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

Helmut Schütz
BEBAC

History

- Bioequivalence
  - Surrogate of clinical equivalence (1985+)
    - Studies in steady state in order to reduce variability
    - Studies based on active metabolite
    - Wider acceptance range if clinical justifiable (not FDA!)
  - Measure of pharmaceutical quality (2000+)
    - Single dose studies preferred
    - Generally parent drug
    - Widening of acceptance range exceptional

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Mid 1980'ies

- Early methods
  - FDA's 75/75 Rule
    BE, if 75% of subjects show ratios of 75%-125%.
    Not a statistic, variable formulations may pass by chance…

BE Cabana
Assessment of 75/75 Rule: FDA Viewpoint
Pharm Sci 72, 98-99 (1983)
JD Haynes
FDA 75/75 Rule: A Response
J Pharm Sci 72, 99-100 (1983)

	T	R	T/R	75%-125%
1	71	81	87.7%	yes
2	61	65	93.8%	yes
3	80	94	85.1%	yes
4	66	74	89.2%	yes
5	94	54	174.1%	no
6	97	63	154.0%	no
7	70	85	82.4%	yes
8	76	90	84.4%	yes
9	54	53	101.9%	yes
10	99	56	176.8%	no
11	83	90	92.2%	yes
12	51	68	75.0%	yes
				75.0%

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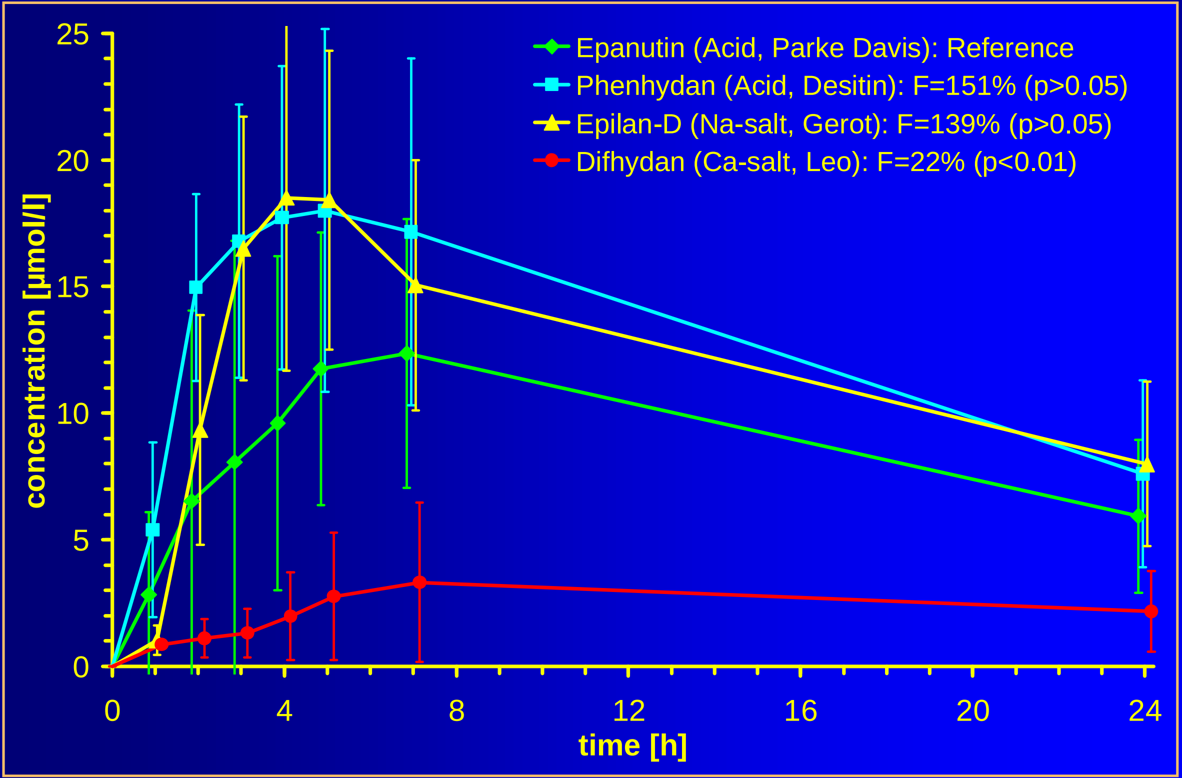
Mid 1980'ies

- Early methods
  - Testing for a significant difference (t-test) at α 0.05 Problem:
    - High variability in differences → formulation will pass (p ≥ 0.05)
    - Low variability in differences → formulation will fail (p < 0.05)
    - This is the opposite of what we actually want!

	T	R	T–R
1	71	81	-10
2	61	65	-4
3	80	94	-14
4	66	74	-8
5	94	54	+40
6	97	63	+34
7	70	85	-15
8	76	90	-14
9	54	53	+1
10	99	56	+43
11	83	90	-7
12	51	68	-17
mean	75	73	+2
SD	16	15	23
CV%	21.4%	20.6%	940%
		t-table	2.2010
		t-calc	0.3687
			n.s.

Example



Nitsche V, Mascher H and H Schütz
Comparative bioavailability of several phenytoin preparations marketed in Austria
Int J Clin Pharmacol Ther Toxicol 22(2), 104-107 (1984)

NCA *vs.* PK Modeling

- Noncompartmental methods do not rely on a pharmacokinetic model
- Also called SHAM (Shape, Height, Area, Moments)
  - 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},…

BE BA C

NCA *vs.* PK Modeling

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

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NCA *vs.* PK Modeling

- Pharmacokinetic models
  - Useful for understanding the drug/formulation
    - 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!

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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 *R²* (Phoenix/WinNonlin, Kinetica)

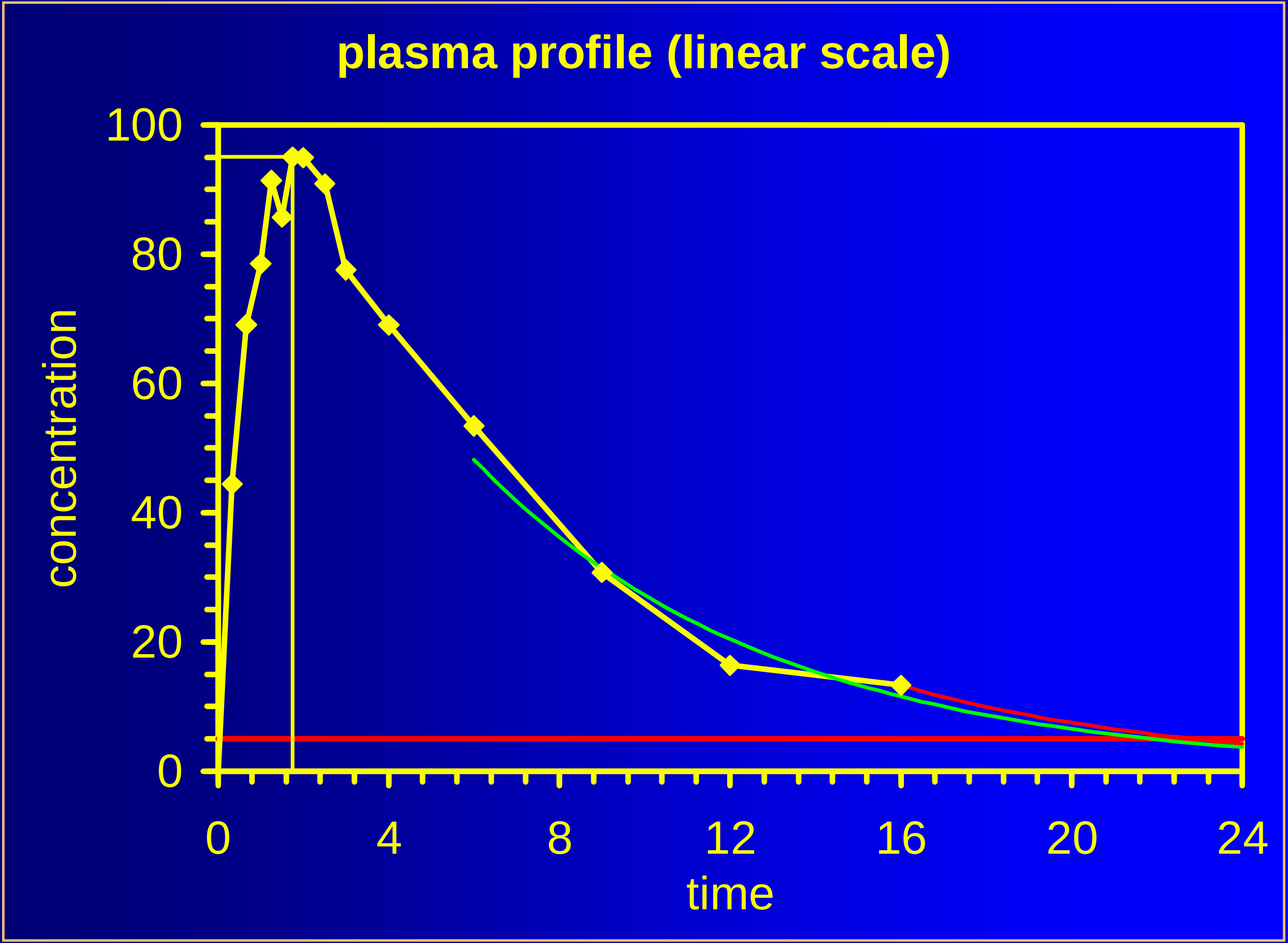
$$R^2_{adj} = 1 - \frac{(1-R^2)\cdot(n-1)}{n-2}$$

WinNonlin ≤5.3: C_{max} **in**cluded
Phoenix/WNL ≥6.0: C_{max} **ex**cluded

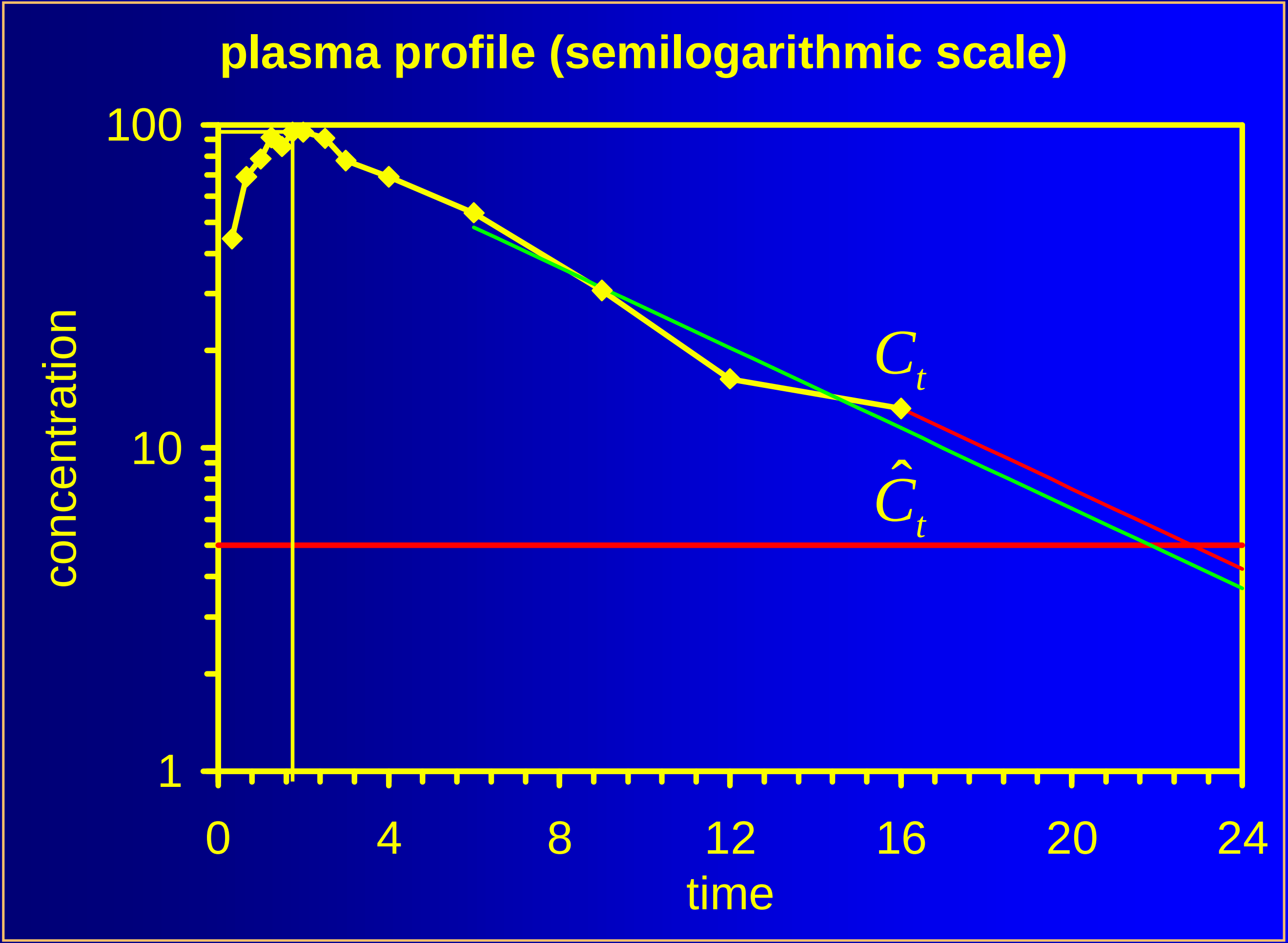
    - Multi-compartment models: starting point = last inflection
    - Minimum AIC $AIC = n \cdot [\ln(2\cdot\pi)+1] + n\cdot\ln(RSS/n) + 2\cdot p$
    - Visual inspection of fit mandatory!

