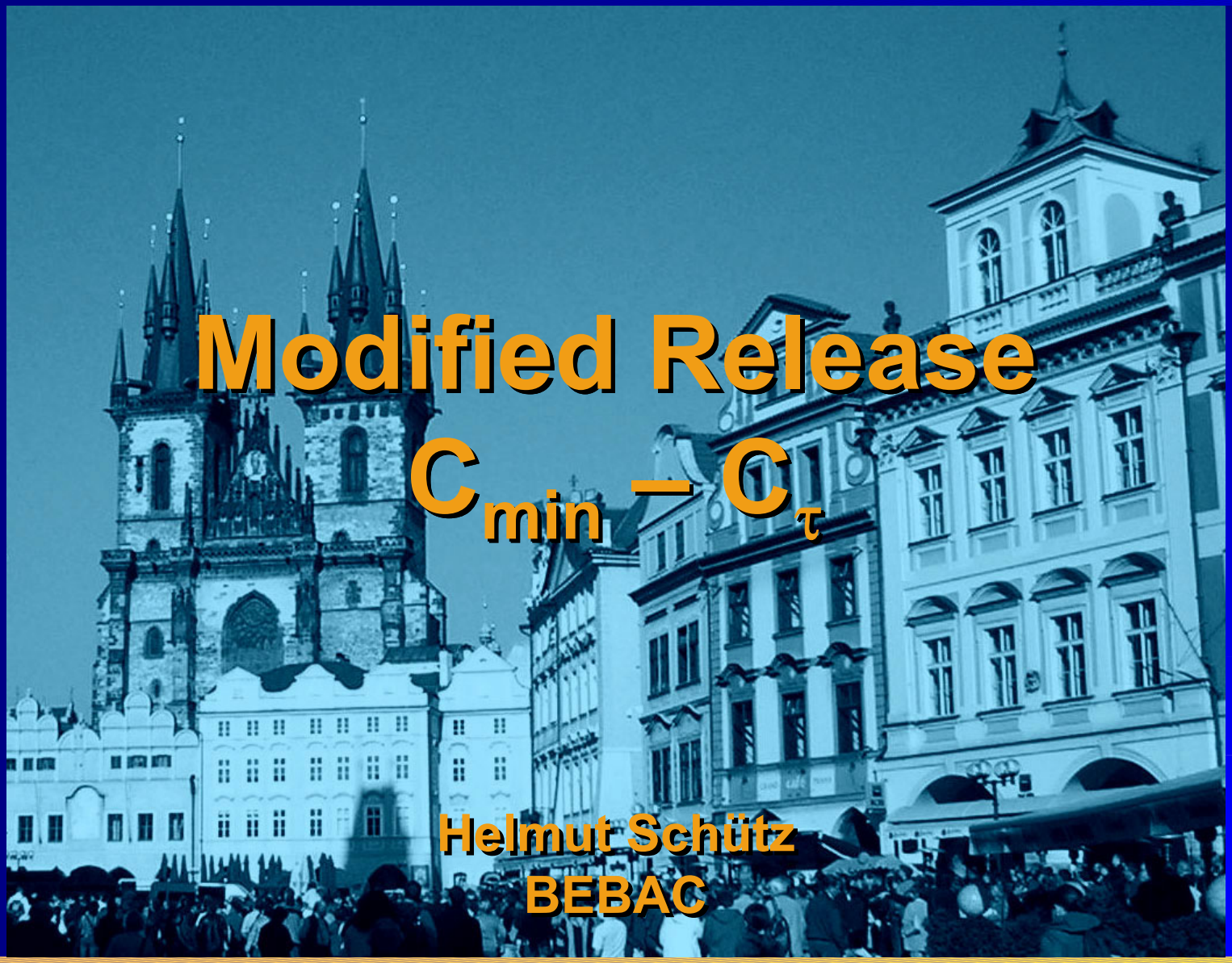


Modified Release
$C_{min} - C_{\tau}$

Helmut Schütz
BEBAC

Another Reminder

Rose
is a rose
is a rose
is a rose.

Gertrude Stein (1913)

Guidelines
are guidelines
are guidelines.

Henrike Potthast (ca. 2004)

No one wants to learn from mistakes,
but we cannot learn enough from successes
to go beyond the state of the art.

