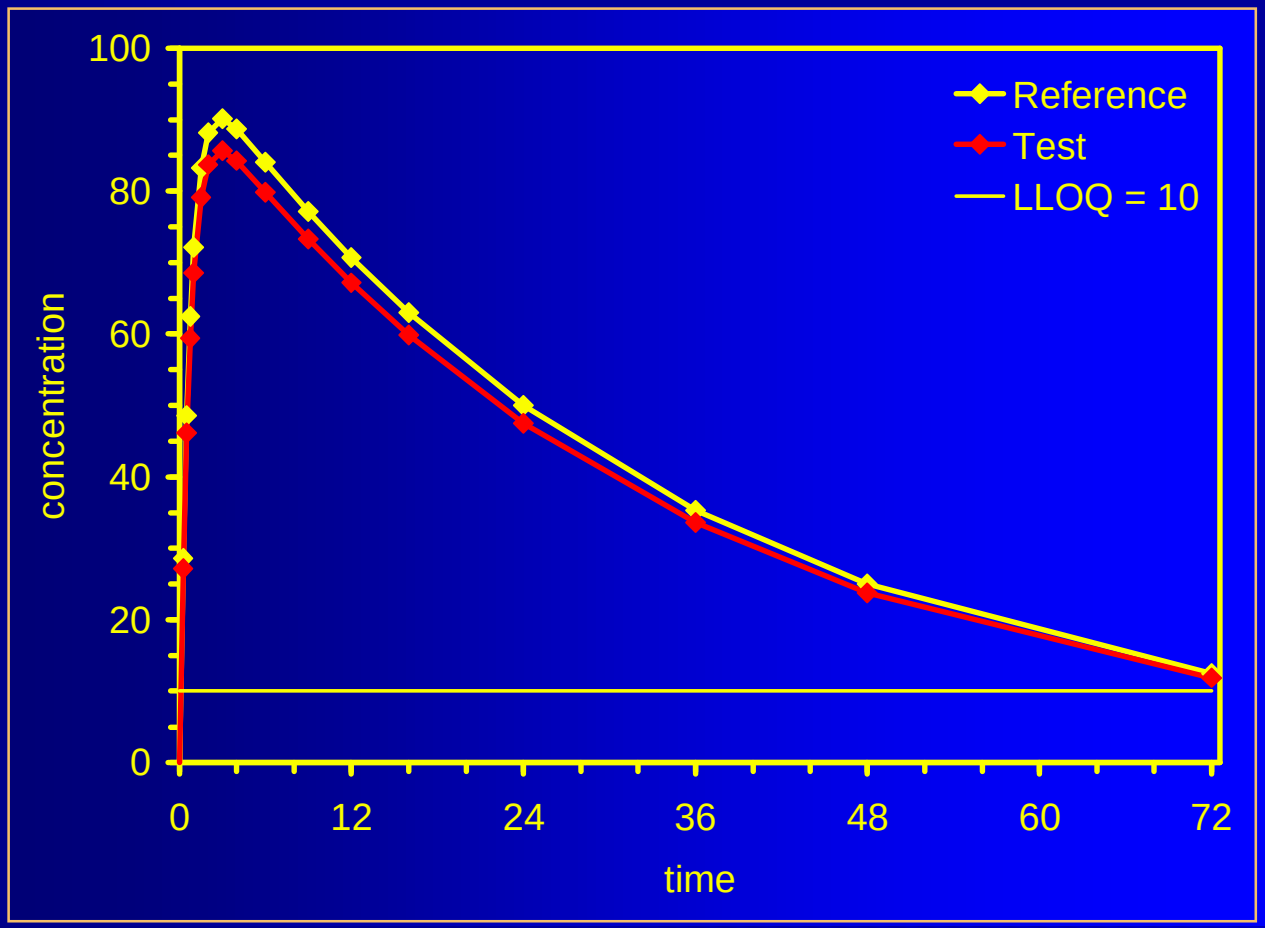
      $T/R_{theoret.}$ = 95%, LLOQ = 10

      AUC_{72}: T = 2835, R = 2984

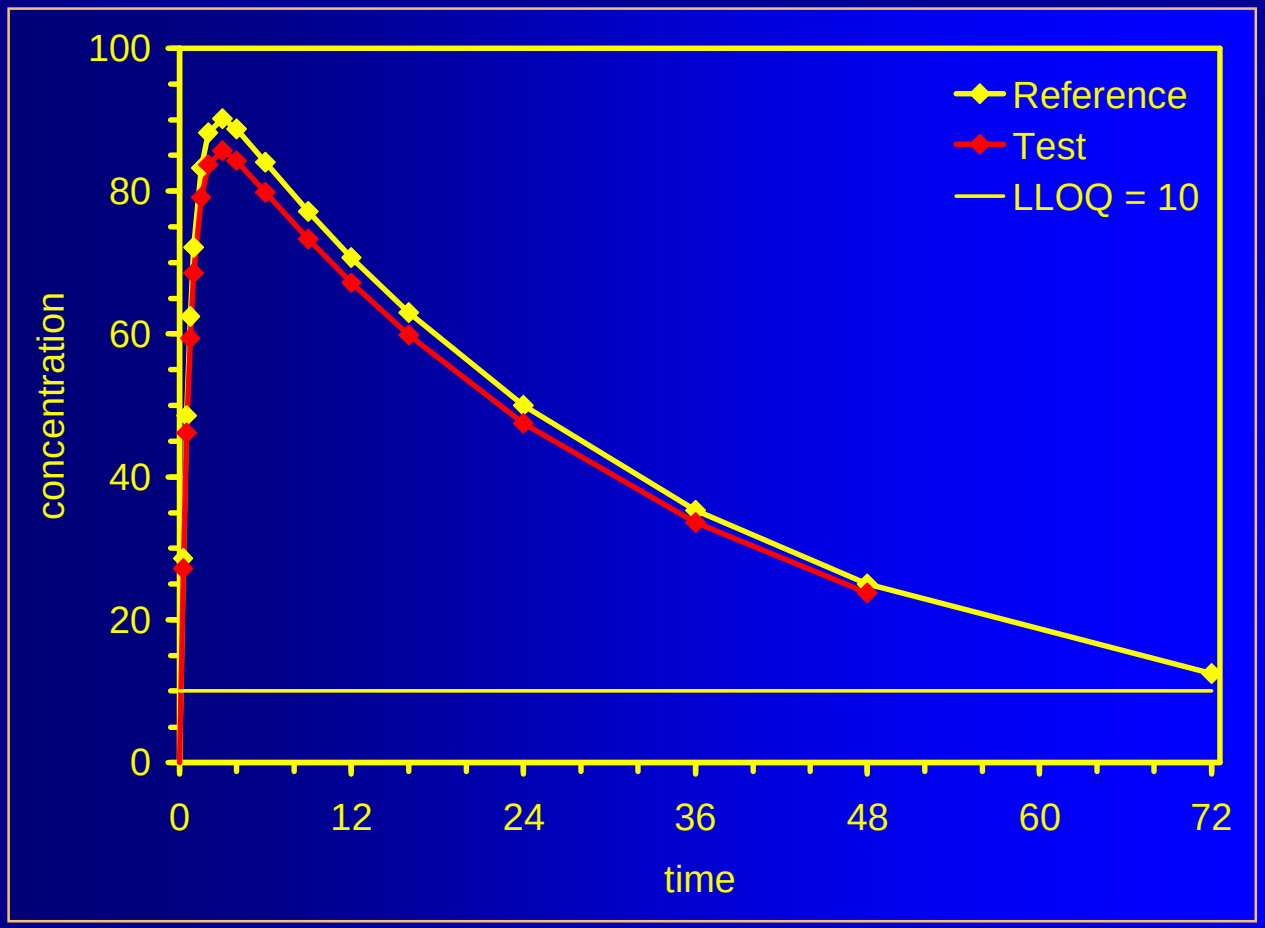
      T/R = 95% ✓

	Reference		Test	
time	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**	11.88	**2835**

Some Problems…



Some Problems…



Some 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≥LLOQ for both formulations (48)
      AUC_{48} T = 2534
      AUC_{48} R = 2407
      T/R = 95% ✓