*) **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)
100
80
60
40
20
0
concentration
0
4
8
12
16
20
24
time

NCA

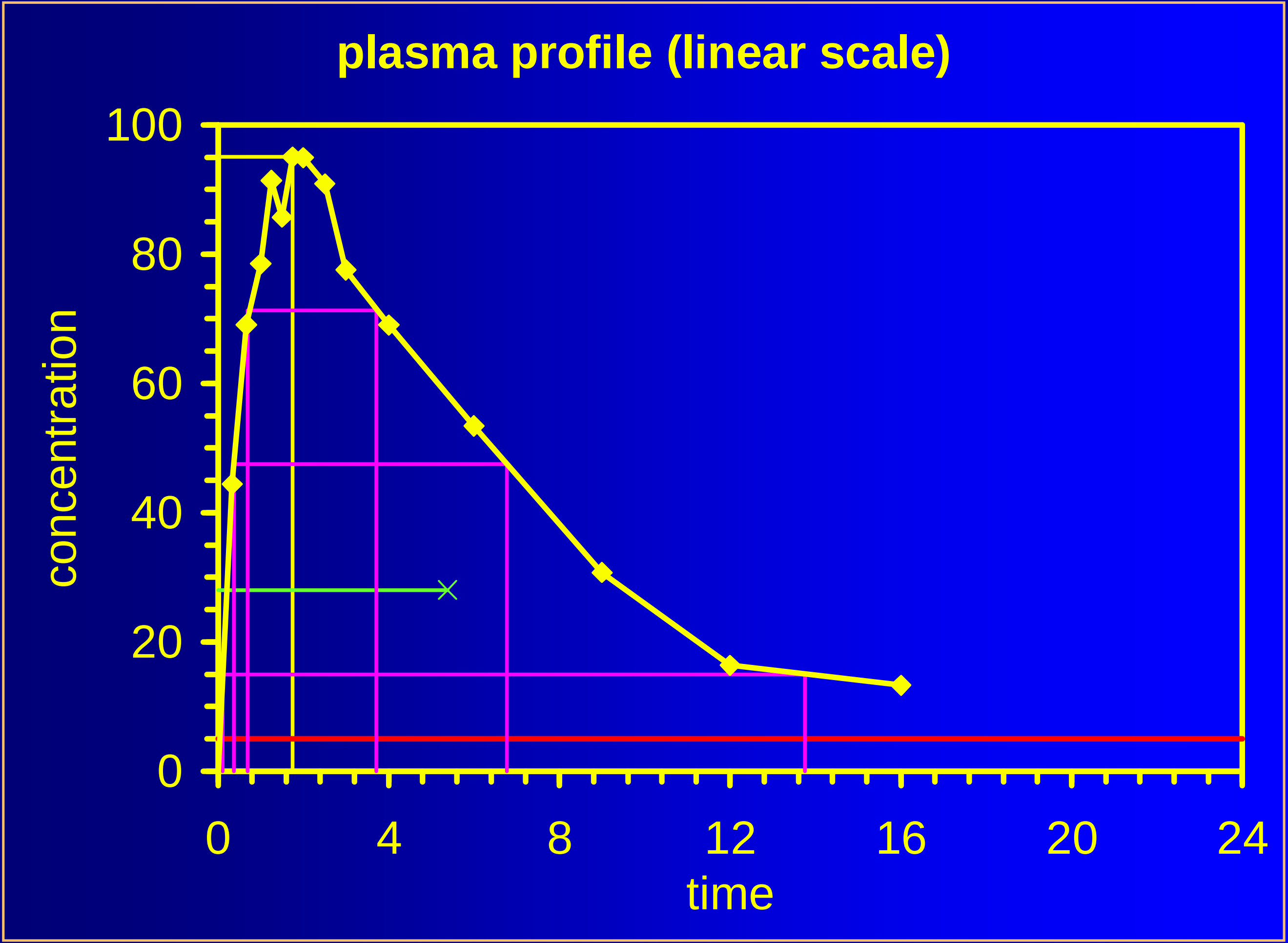


plasma profile (semilogarithmic scale)
100
10
1
concentration
0
4
8
12
16
20
24
time
C_t
$\hat{C}_t$

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)
100
80
60
40
20
0
concentration
0
4
8
12
16
20
24
time

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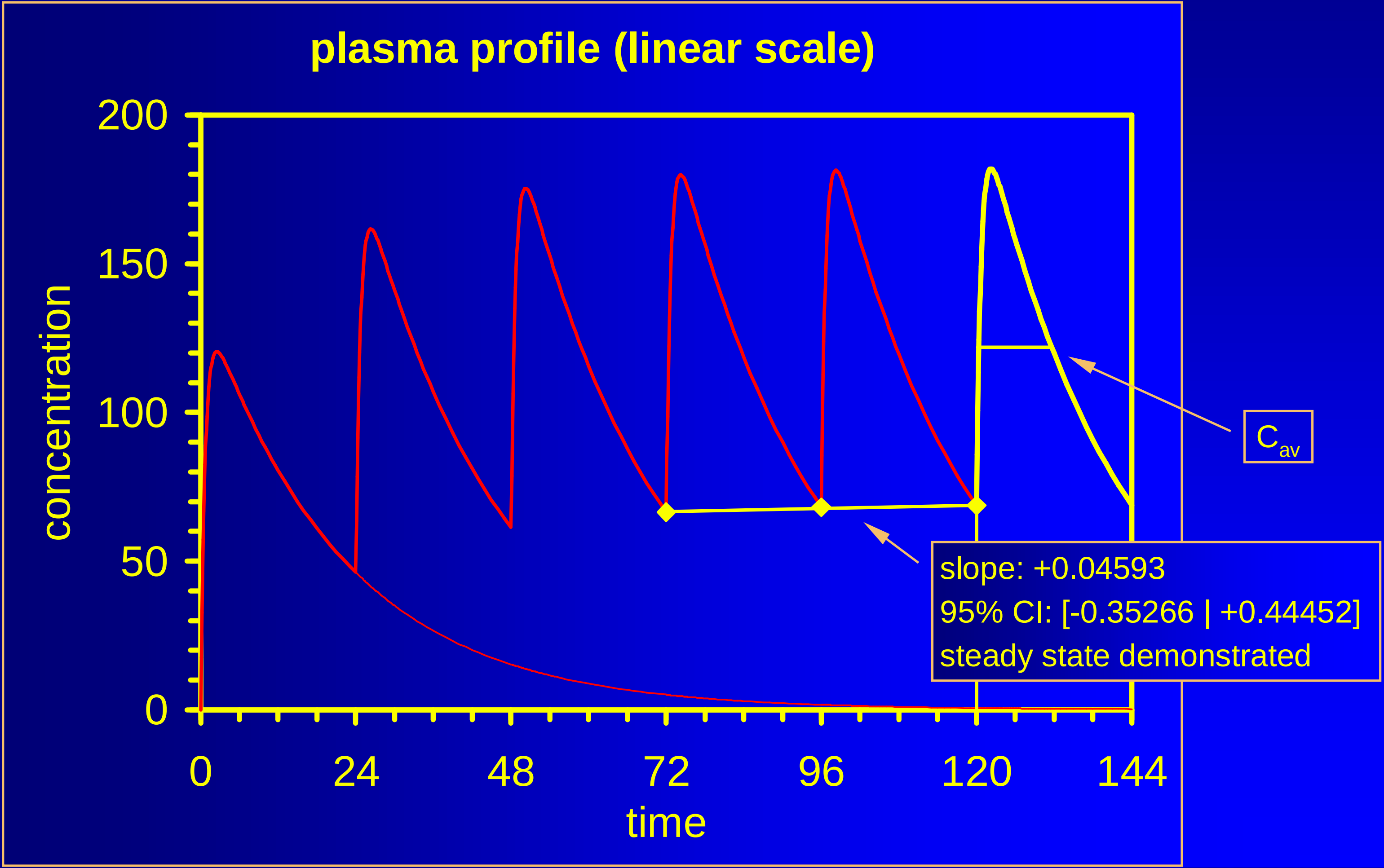
NCA

- Multiple dose
  - Calculation of AUC_τ (τ: dosage interval); $AUC_{ss,24h}$ if more than *o.a.d.* and chronopharmacological 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: $(C_{ss,max} – C_{ss,min}) / C_{ss,min}$