Henry Petroski

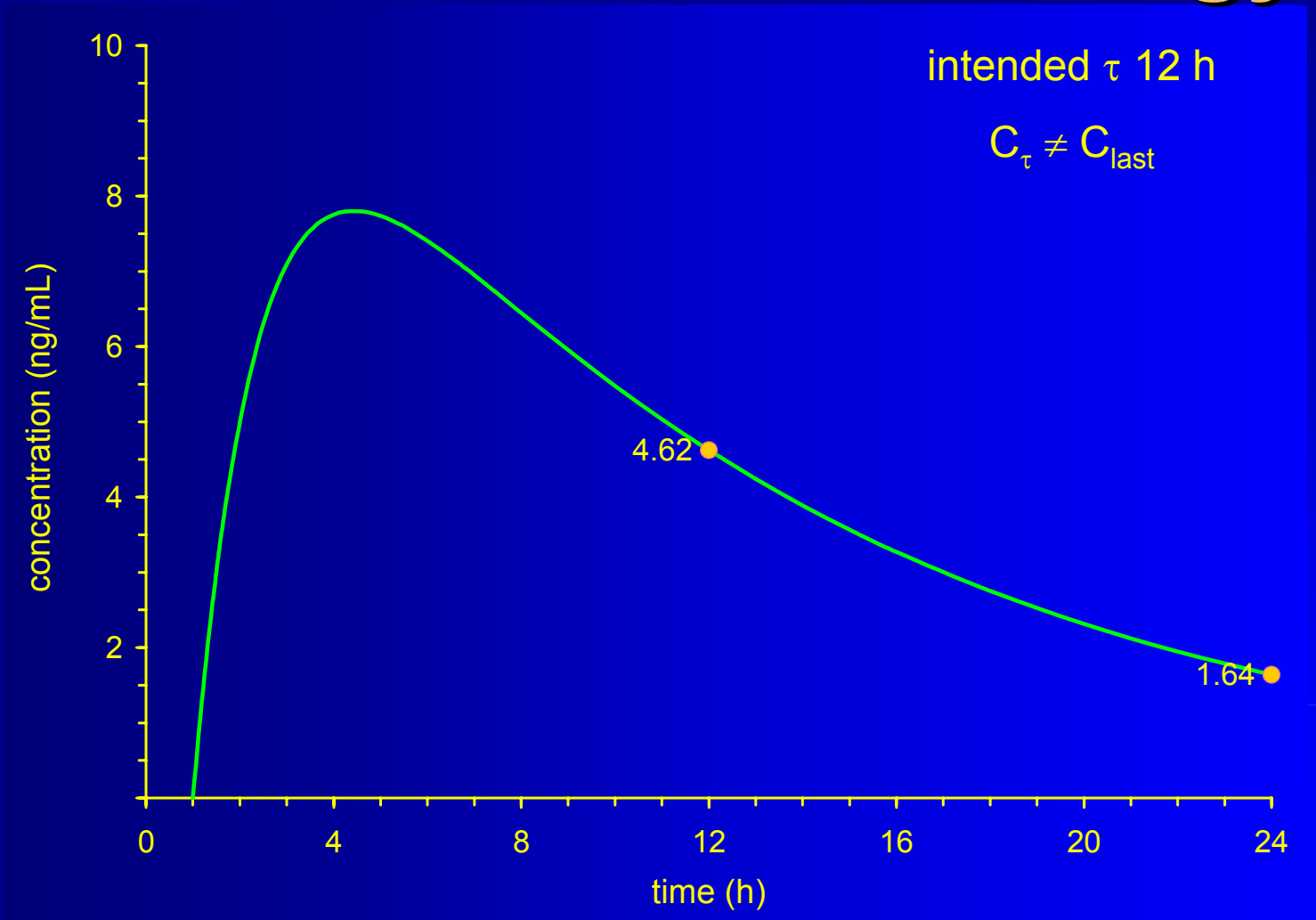
EMA's confusing Terminology

- $C_{min,ss}$
  - *"By $C_{min,ss}$ we mean the concentration at the end of the dosing interval, i.e. C_{trough}."* (2010 BE GL Commentary p89)
- $C_{min,ss}$
  - Minimum concentration at steady state.
- C_{τ}
  - Concentration at the end of the dosing interval.
- $C_{\tau,ss}$
  - Concentration at the end of τ at steady state.