      - Not available in software
      - Regulatory acceptance?

	Reference		Test	
time	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
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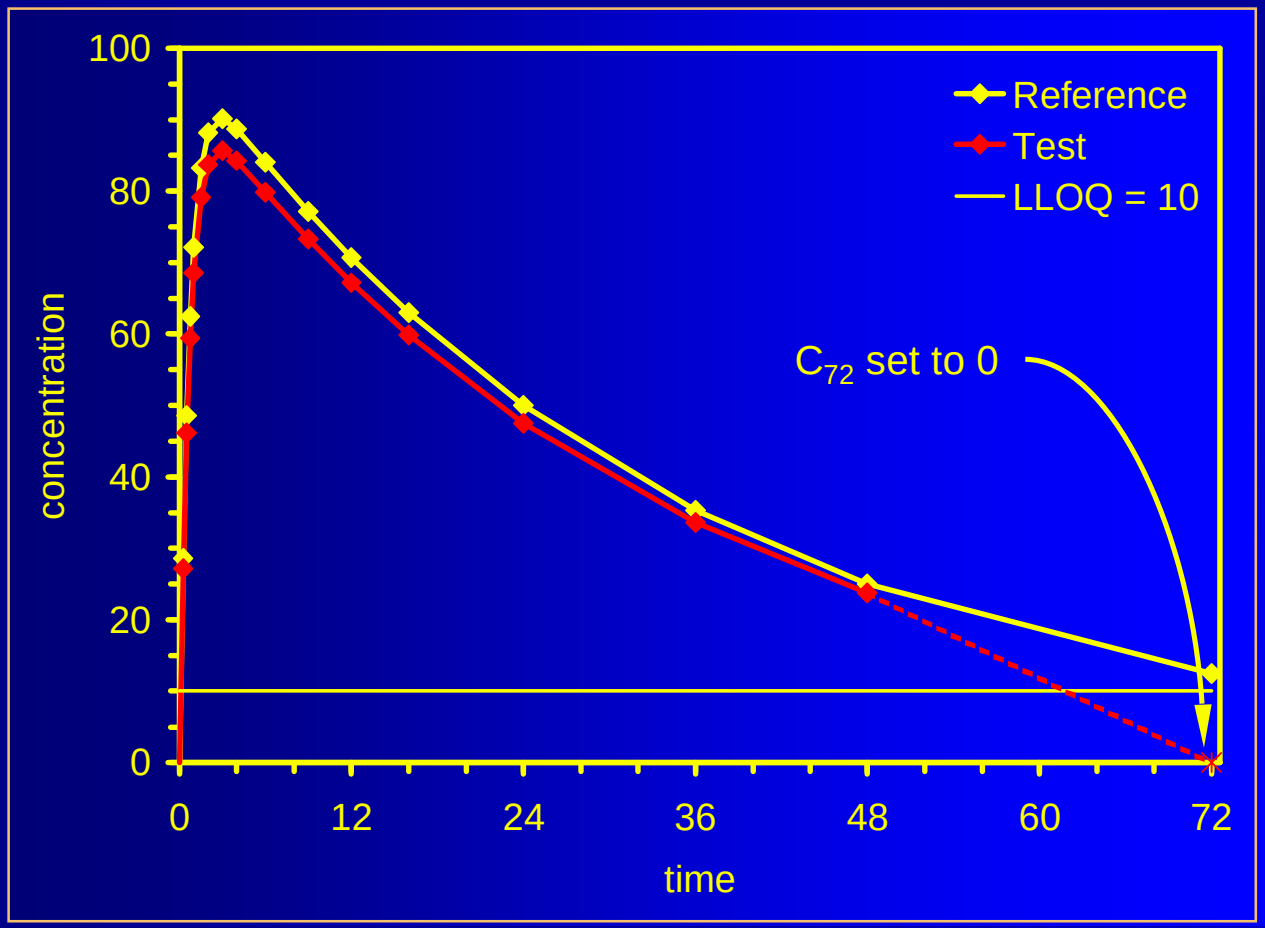
24	50.00	1660	47.50	1577
36	35.36	2172	33.59	2063
48	25.00	**2534**	23.75	**2407**
72	12.50	**2984**	Missing	NA

Some Problems…



Some 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 WinNonlin, Kinetica
      - Regulatory acceptance?