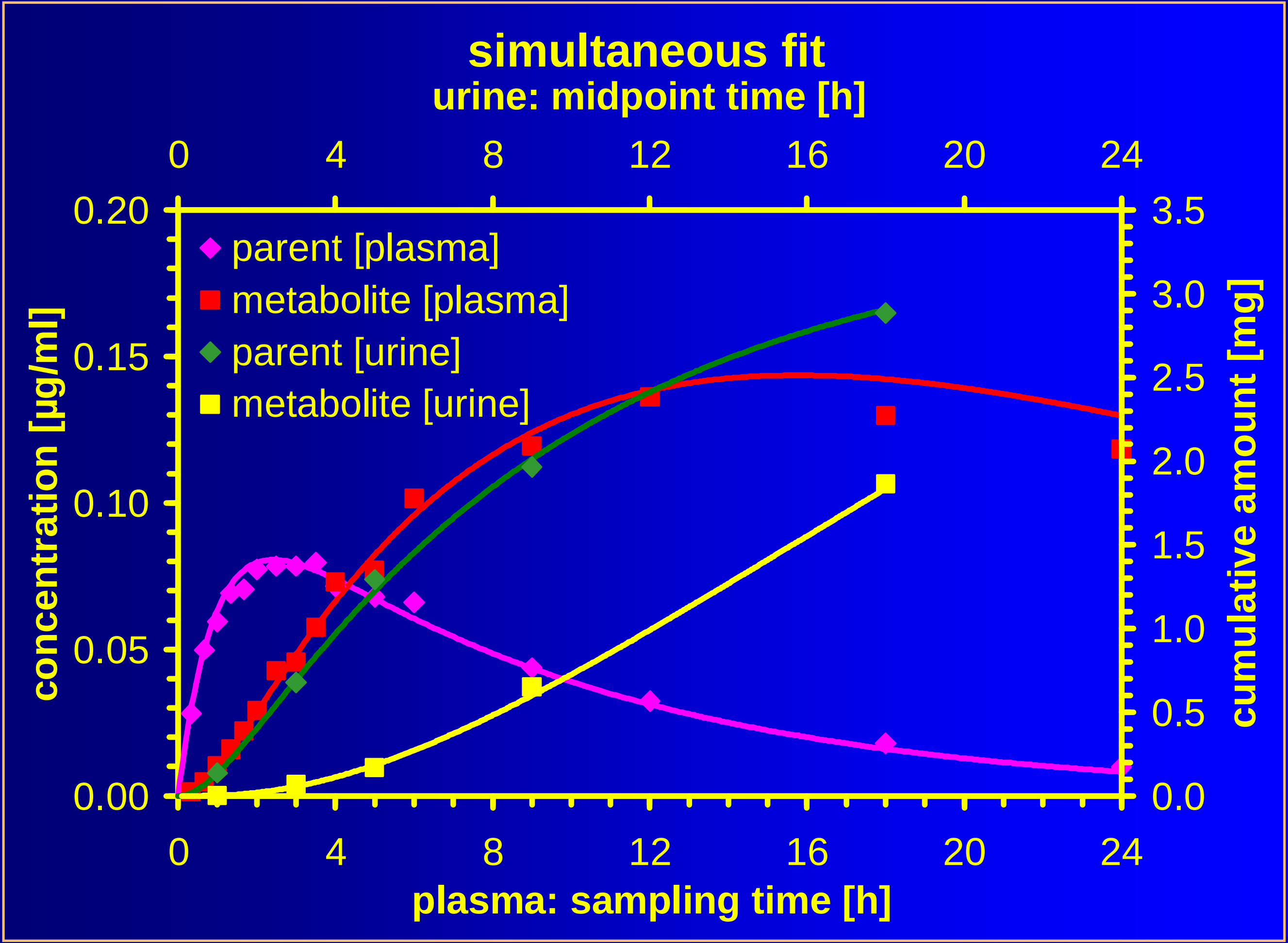
NCA

- Multiple dose
  - Assessment whether steady state is reached (in a linear PK system: $AUC_\tau = AUC_\infty$)
    - No recommendations in GLs (except EU/US Veterinary)
    - 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
Cav
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
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
parent [plasma]
metabolite [plasma]
parent [urine]
metabolite [urine]
concentration [µg/ml]
cumulative amount [mg]
plasma: sampling time [h]

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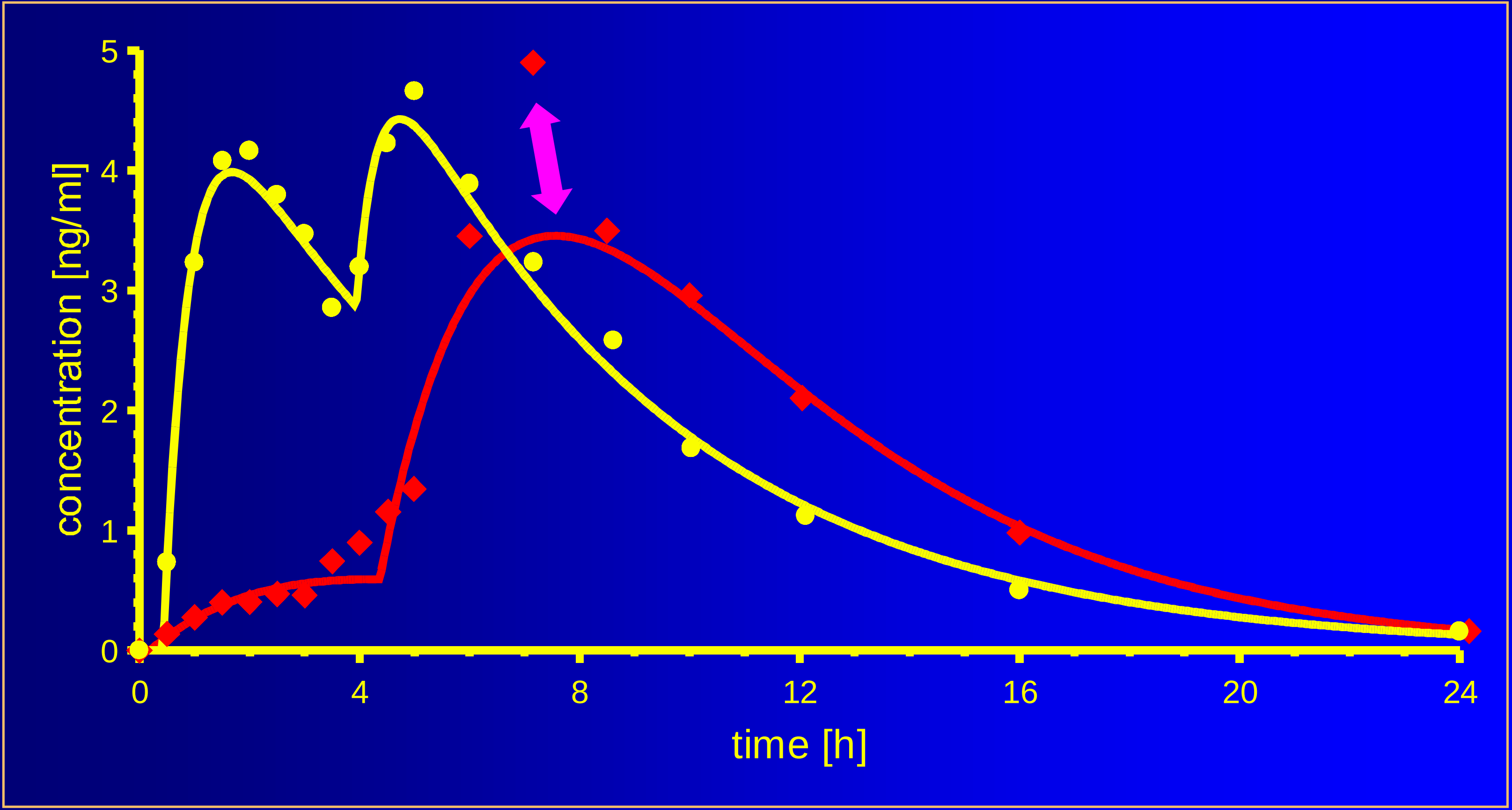
PK Modeling



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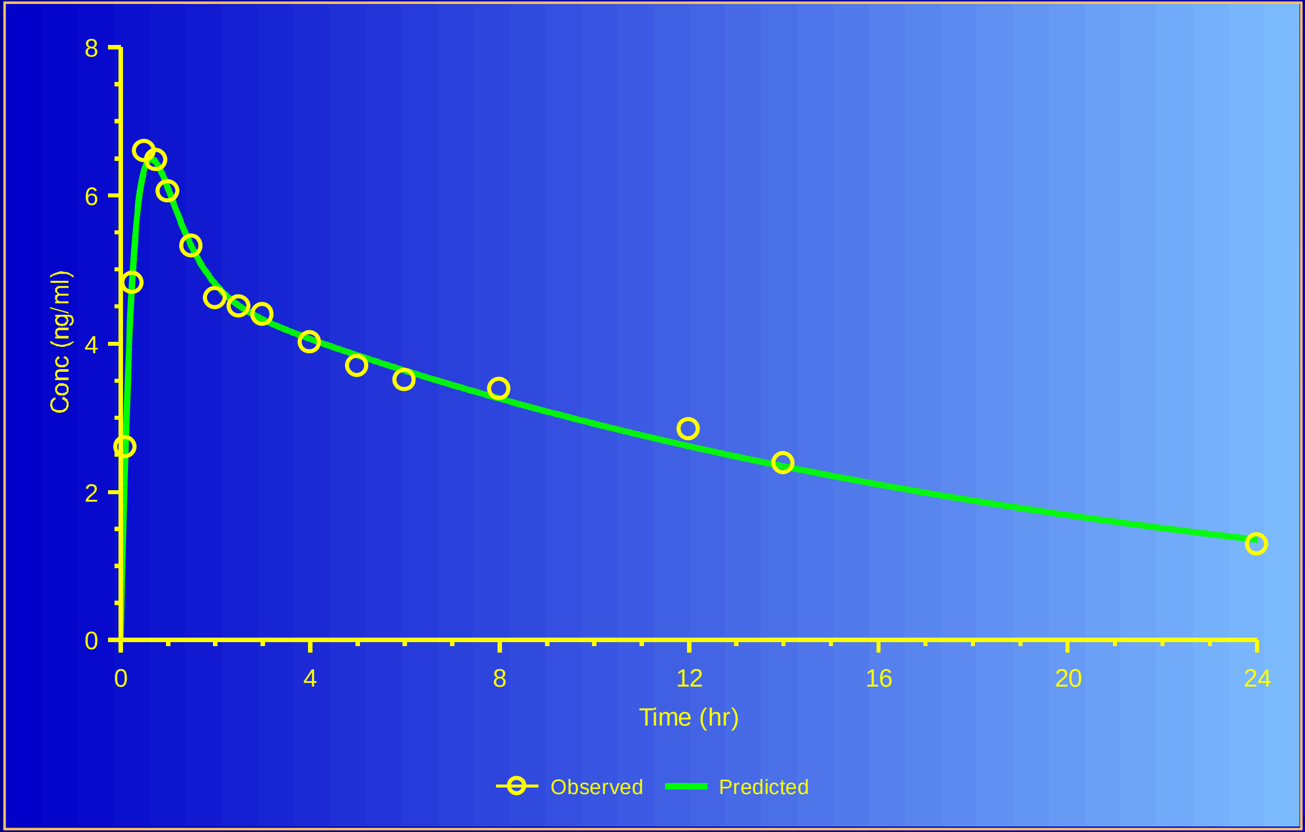
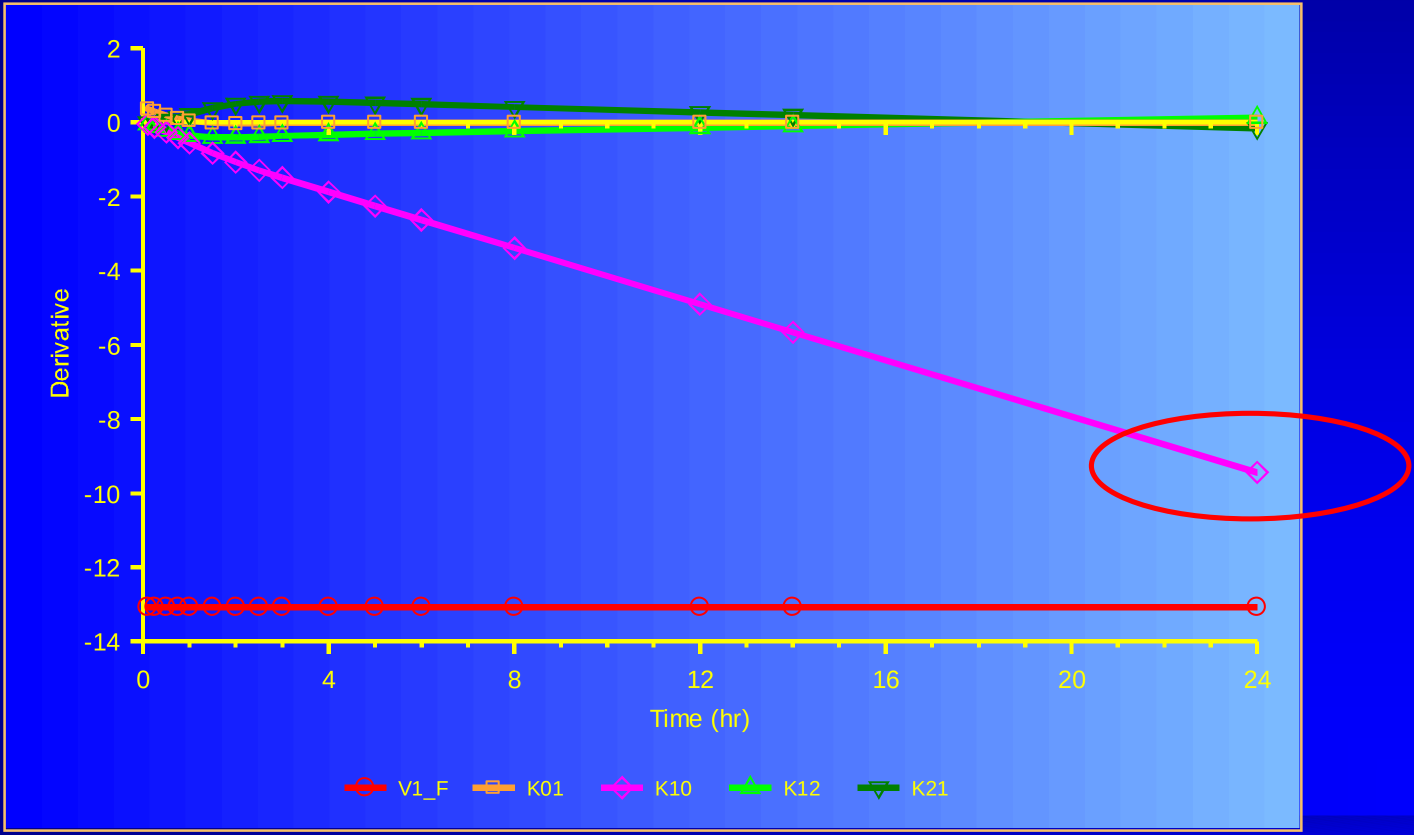
PK Modeling