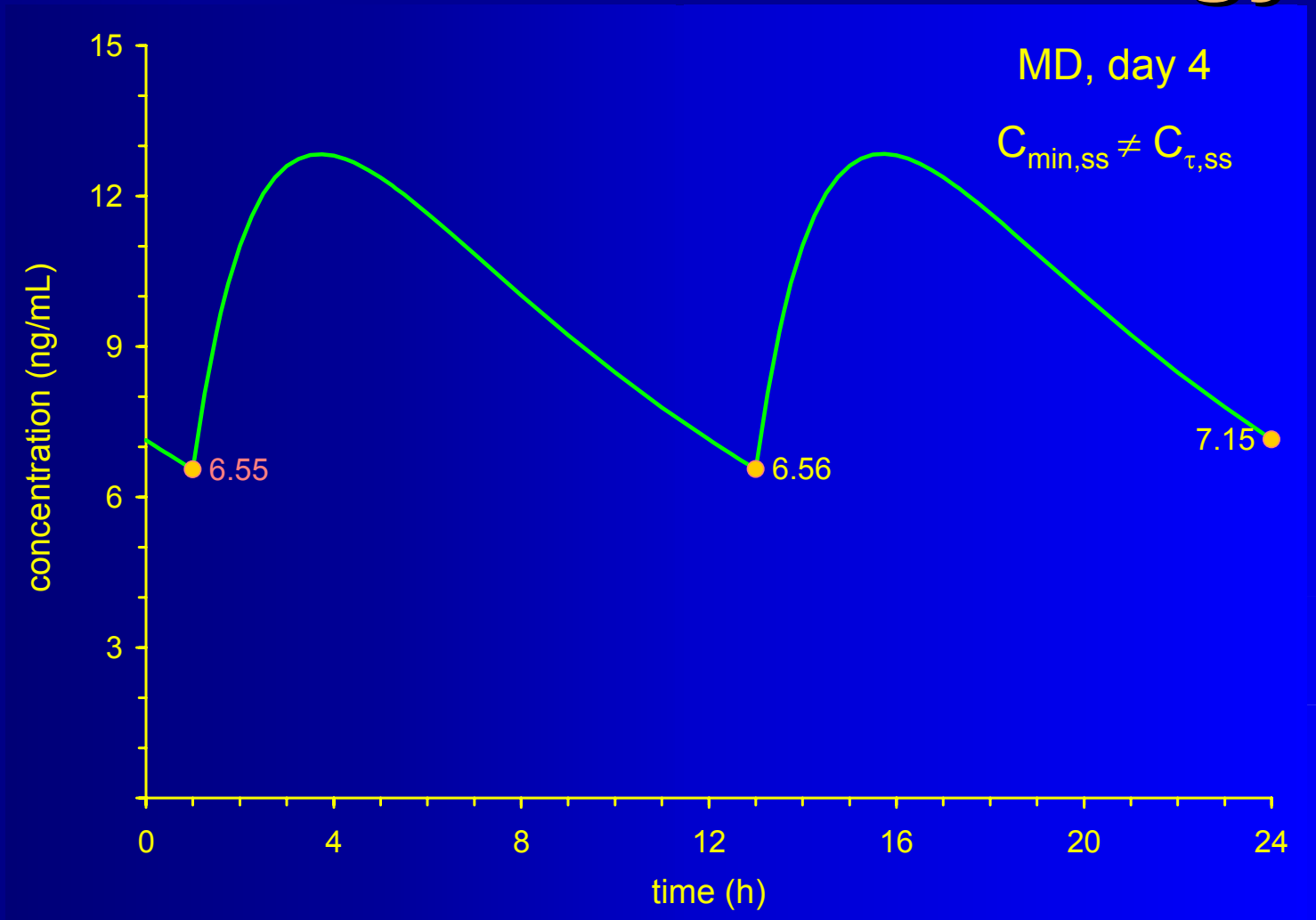
EMA's confusing Terminology

- Clarifications and interpretations
  - Single dose metrics
    - C_{τ} Concentration at the end of the [intended] dosing interval. Not necessarily C_{last}!
  - Multiple dose metrics
    - $C_{\tau,ss}$ Concentration at the end of the dosing interval. PK metric if reference is MR.
    - $C_{min,ss}$ [Global] minimum concentration at steady state. PK metric if reference is IR.
  - Cave: Only $C_{min,ss}$ implemented in PK software (minimum concentration within τ) – requires adaption!

EMA's confusing Terminology



EMA's confusing Terminology



Guidelines etc.

- EMEA MR (1999)
  - MR developed after an IR formulation
    - It should be demonstrated that the MR formulation […] produces similar or less fluctuations as the IR product and comparable total systemic exposure that is acceptable in comparison to that of the IR product.
    - The pharmacokinetic parameters of interest are AUC, C_{max} and C_{min} or other means reflecting fluctuation.
  - BE of prolonged release formulations
    - BE of AUC_{τ}, C_{max} and C_{min} applying similar statistical procedures as for the IR formulations.