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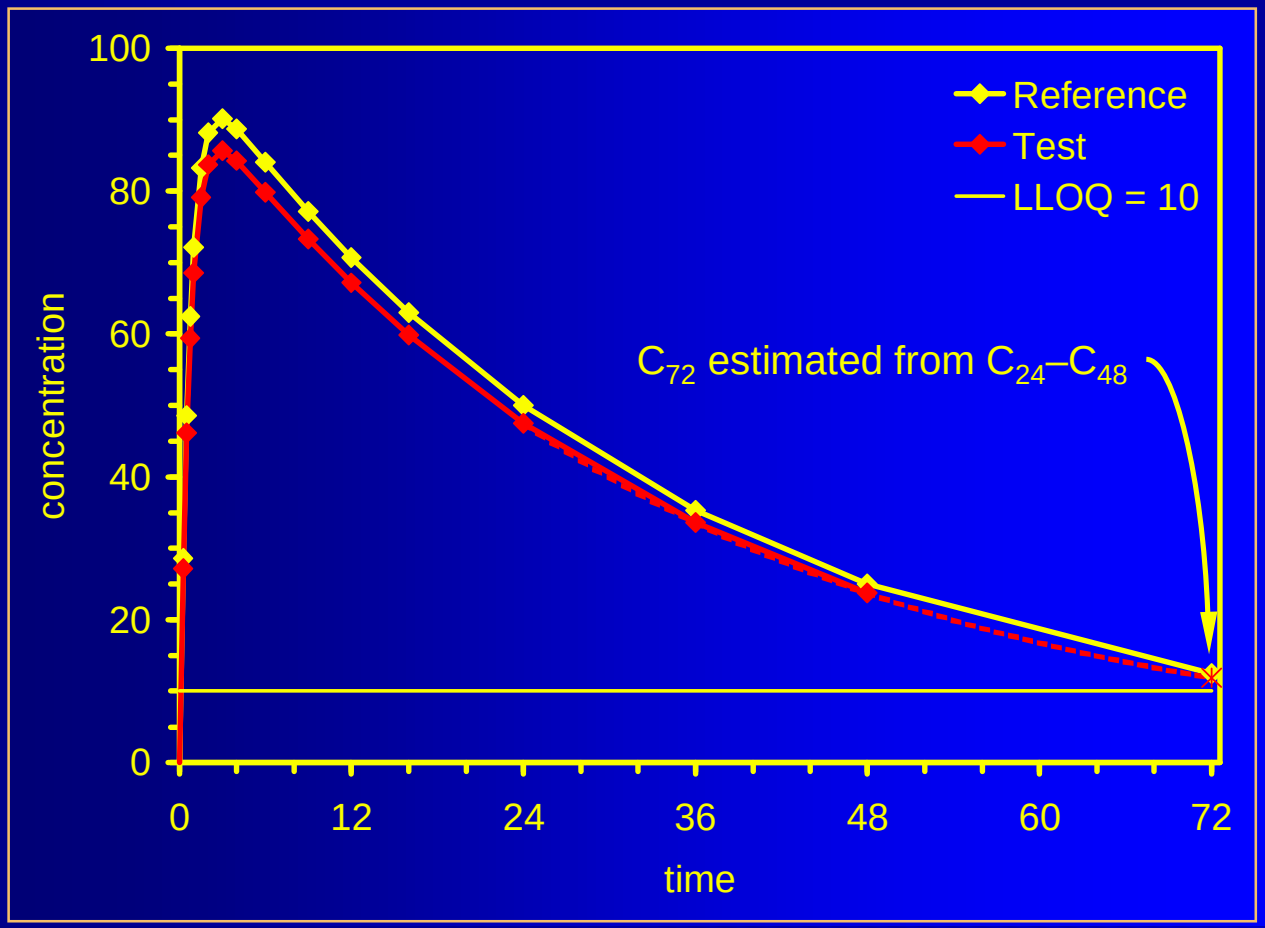
24	50.00	1660	47.50	1577
36	35.36	2172	33.59	2063
48	25.00	2534	23.75	2407
72	12.50	**2984**	= *0	**2692**

Some Problems…



Some 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 ±

	Reference		Test	
time	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**

Some 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 = ?