- WinNonlin's Exp1.pwo, Model 11, w=1/pred²



PK Modeling

- Partial Derivatives



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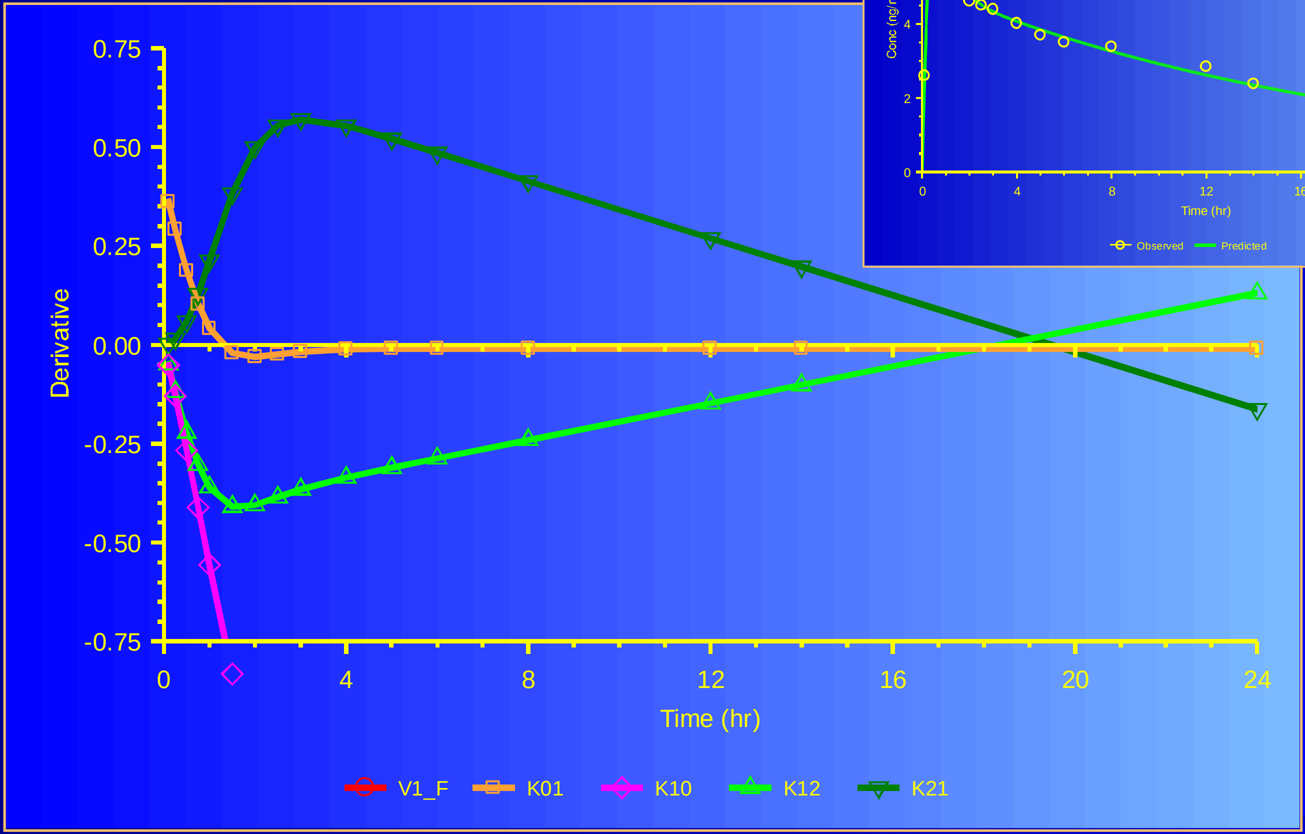
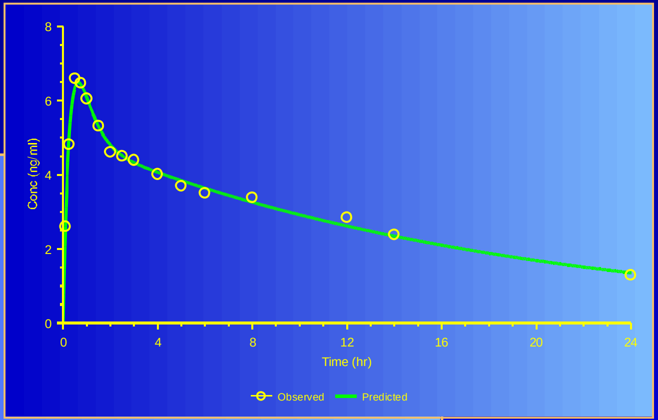
PK Modeling

- Partial Derivatives



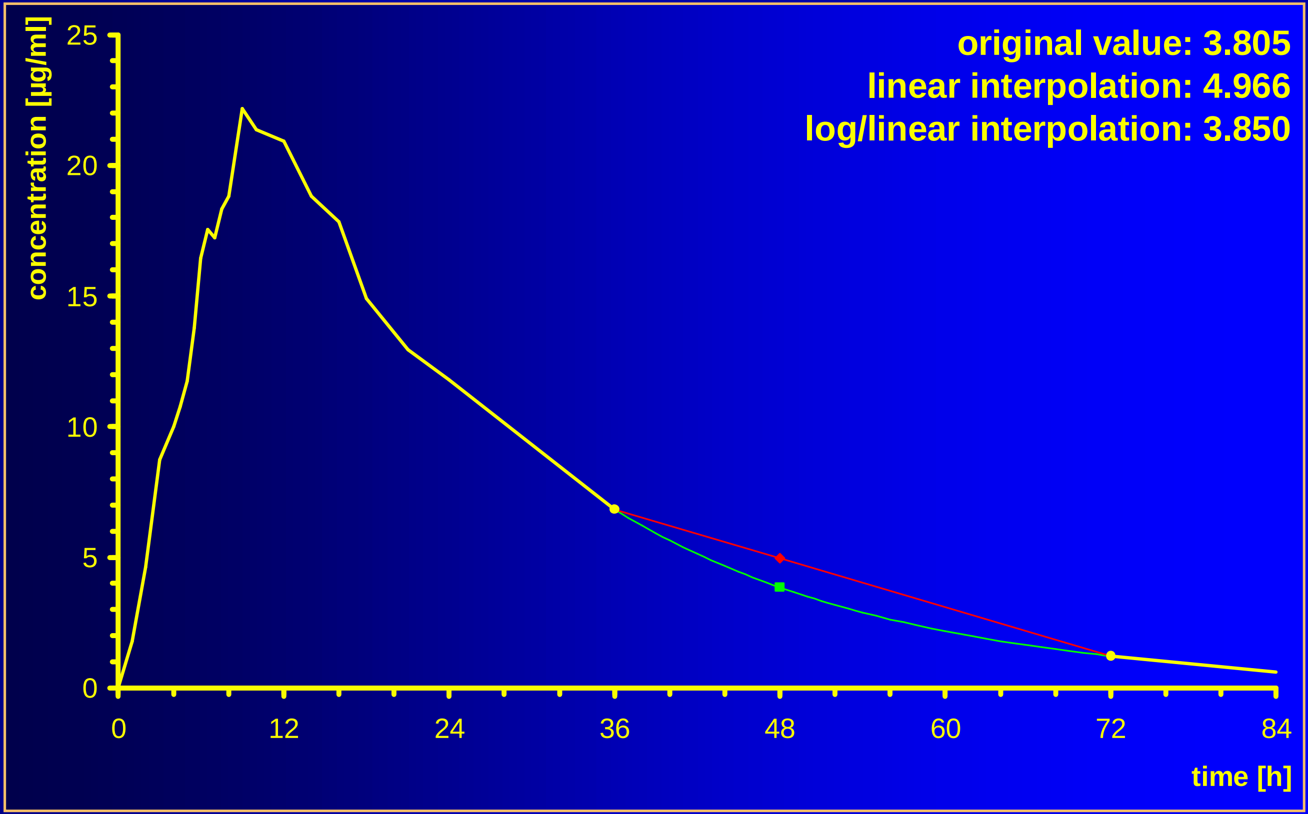


Some Problems…

- 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…

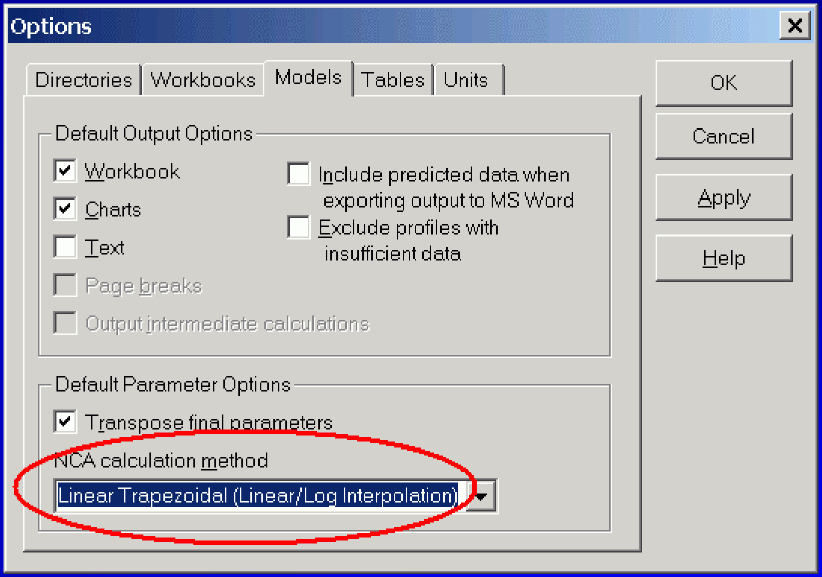
- Missing values I



Some Problems…

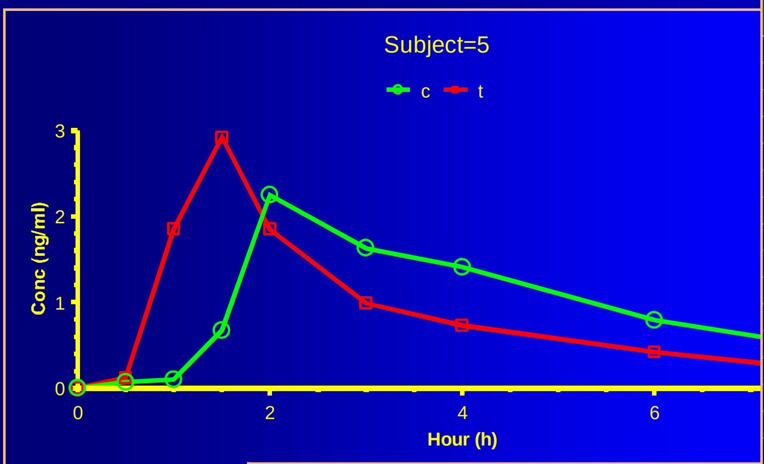
- Missing values I

  Recommended Procedure may not be the ‘default’ in your software (has to be actively set, *e.g.*, in WinNonlin 5+)