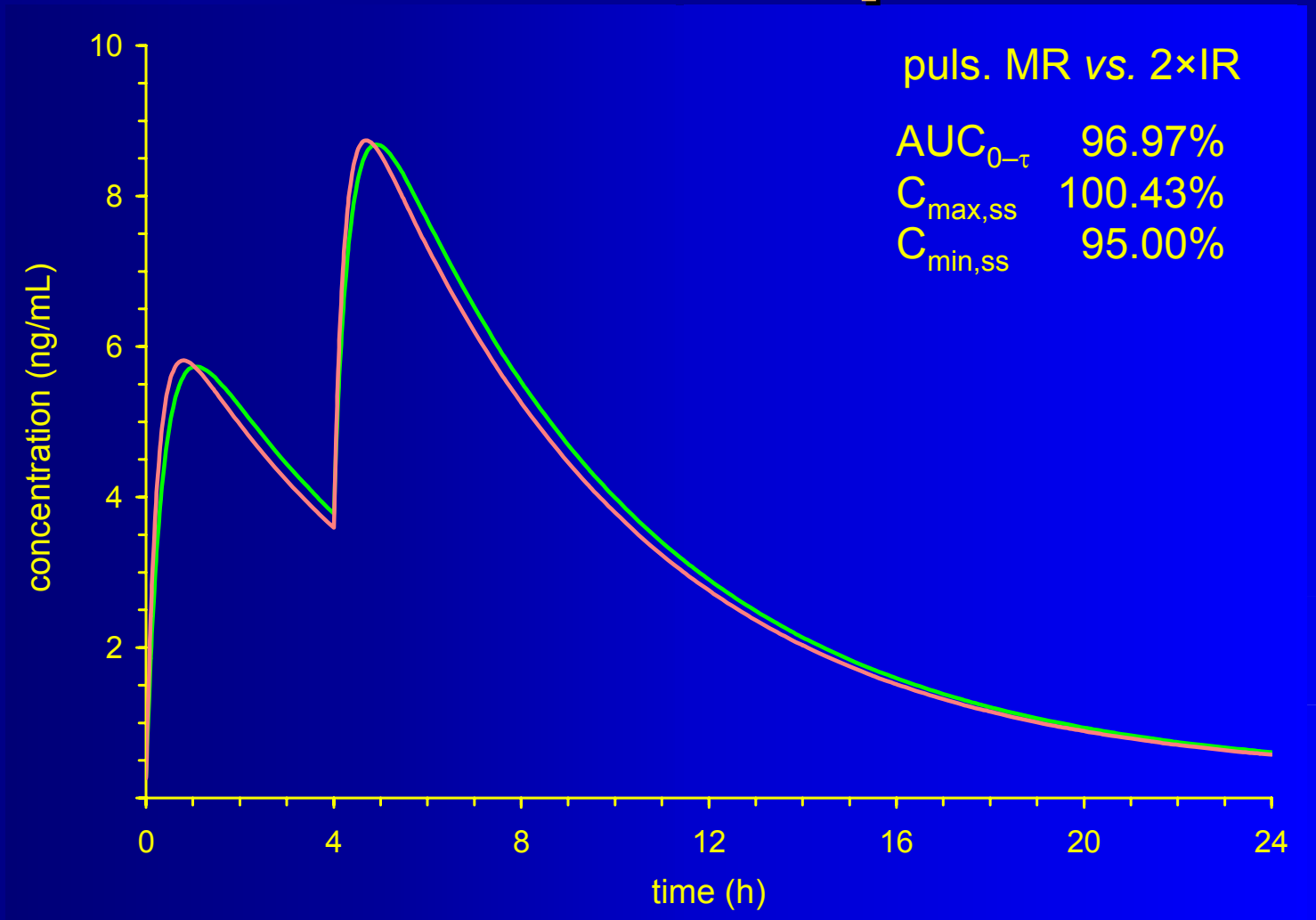
Guidelines etc.

- EMA MR Draft XXIII (March 2013)
  - MR developed after an IR formulation
    - […] by comparison with an IR formulation following single dosing and generally also repeated dosing.
    - The pharmacokinetic parameters of interest may be for single dose studies AUC_{0-t}, $AUC_{0-\infty}$, residual area, C_{max}, t_{max} and t_{lag} and for multiple dose studies $AUC_{0-\tau}$, $t_{max,ss}$, $C_{max,ss}$, $C_{min,ss}$ and fluctuation.
    - Fluctuation in drug concentrations should be studied following repeated dosing. Unless otherwise justified, the MR product should produce similar or less fluctuations as the IR product.

Guidelines etc.

- EMA MR Draft XXIII (March 2013)
  - In principle therapeutic studies are necessary. However, therapeutic studies might be waived when:
    - BE between the IR and the MR product is shown in terms of C_{max}, C_{min} and AUC at steady state because the MR product is developed to actually mimic the performance of an IR product and its dosage regimen e.g. a pulsatile multiphasic release dosage form containing pellets with different lag time[s].