	Reference		Test	
time	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

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

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time	conc	AUC_{0-t}	conc	AUC_{0-t}
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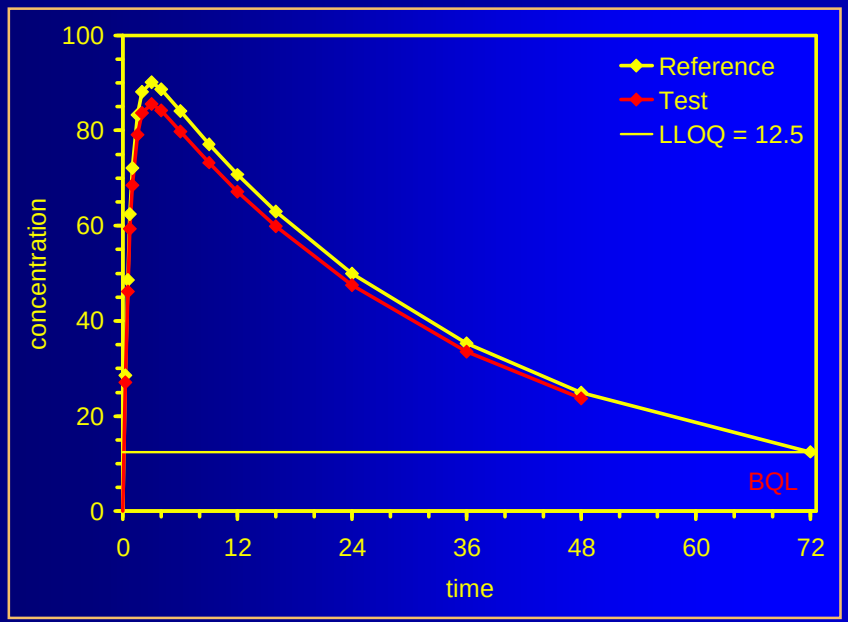
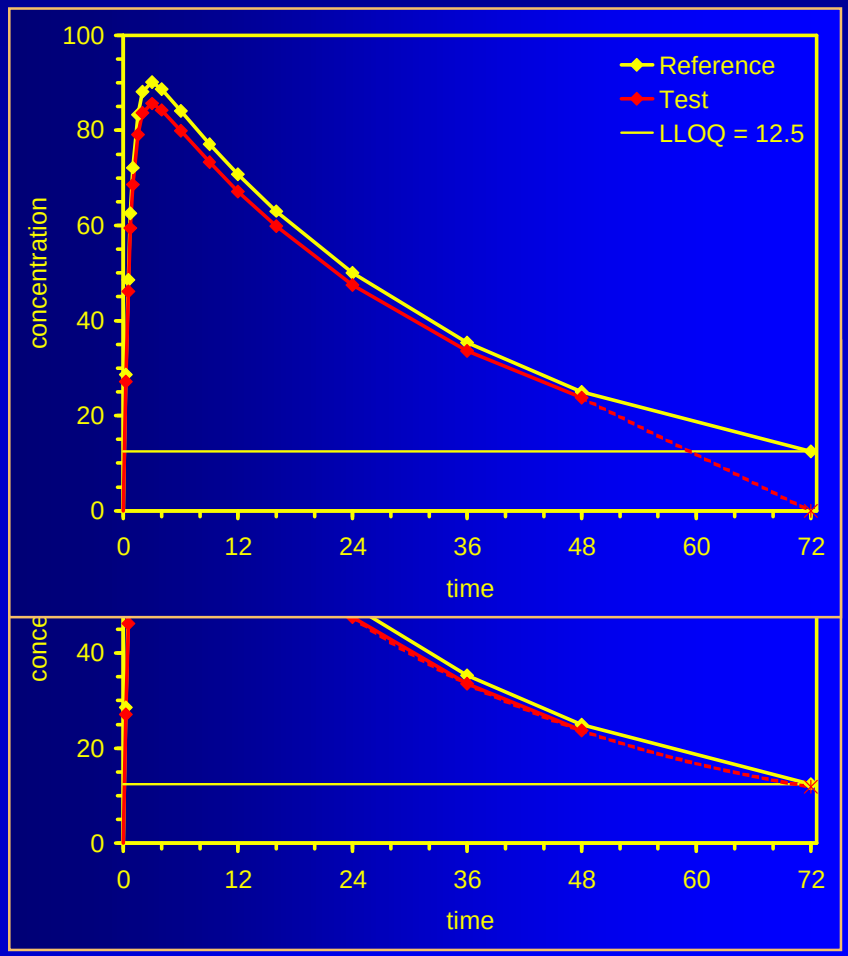
36	35.36	2172	33.59	2063
48	25.00	2534	23.75	2407
72	12.50	**2984**	*11.88	NA

Some Problems…

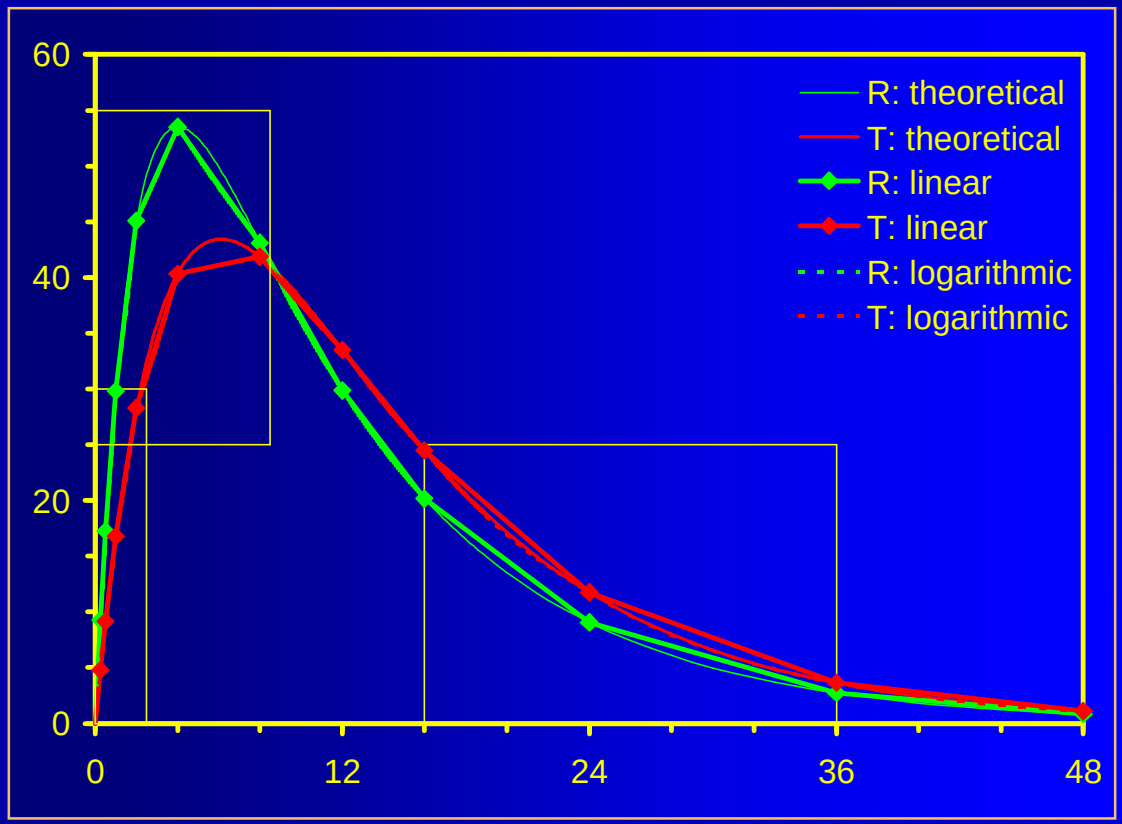
What would you do?