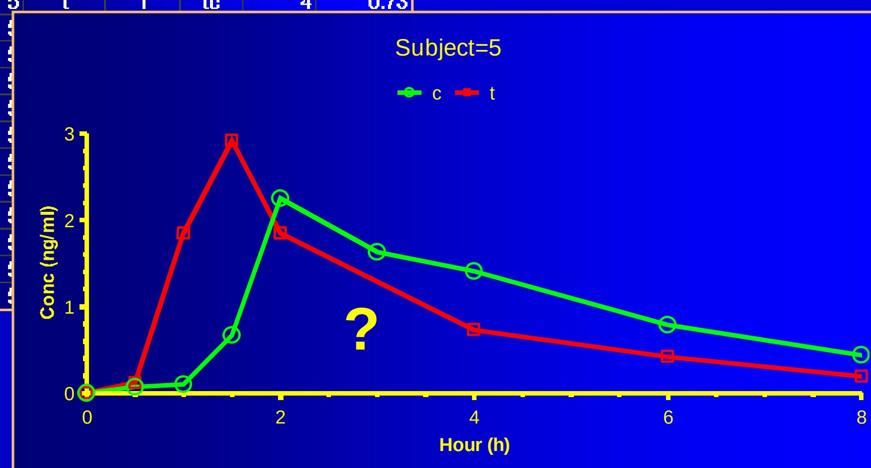
Some Problems…

- 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%



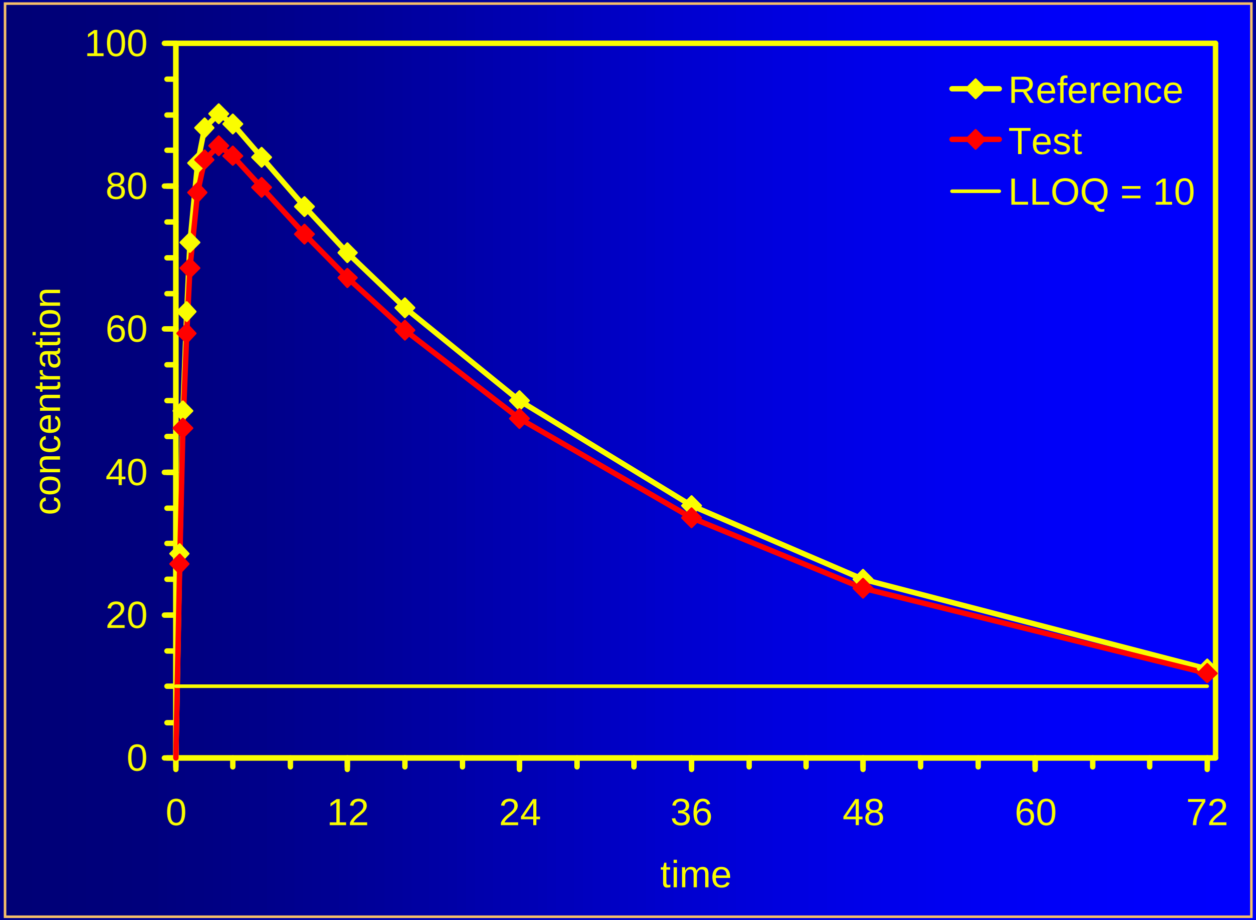
Some Problems…

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

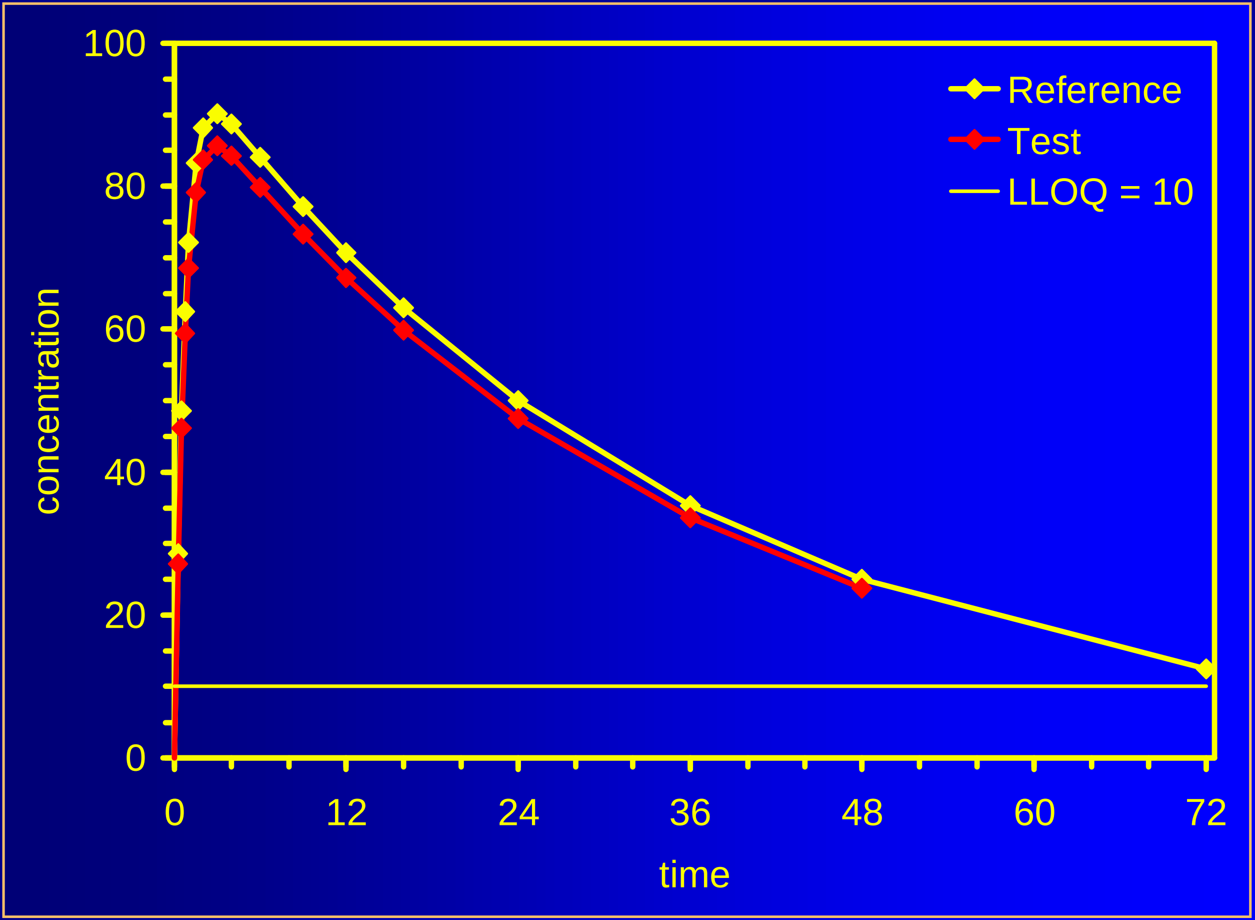
      $t_{½abs}$ = 0.5, $t_{½el}$ = 24
      T/$R_{theoret.}$ = 95%, LLOQ = 10
      AUC_{72}: T = 2835, R = 2984
      T/R = 95% ✓

	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…



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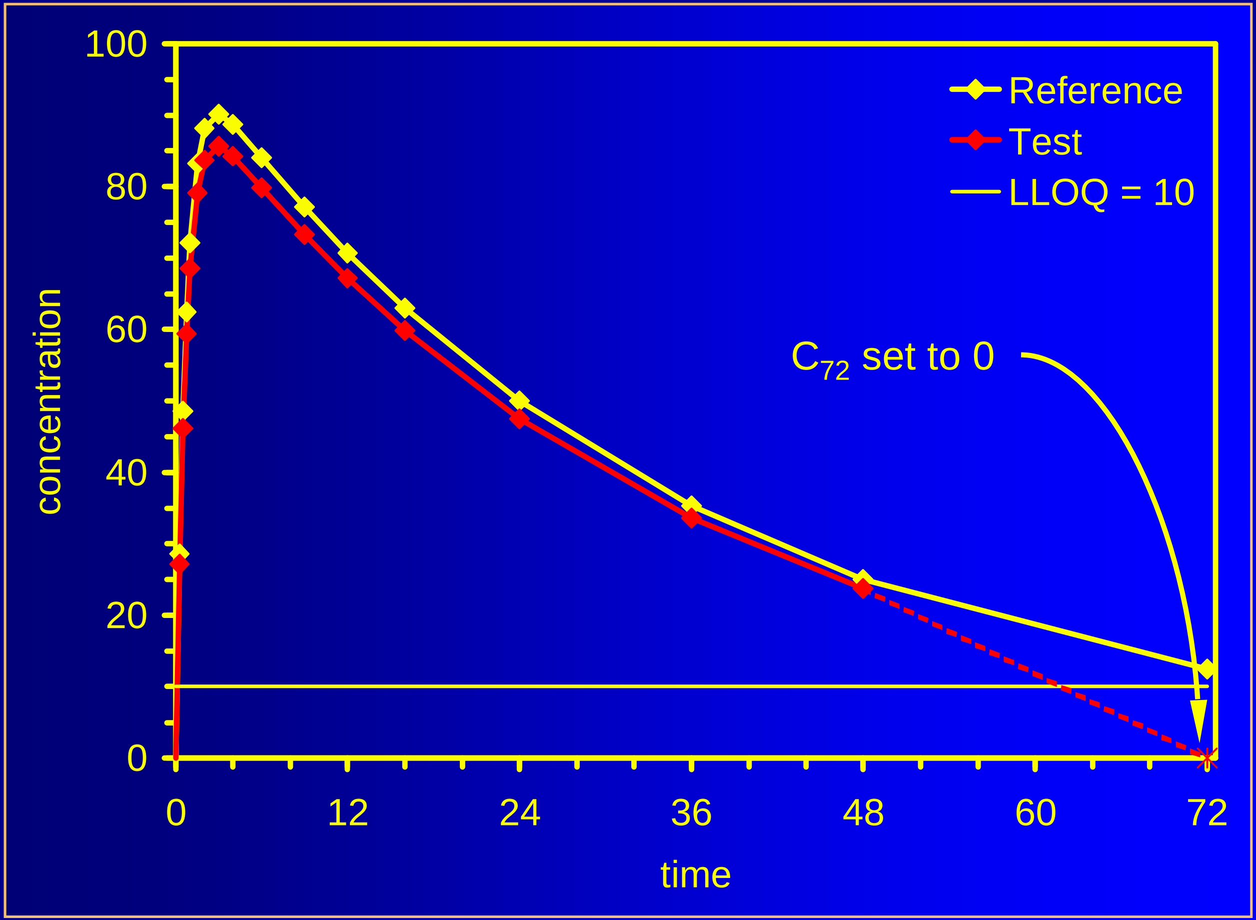
24	50.00	1660	47.50	1577
36	35.36	2172	33.59	2063
48	25.00	**2534**	23.75	**2407**
72	12.50	**2984**	Missing	NA