Pulsatile multiphasic



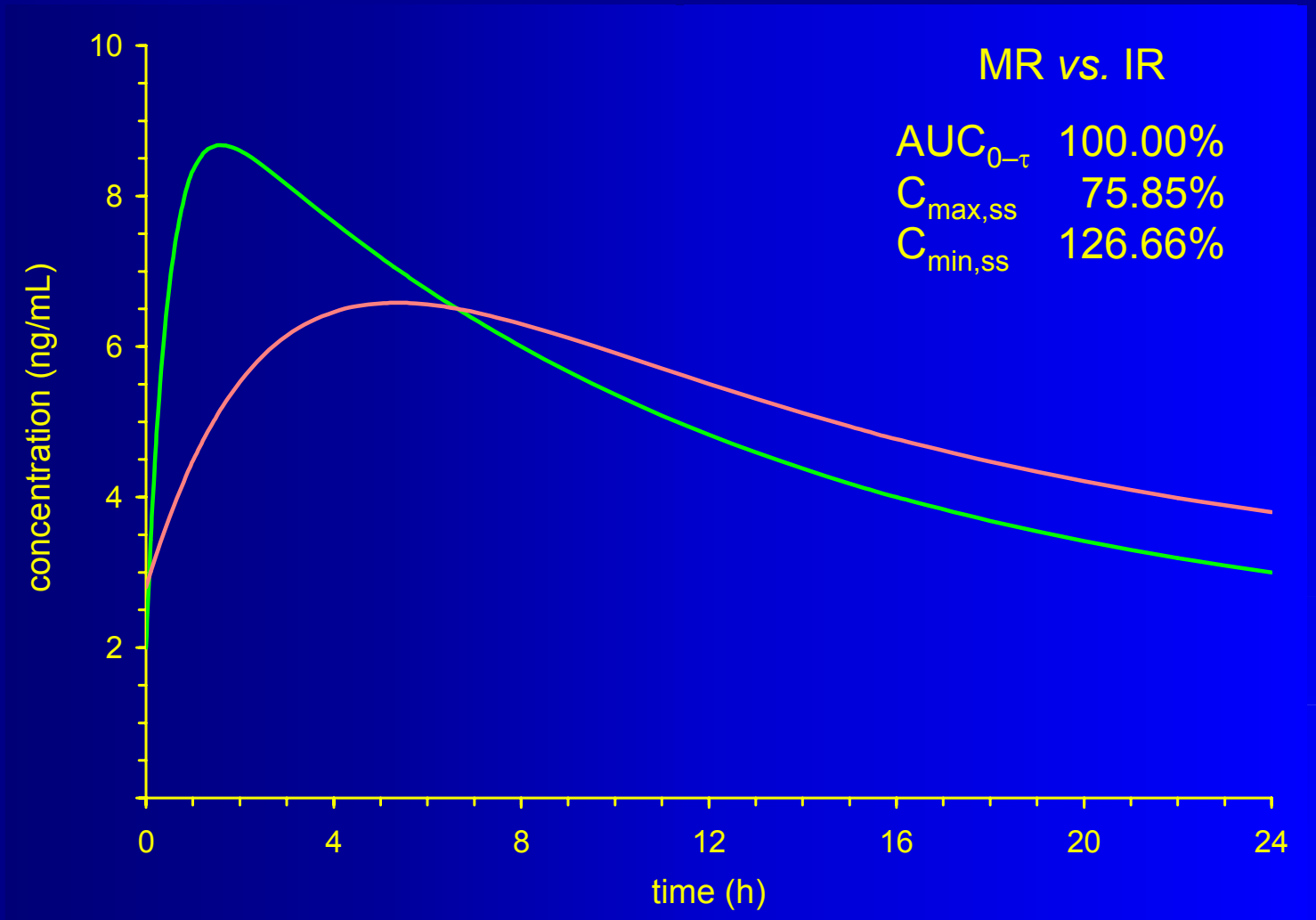
Guidelines etc.

- EMA MR Draft XXIII (March 2013)
  - In principle therapeutic studies are necessary. However, therapeutic studies might be waived when:
    - BE bioequivalence between the IR and the MR product is shown in terms of C_{max}, C_{min} and AUC at steady state despite differences in the shape of the plasma concentration-time profile if it is possible to justify that the difference in shape has no relevance for efficacy and safety based on the exposure – response and profile shape-response relationships.

Guidelines etc.

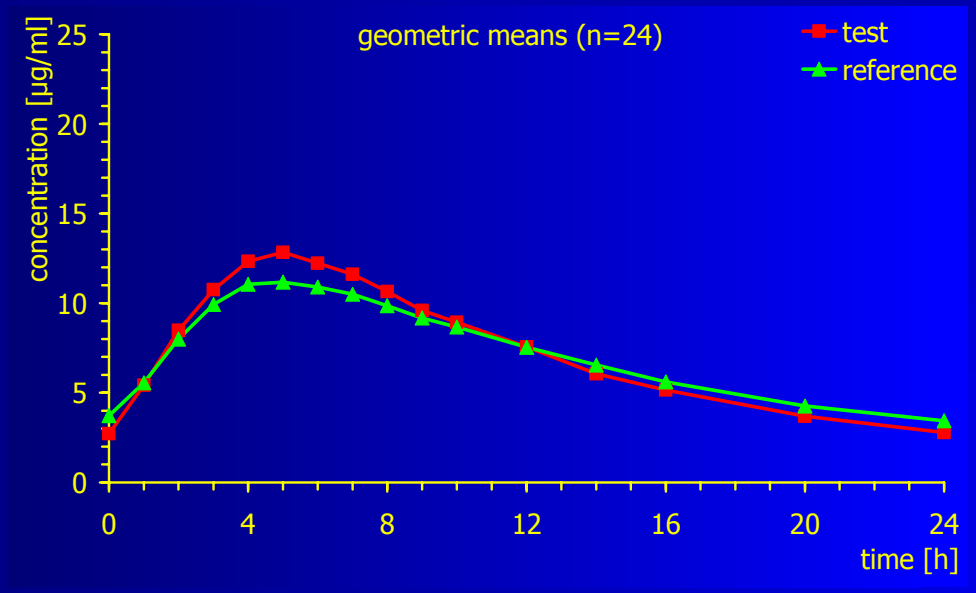
- EMA MR Draft XXIII (March 2013)
  - In principle therapeutic studies are necessary. However, therapeutic studies might be waived when:
    - There is a well-defined therapeutic window in terms of safety and efficacy, the rate of input is known not to influence the safety and efficacy profile or the risk for tolerance development and strict bioequivalence between the IR and the MR product is shown in terms of AUC at steady state and $C_{max,ss}$ for the MR formulation is below the $C_{max,ss}$ for the IR formulation and $C_{min,ss}$ for the MR formulation is above the $C_{min,ss}$ for the IR formulation.