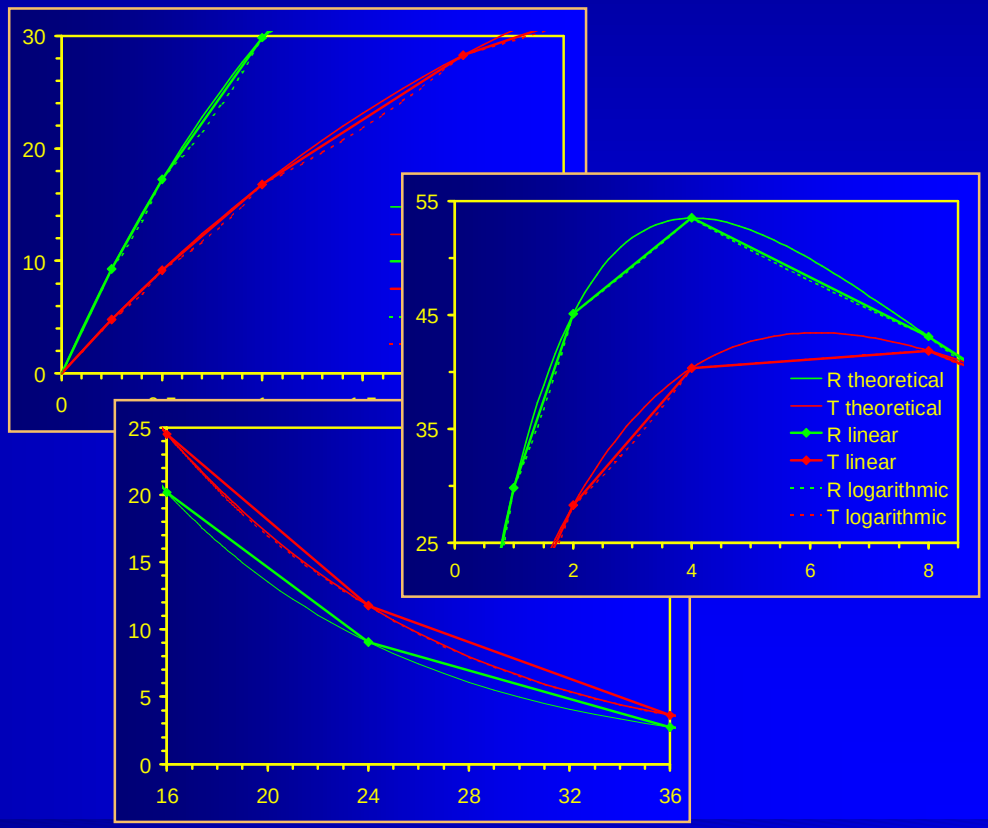
Trapezoidal rule(s!)

- Yes, but which one?
  - linear
  - logarithmic
  - lin/log
  - R. Purves
  - Lagrange



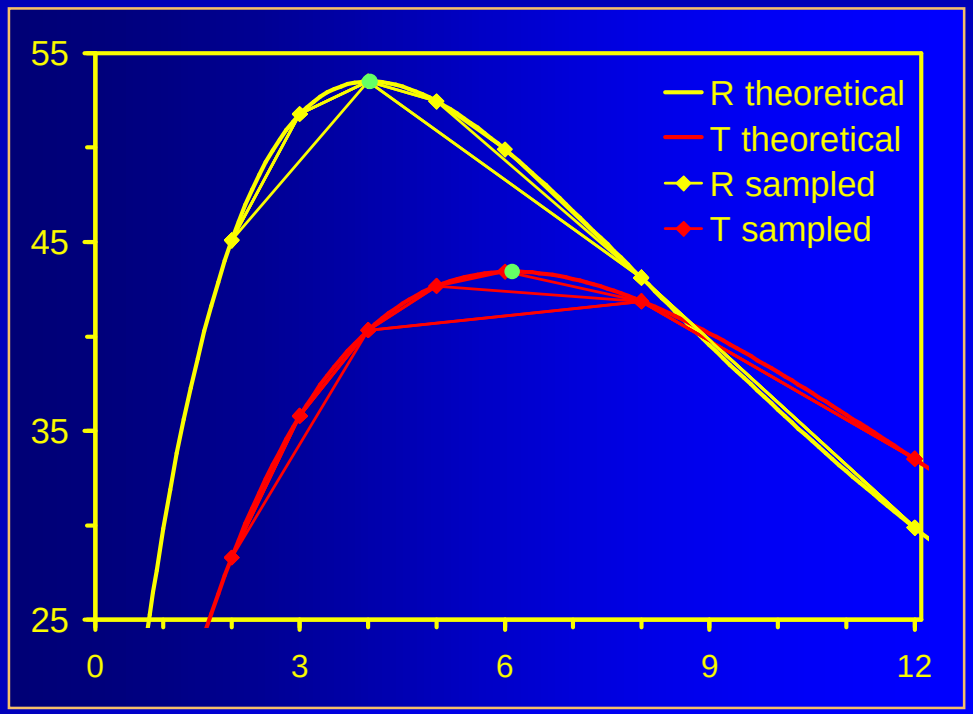
Trapezoidal rule(s!)