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
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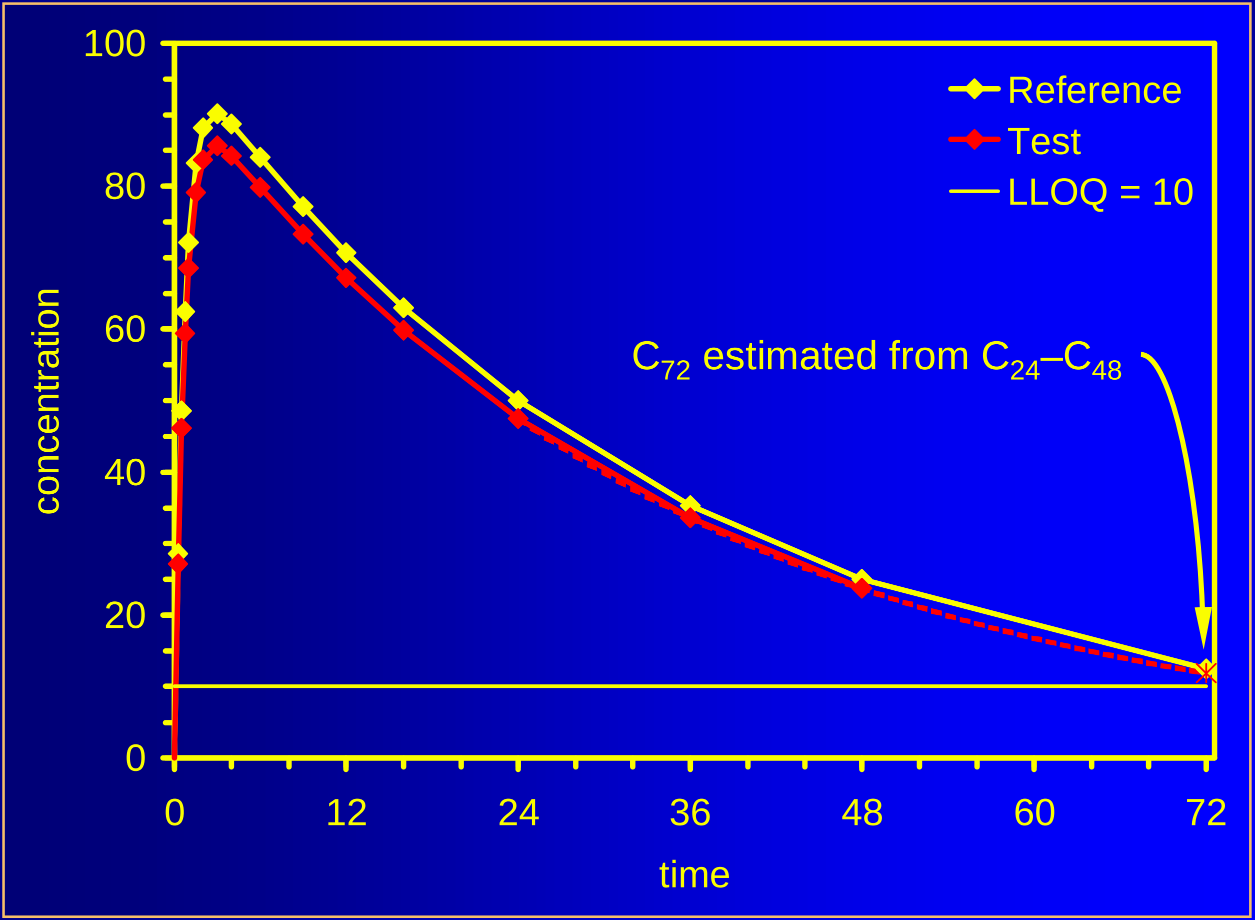
36	35.36	2172	33.59	2063
48	25.00	2534	23.75	2407
72	12.50	**2984**	= *0	**2692**

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
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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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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}
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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

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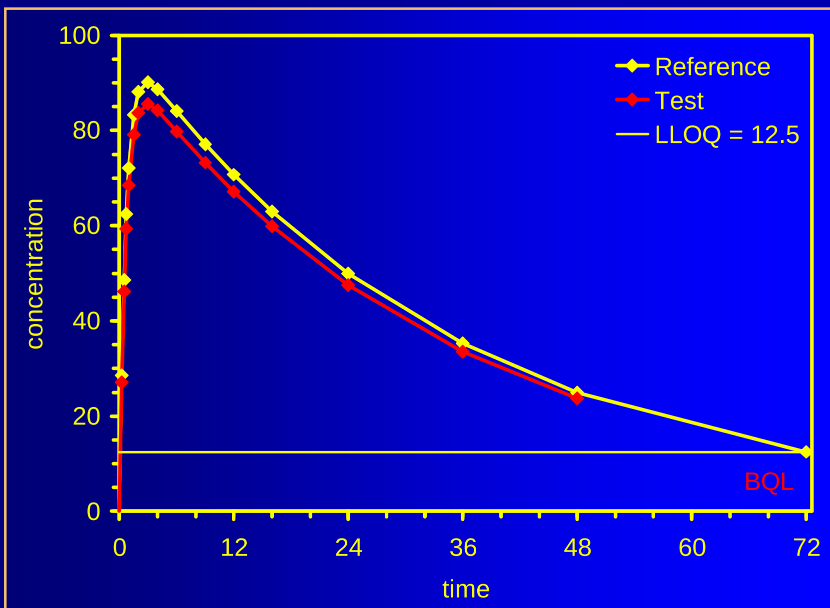
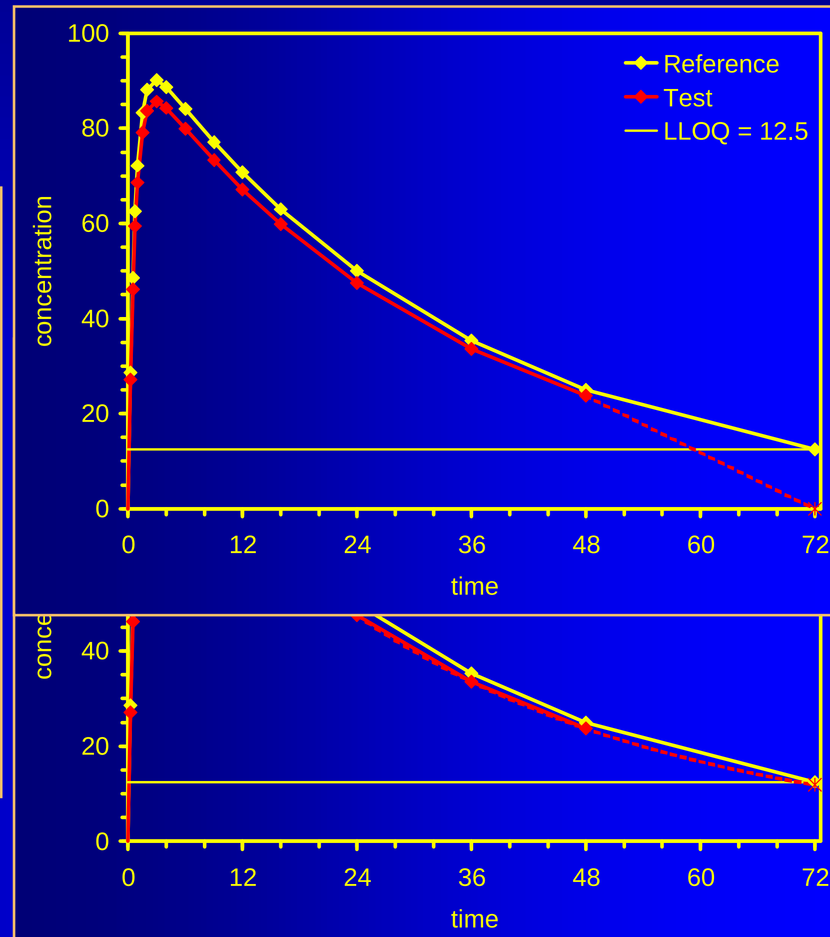
Some Problems…

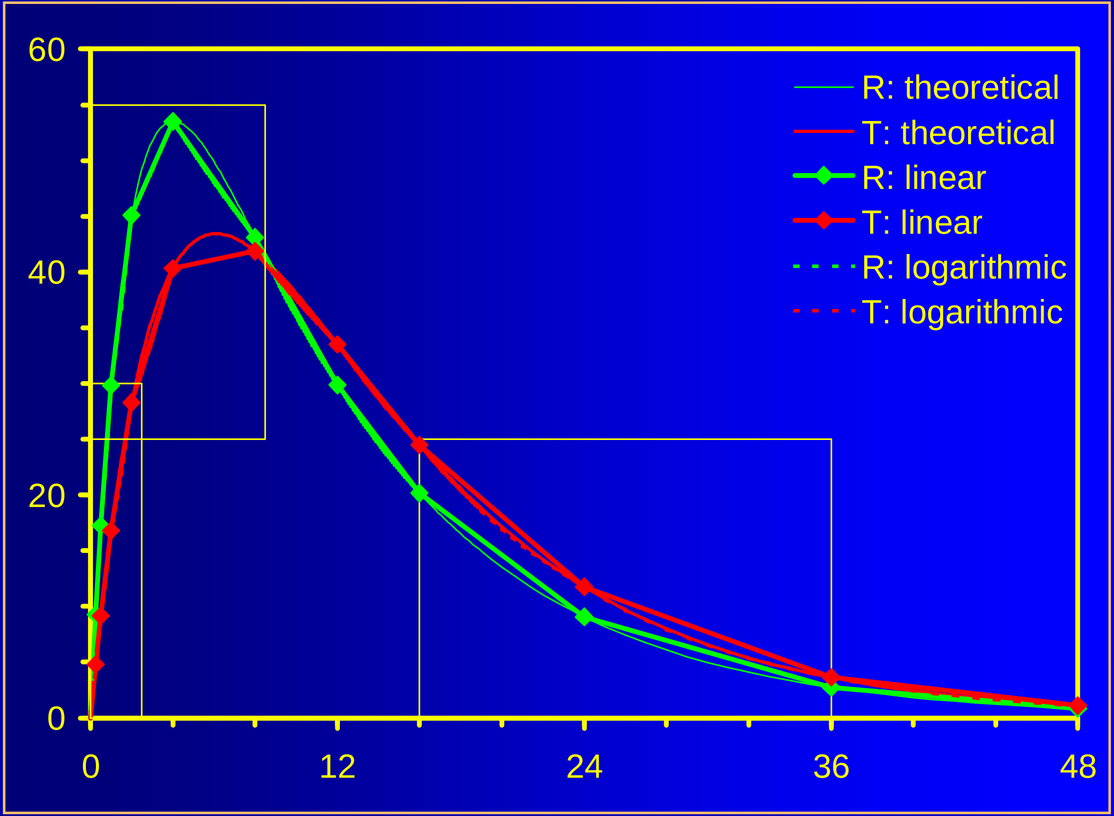
What would you do?