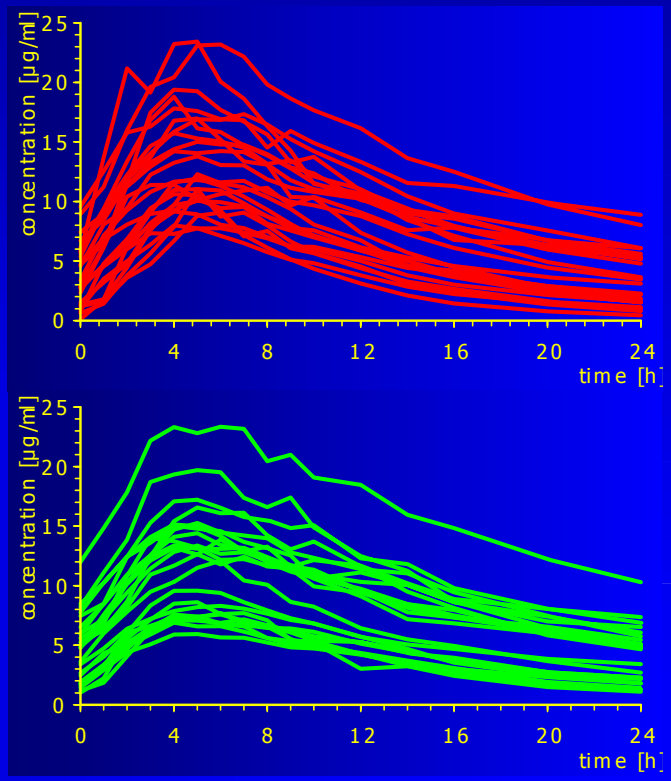
The flatter is better



Case Study

- MR theophylline 400 mg o.a.d. fasting (n=24)





Case Study

- MR theophylline 400 mg o.a.d. fasting (n=24)
  - Extremely high variability of $C_{\tau,ss}$
  - Discussion in Bonn (June 2013) whether the pre-dose conc. and $C_{\tau,ss}$ can be used for reference-scaling. Since we are in steady state, that's a replicated value. No objections from members of the PK working party.
  - Does that really work? Sequences RRTT | TTRR…

PK metric	90% CI		CV%
AUC_{τ}	96.6%	108.3%	11.6
$C_{max,ss}$	107.9%	123.9	14.0
$C_{\tau,ss}$	56.2%	92.6%	53.7
MRT_{τ}	93.2%	97.0%	4.0
%PTF	116.9%	132.8%	12.9
Swing	136.4%	228.9%	56.0

Problems in NCA

- C_τ and $C_{\tau,ss}$
  - Missing samples or sampes with time deviations may lead to *'Apples-and-Oranges'* statistics
  - If a reliable estimate of λ_z is possible (≥3 data points), we can use the estimate

    (1) ± shift of C_τ based on λ_z*

    $$\hat{C}_\tau = C_{last} e^{-\hat{\lambda}_z (\tau - t_{last})}$$

    (2) Estimation independent from measured C_{last}

    $$\hat{C}_\tau = e^{\hat{C}_0 - \hat{\lambda}_z \cdot (t_0 + \tau)}$$

* **Gabrielsson J and D Weiner**
Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts and Applications
Swedish Pharmaceutical Press, Stockholm, p163 (4th ed. 2006)