- Bias of methods and effects on T/R
  - AUC_{th} 100%
    - lin
      - AUC_t 100.5%
      - AUC_∞ 100.5%
    - lin-log
      - AUC_t 100.6%
      - AUC_∞ 100.2%
    - Purves
      - AUC_t 99.50%
      - AUC_∞ 99.11%



Sampling at C_{max}

- Theoretical (T/R)
  t_{max}: 6.11/4.02 (Δ 2.09), C_{max}: 41.9/53.5 (81.2%)
  - Sampling [2 | 12]
    - 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



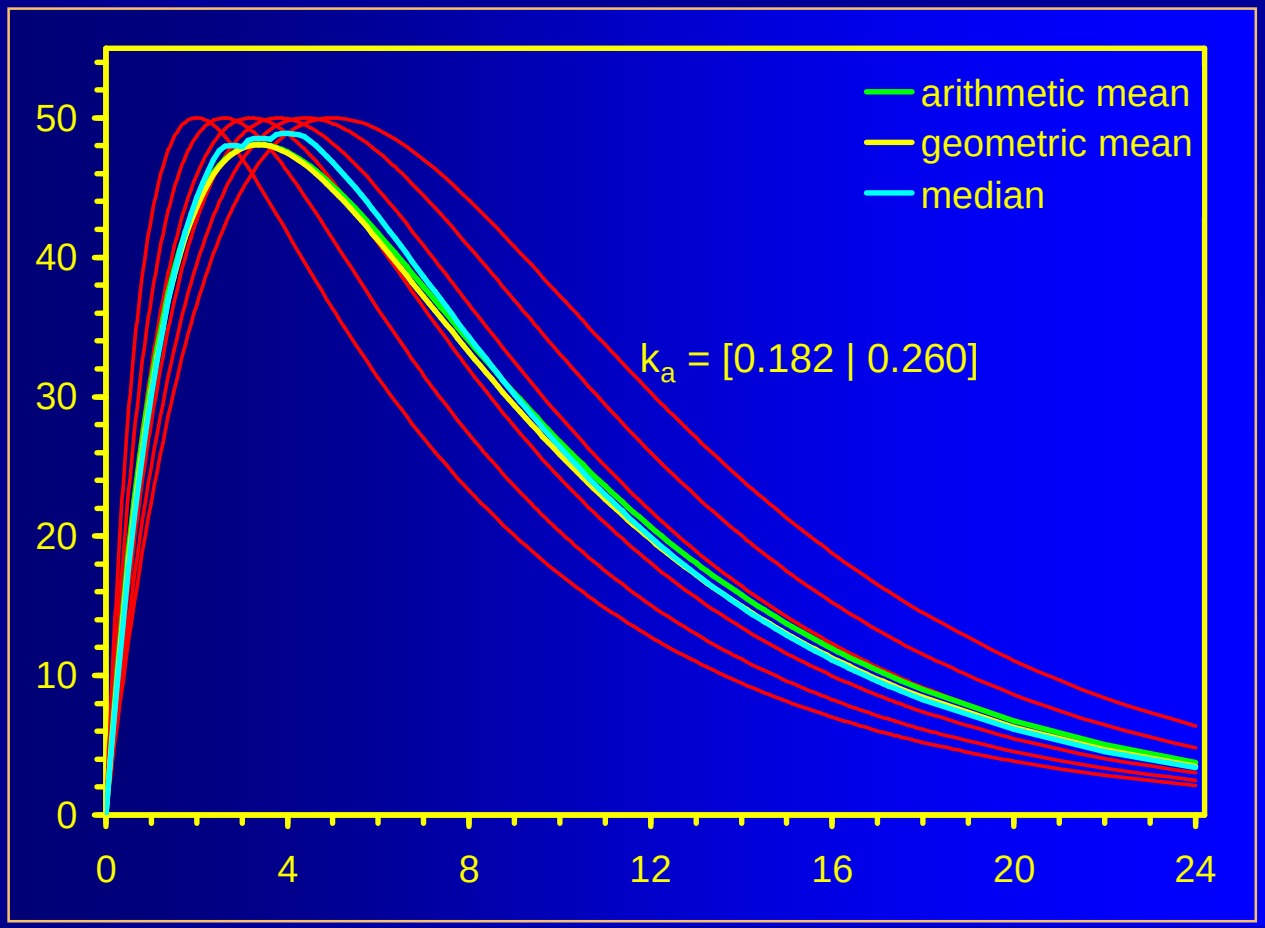
Sampling at C_{max}

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

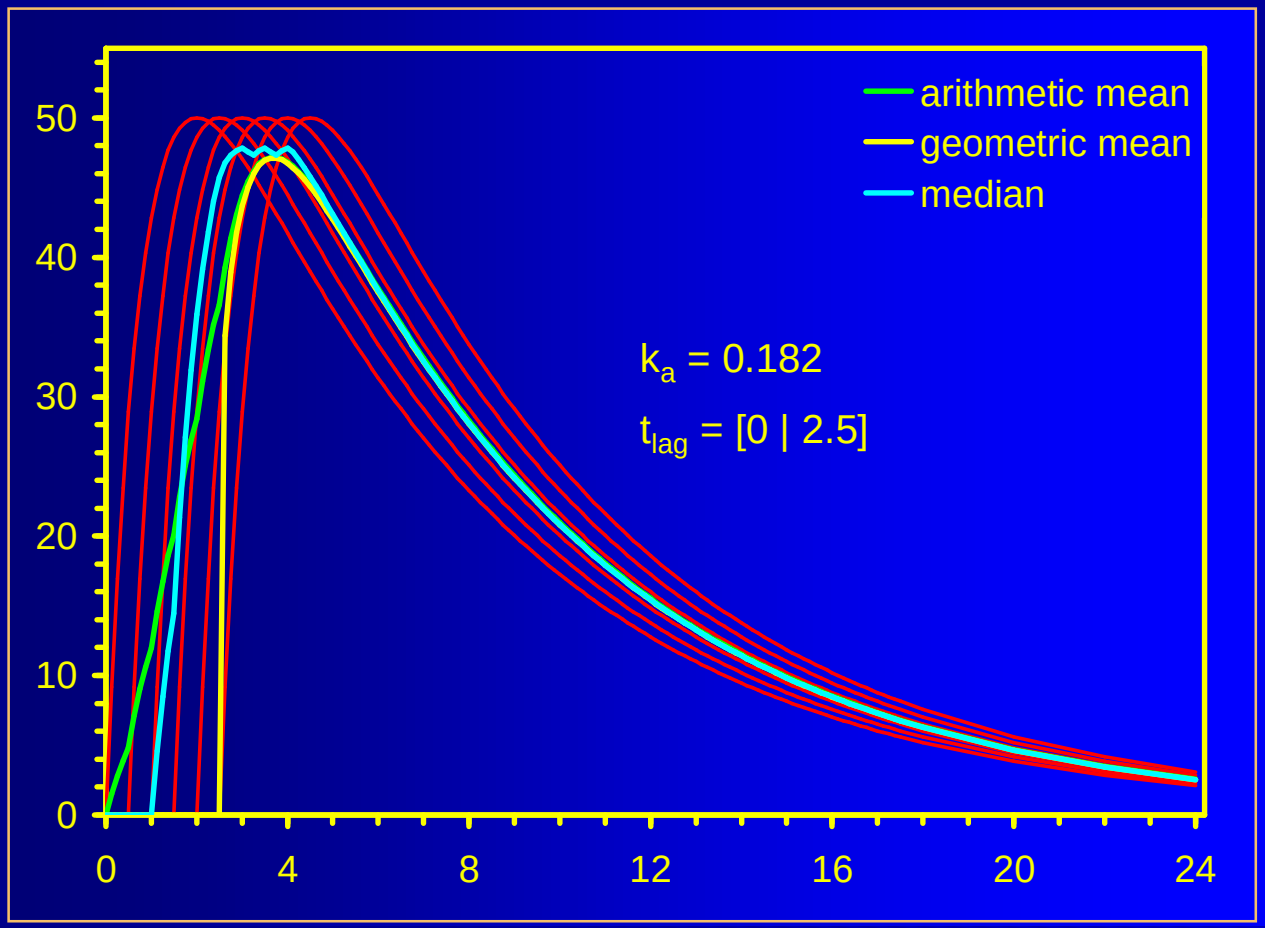
Sampling at C_{max}

- 'C_{max} was observed within two to five hours after administration…'
  - Elimination is drug specific,
  - but what about absorption?
    - Formulation specific!

Sampling at C_{max}



Sampling at C_{max}



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 Efficacy Working Party therapeutic subgroup on Pharmacokinetics (EWP-PK)
Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics
EMEA/618604/2008, 22 January 2009
http://www.emea.europa.eu/pdfs/human/ewp/61860408en.pdf