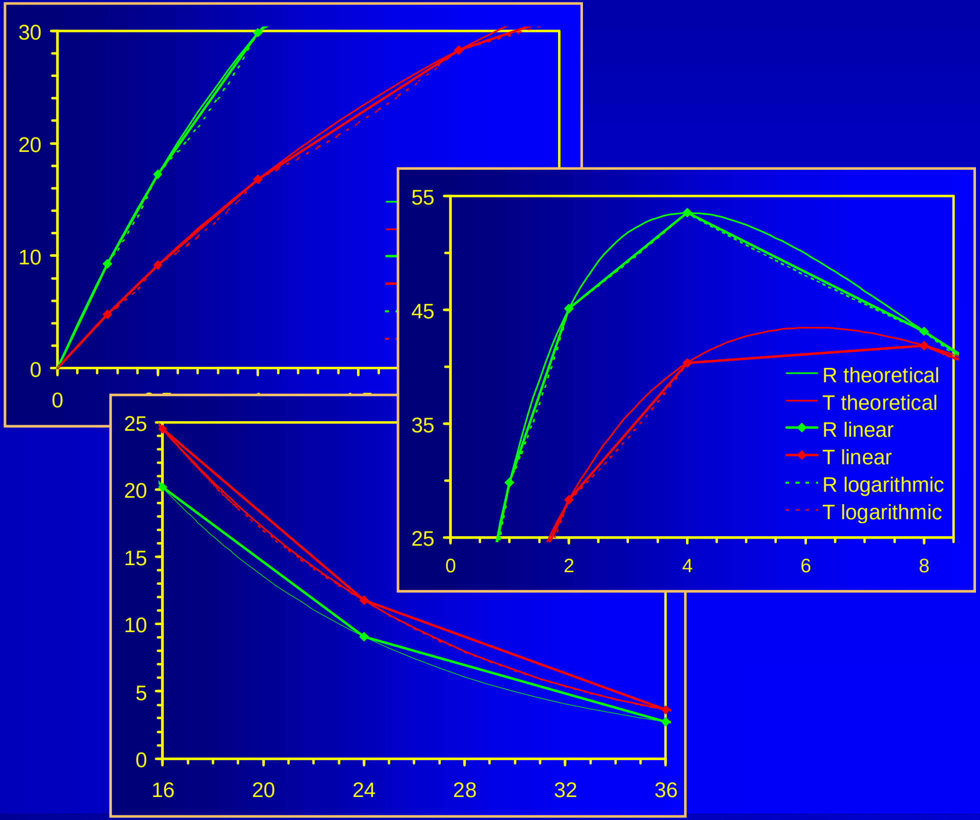
Trapezoidal rule(s!)

- 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%

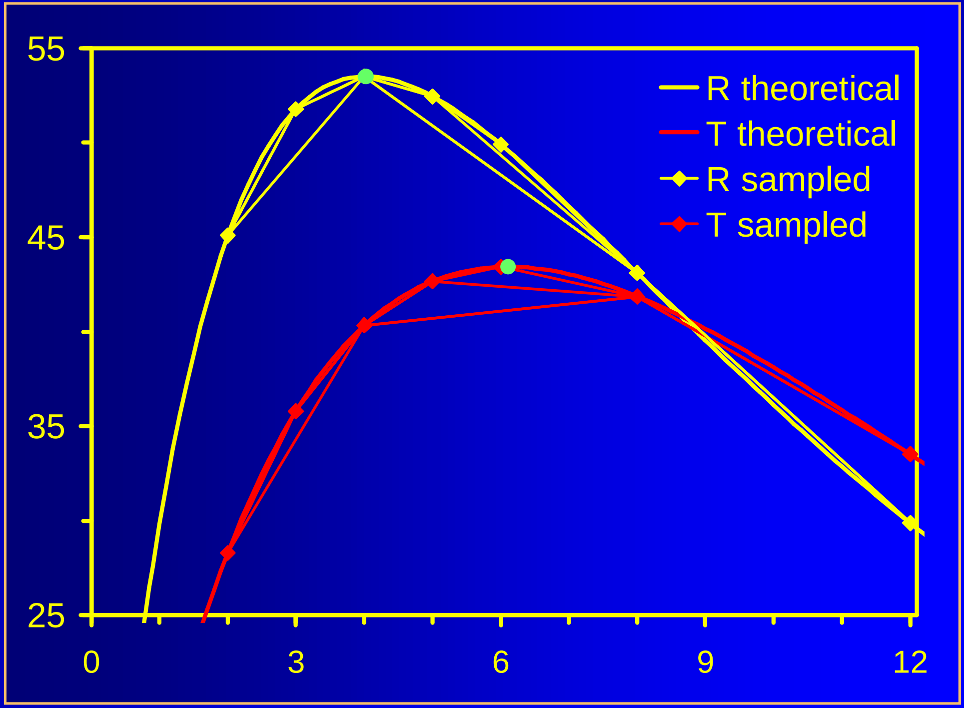


Sampling at C_{max}

- 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



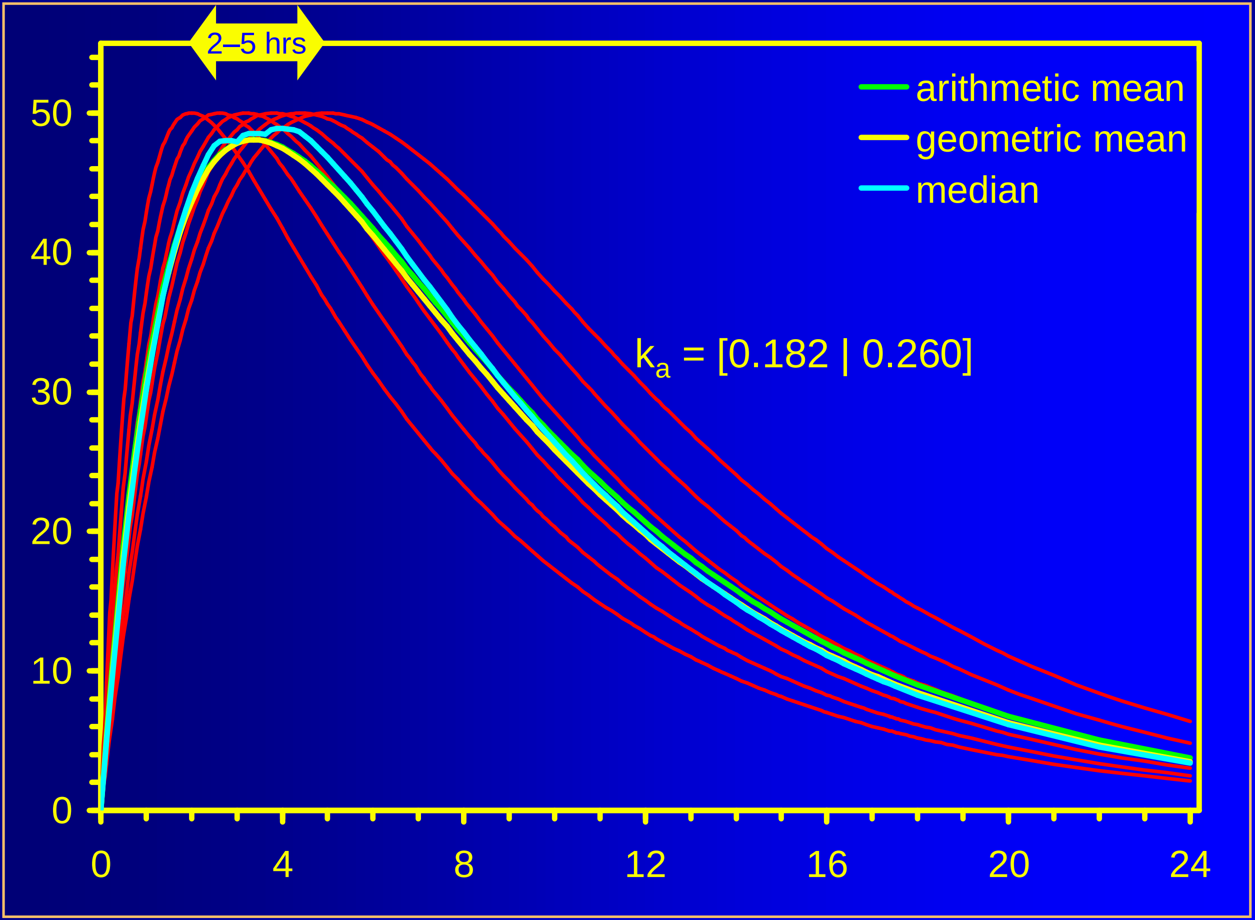
Sampling at C_{max}

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

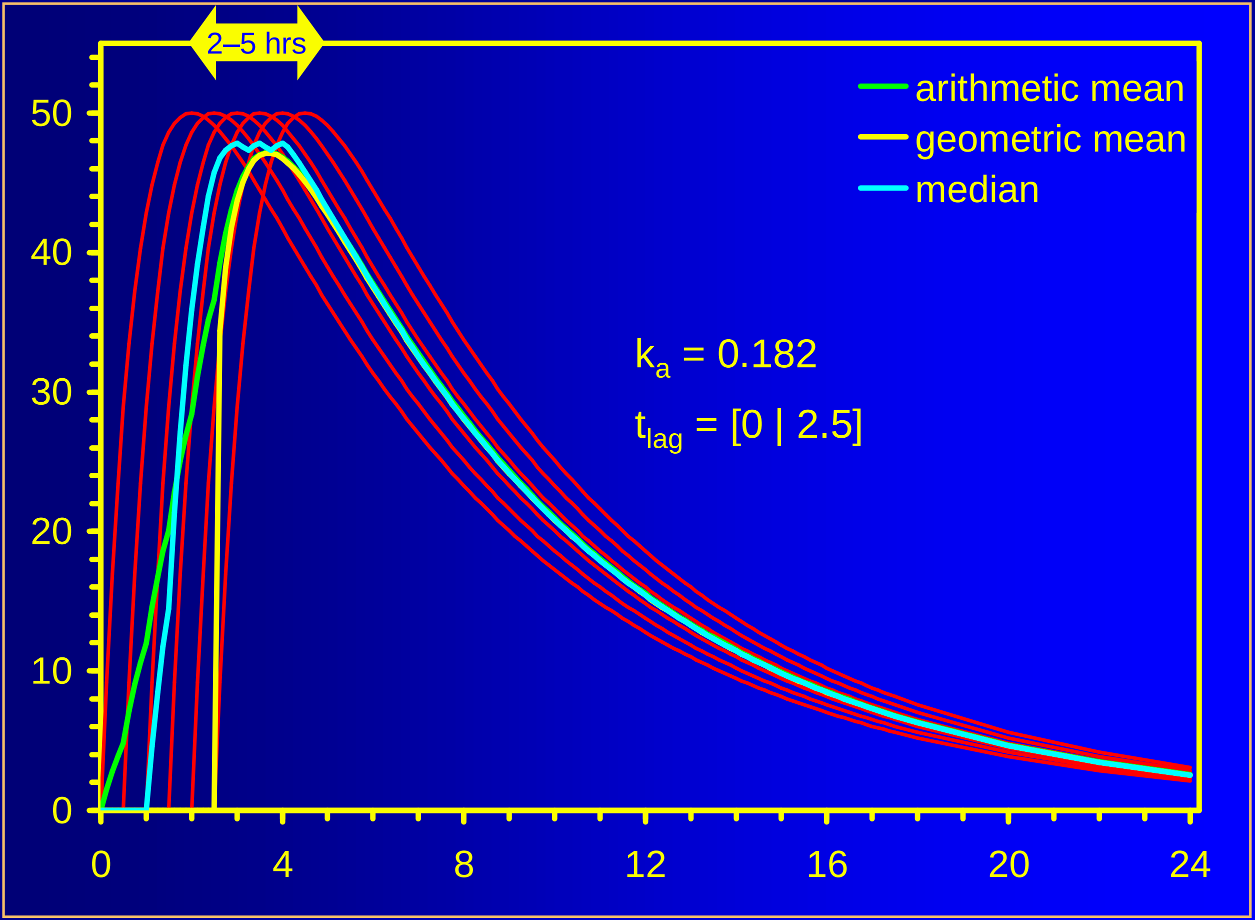
Sampling at C_{max}

- 'C_{max} was observed within two to five hours after 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}



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.