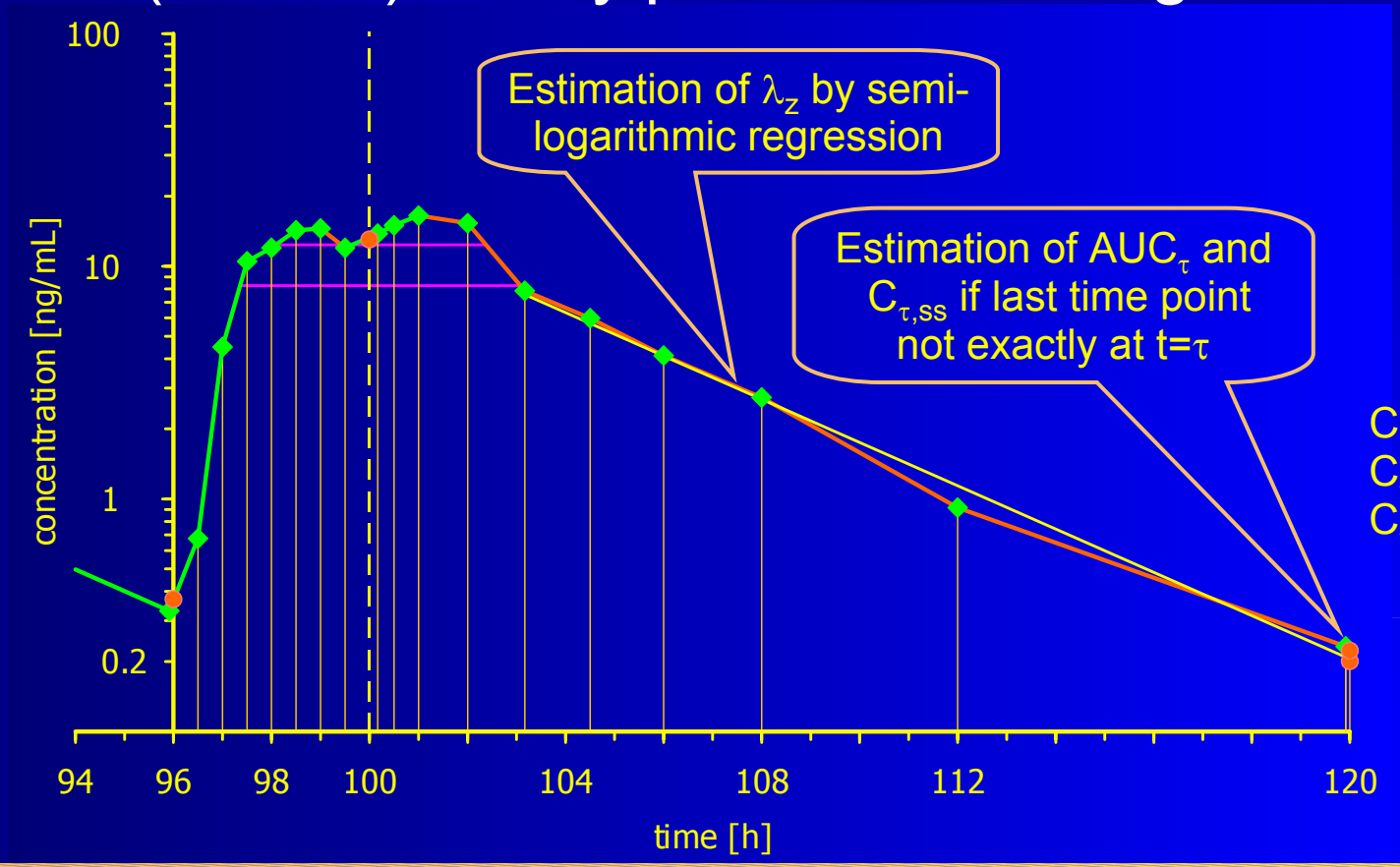
Problems in NCA

- C_τ and $C_{\tau,ss}$
  - Must unambiguously be described in the protocol.

Partial AUCs will be calculated from *t*=0 to *t*=4 h and from *t*=4 h to *t*=τ. If sampling times deviate from these nominal times or samples are missing, the linear-up / logarithmic-down trapezoidal rule accounts for these deviations (*i.e.*, interpolated values are used). Since only in the second profile the last sample is drawn exactly at τ (in the first profile five minutes prior to the administration), the concentration *estimated* at *t*=τ $\hat{C}_\tau$ (instead of the last *measured* concentration C_{last}) will be used in order to obtain an unbiased comparison between treatments. The estimation is based on fitting terminal concentration values (at least three) to a monoexponential model by means of unweighted semilogarithmic regression and subsequently calculating $\hat{C}_\tau = C_{t_{obs}} e^{-\hat{\lambda}_z(\tau - t_{obs})}$. The method accounts also for delayed sampling or cases where the concentration at τ is below the LLOQ. Note that if a sample is drawn at the scheduled time point, no corrective estimation is done, since $\tau - t_{obs} = 0$ and $e^0 = 1$; therefore $\hat{C}_\tau = C_{t_{obs}}$.