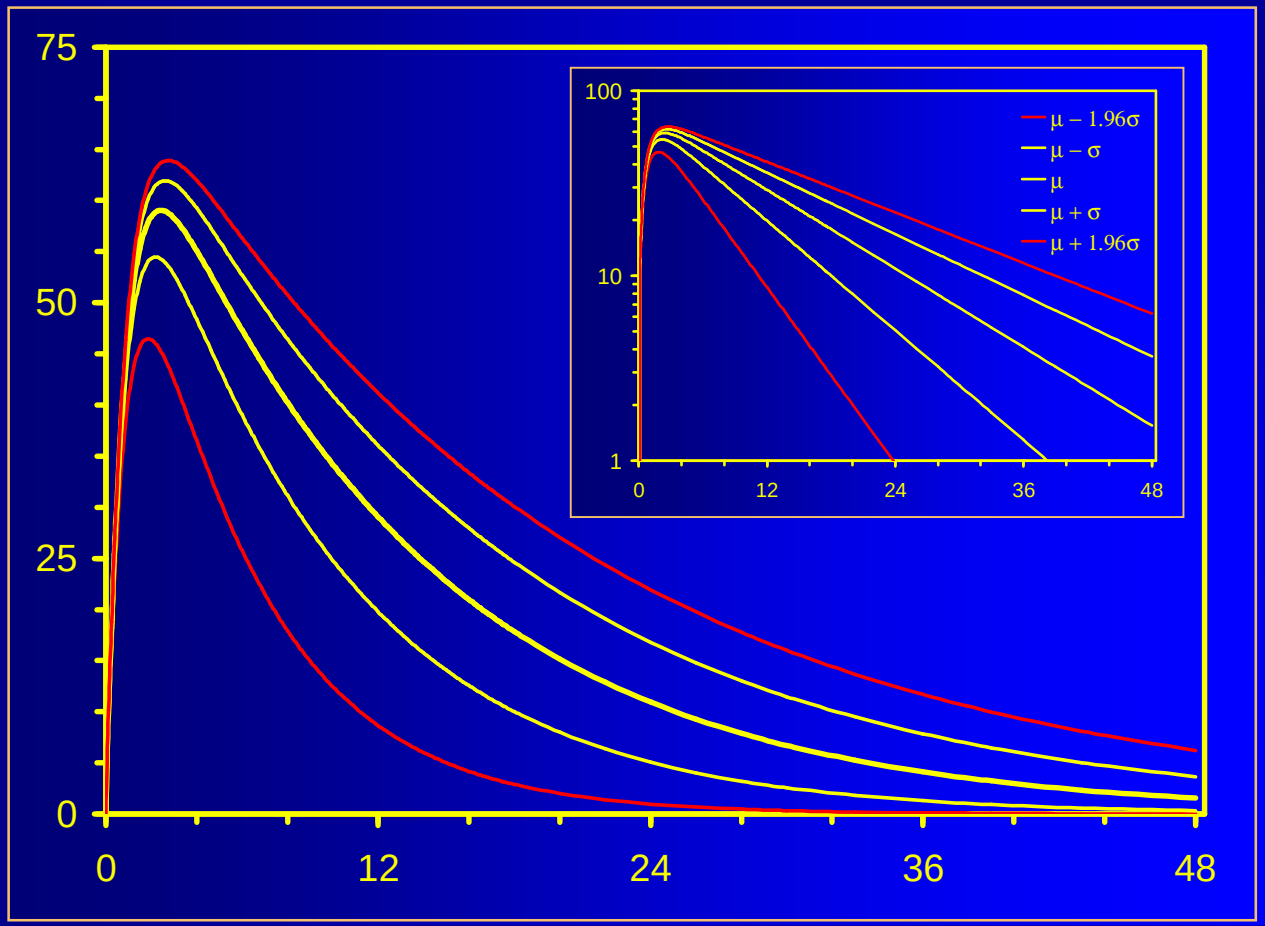
Half lives

- Drug specific, but…
  - The terminal phase presents the slowest rate constant (controlled release, topicals, transdermals) – not necessarily elimination!
  - Important in designing studies
    - To meet $AUC_t \geq 80\% AUC_\infty$ criterion
    - To plan sufficiently long wash-out
    - To plan saturation phase for steady state

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 $> \mu \pm \sigma$)
    - Example: 8.5 ± 2.4 hours, 36 subjects.
      $0.1587 \times (8.5 + 2.4) = 5.71$ or in at least five subjects we may expect a half life of > 10.9 hours.
    - Plan for 95% coverage ($z_{0.95} = 1.96$):