BE BAC

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, 23 July 2009
http://www.emea.europa.eu/pdfs/human/ewp/61860408en.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).

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!

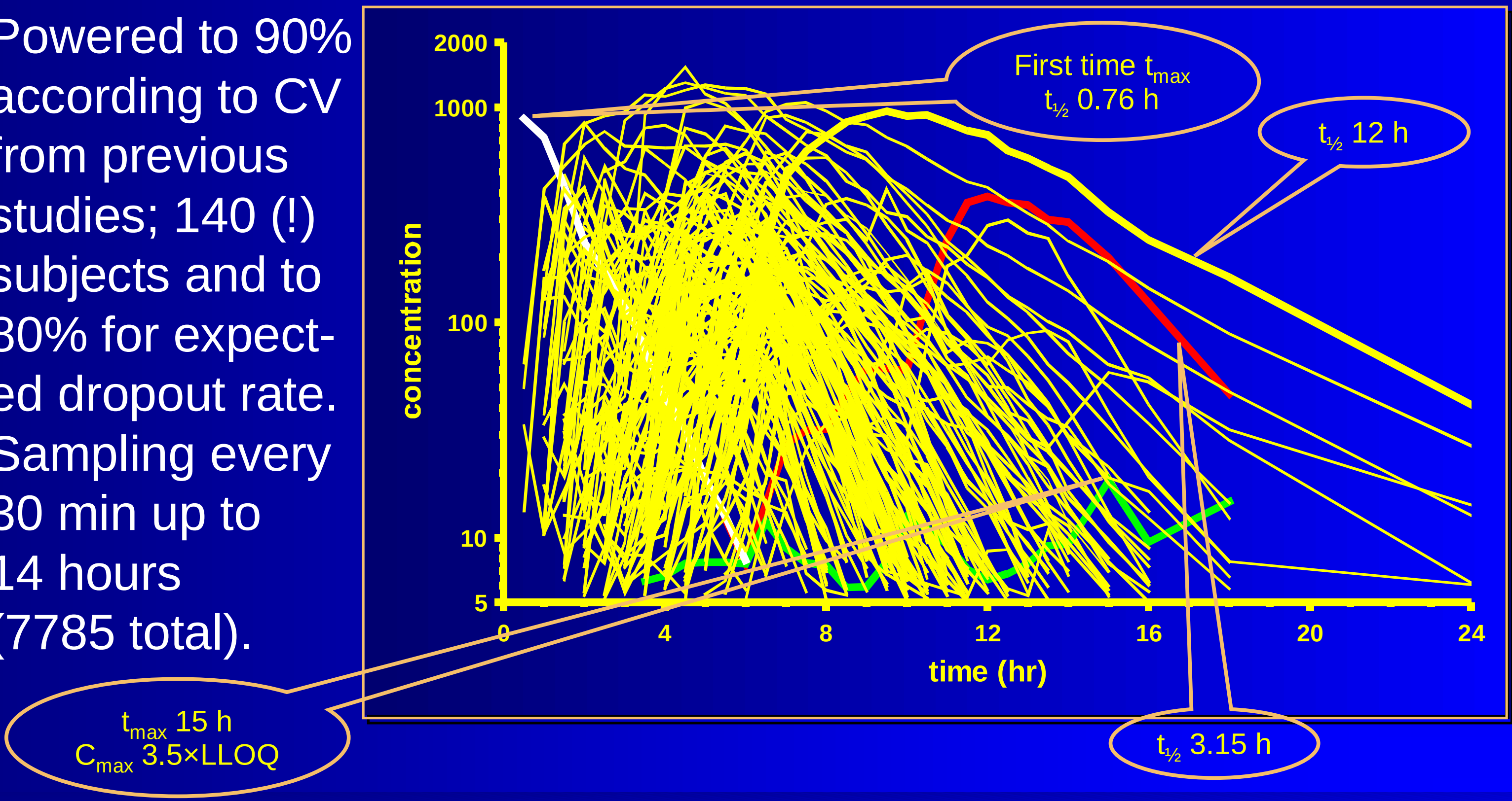
Another Problem

- 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.

Case Study (PPI)

- Attempt to deal with high variability in C_{max}

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 (7785 total).



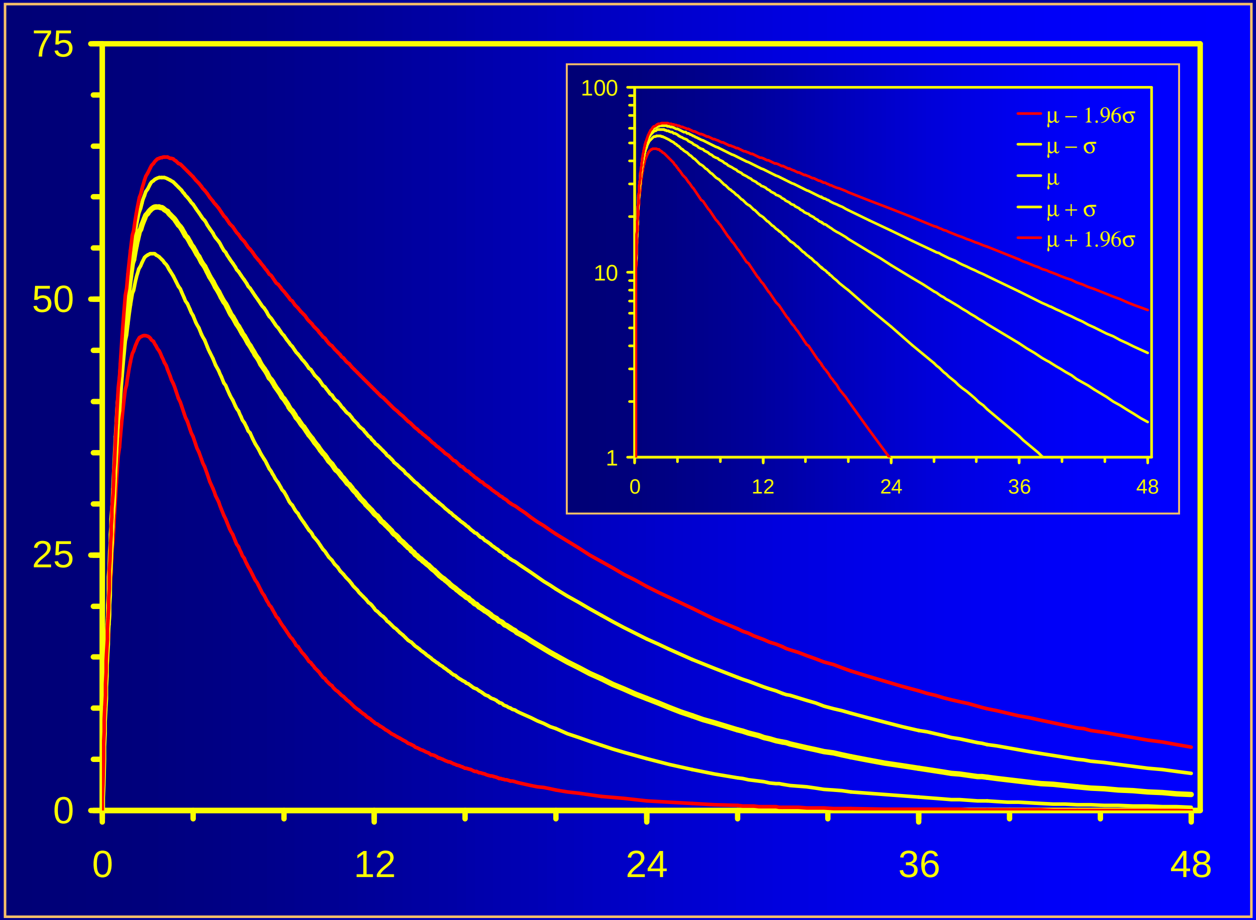
Half lives

- Drug specific, *but*…
  - The *apparent* elimination presents 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
    - 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 outside $\mu \pm \sigma$)
    - 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):
      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



BE BAC

Washout in MD Studies

- EMA GL on BE (2010)

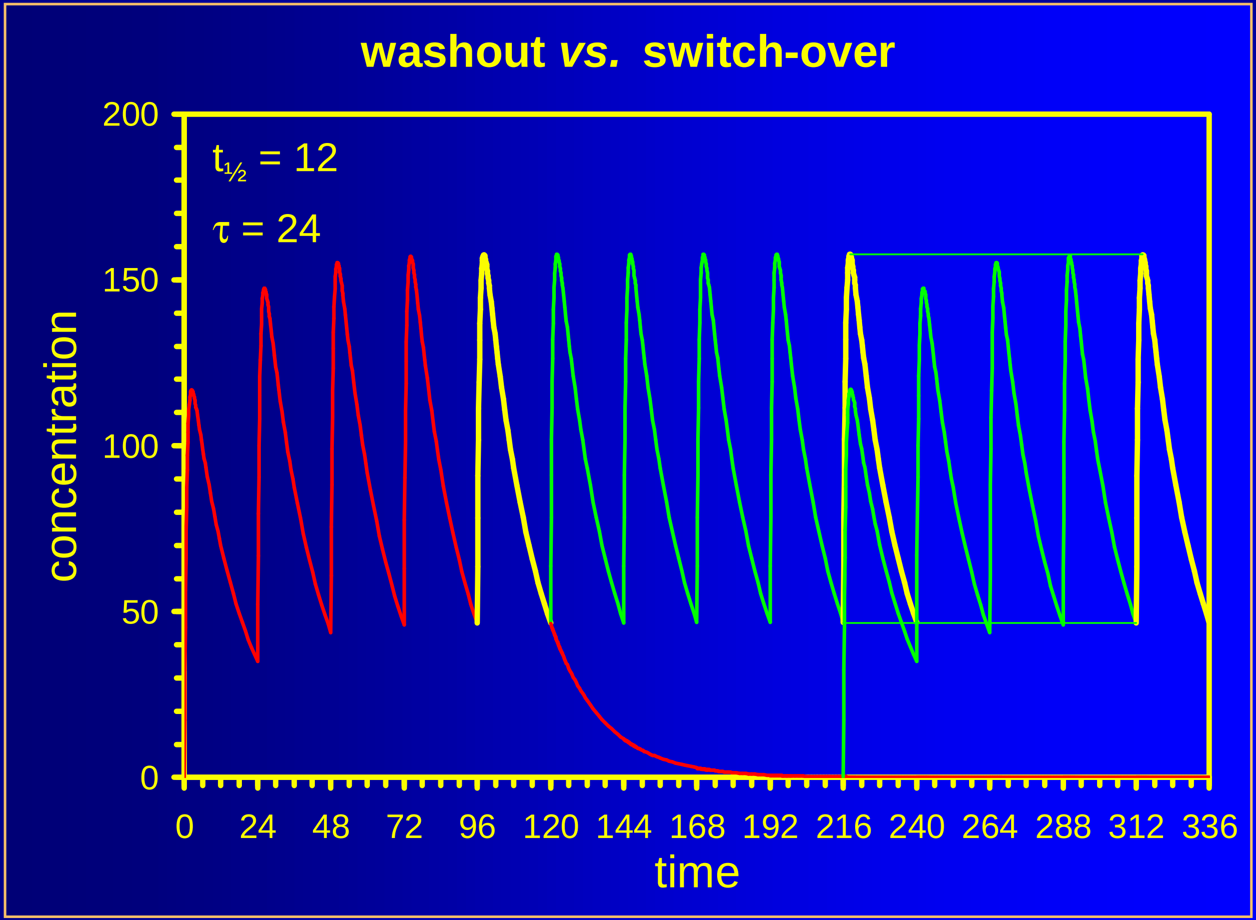
  The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally at least 5 elimination half-lives are necessary to achieve this. In steady-state studies, the wash out period 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 5 times the terminal half-life).

  - Justified by Superposition Principle
  - 'Switch-over Design'

2001 NfG:
3 half-lives

informa
life sciences

Washout in MD Studies



Thank You!
Noncompartmental Analysis (NCA) in PK, PK-based Design
Open Questions?

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