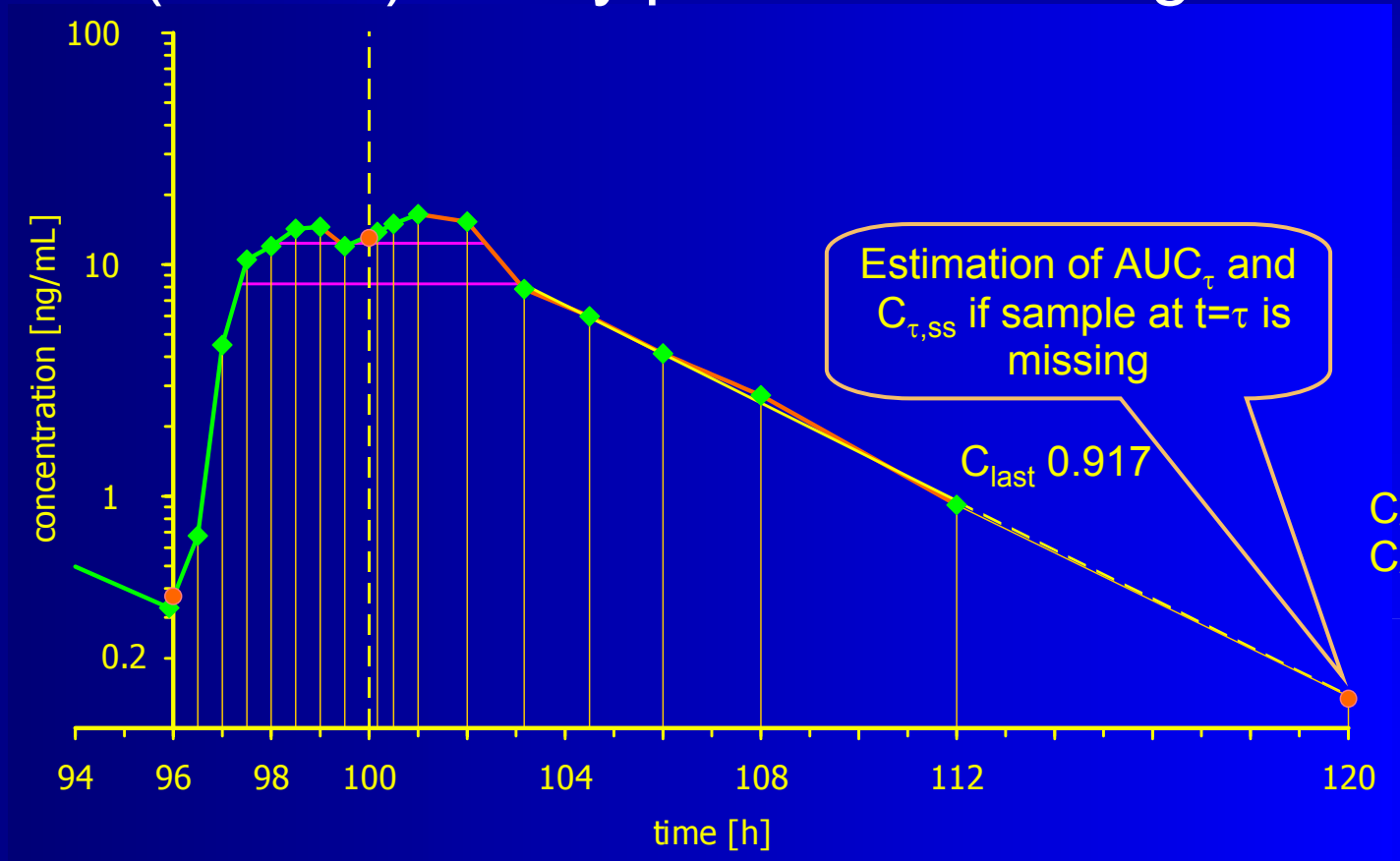
Case Study

- MR (IR+PR) methylphenidate 60 mg o.a.d. fed



Case Study

- MR (IR+PR) methylphenidate 60 mg o.a.d. fed



Waiving MD Studies

- Can we make a prediction about similarity of formulations in steady state from SD data (*i.e.*, waiving the MD study)?
  - Concentration at the intended dosage interval C_{τ} in discussion (EUFEPS Barcelona 2011)
  - C_{τ} is dependend on all formulation-specific PK parameters (F, k_a, t_{lag})
  - Exhaustive simulations by Paixão *et al.* (2012)
    - Monophasic elimination, linear PK
    - Various input types (first order, mixed with zero-order, biphasic input; all models with/without lag-time = six szenarios)

Waiving MD Studies

- Paixão *et al.* (2012)
  - Parameters chosen to give accumulation ($AUC_{0-\tau}$ <80% $AUC_{0-\infty}$)
  - Each scenario simulated with different CVs
  - Sample sizes 12–48
  - Results
    - C_{τ} is indeed predictive of MD performance
    - Requires higher sample sizes of the SD study in order to maintain power (CV 30–40% as compared to 20–30% of other PK metrics)

Waiving MD Studies

- EMA MR Draft XXIII (March 2013)
  - The discussion of the opportunity of using equivalence in C_τ in single dose studies as basis for waiving the multiple dose study has been recognized. However, there is not considered to be sufficient scientific evidence at the moment to encourage this approach.
    - García-Arieta *et al.* (2012)
      - Six case studies; five failing in MD failed on C_τ in SD as well. The remaining one is inconclusive. All SD studies underpowered.
      - Number of passing studies not reported (relevance?)

Thank You!

Modified Release

$C_{min} - C_{\tau}$

Open Questions?

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  - Note for Guidance on Modified Release oral and Transdermal Dosage Forms: Section II – Pharmacokinetic and Clinical Evaluation (1999)
  - Guideline on the Investigation of BE (2010)
  - Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmaco-kinetics (2013)
  - Draft Guideline on the Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms (2013)
- Paixão *et al.*
  An alternative single dose parameter to avoid the need for steady-state studies on oral extended-release drug products
  Eur J Pharmaceut Biopharmaceut 80(2), 410–7 (2012)
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- García-Arieta *et al.*
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  Int J Pharmaceut 423(2), 321–5 (2012)
  DOI: 10.1016/j.ijpharm.2011.11.022