      $8.5 \pm 1.96 \times 2.4 = [3.80,13.2]$ hours. We may expect a half life of > 13.2 hours in ~one subject ($0.05/2 \times 36 = 0.90$).

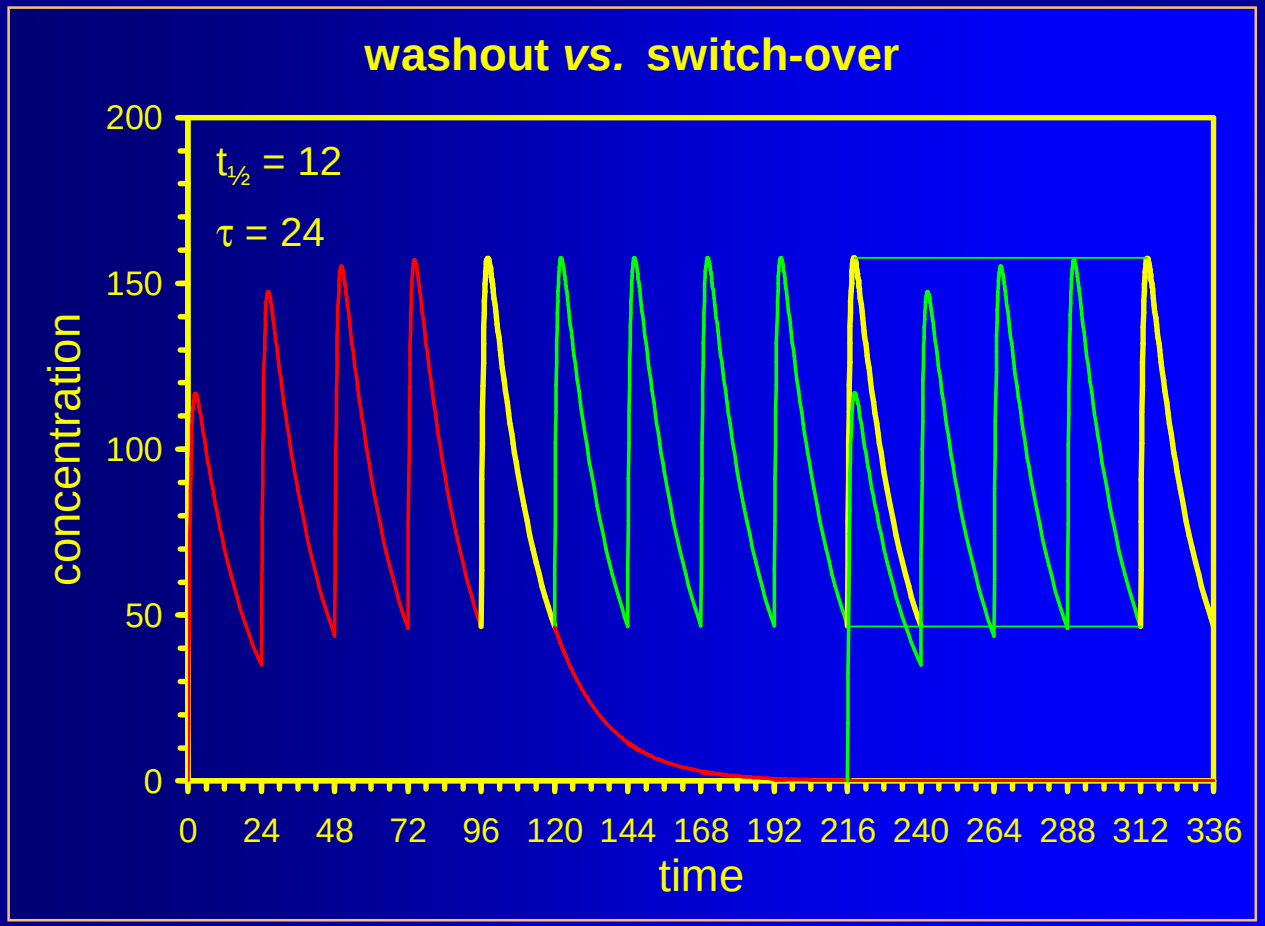
Half lives



Washout in MD Studies

- EMEA (2001)
  Subsequent treatments should be separated by adequate wash out periods. In steady-state studies wash out of the previous treatment last dose can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least three times the terminal half-life).
  - Justified by Superposition Principle
  - 'Switch-over Design'

Washout in MD Studies



Thank You!

Noncompartmental Analysis (NCA) in PK, PK-based Design

Open Questions?

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