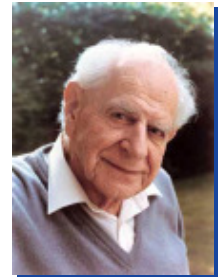


# Primary and secondary PK metrics for evaluation of steady state studies, $C_{min}$ vs. $C_T$ , relevance of $C_{min}/C_T$ or fluctuation for bioequivalence assessment

Helmut Schütz

# Keep in memory...

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!*

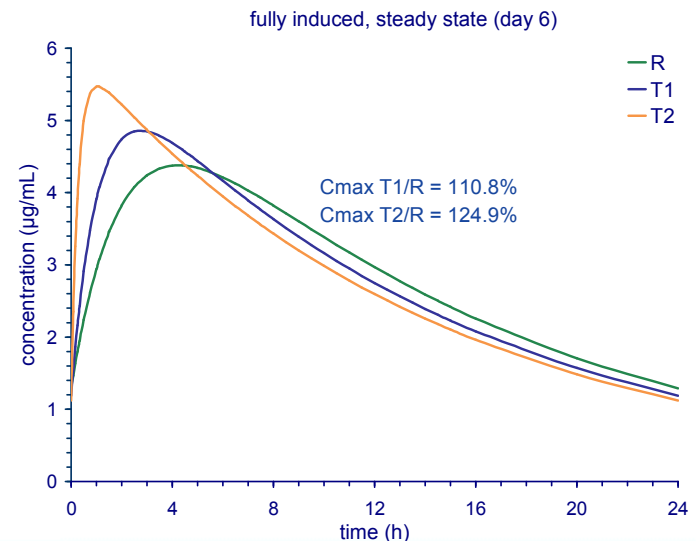
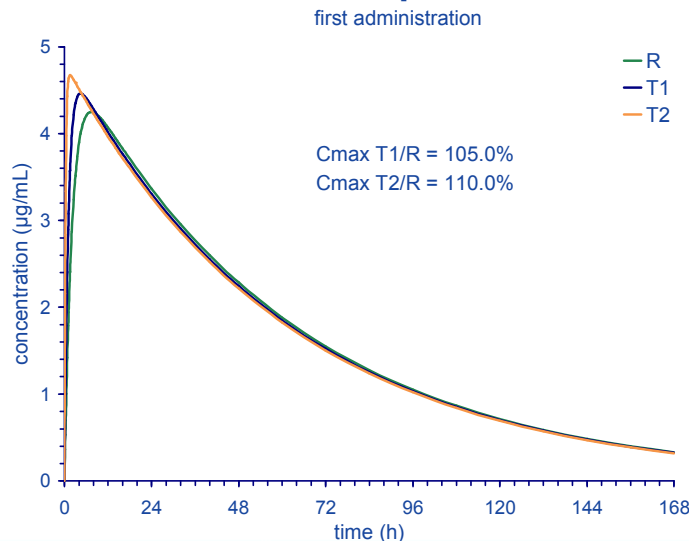


Leslie Z. Benet

# Regulatory demands for study design in BE

Design should allow accurate (unbiased) assessment of the treatment effect

- Carbamazepine ( $k_{a(R)} 0.472 \text{ h}^{-1}$ ,  $k_{a(T1)} 0.94 \text{ h}^{-1}$ ,  $k_{a(T2)} 3.6 \text{ h}^{-1}$ ).
  - $t_{1/2}$  after first administration 43 h ( $\gg 10$  h after full auto-induction)
  - A rare [*sic*] example where MD is more sensitive to detect differences in the rate of absorption than SD



# Differences in the rate of absorption

$C_{max}$  and  $C_{min}$  are composite metrics

- Depend on
  - the rate of absorption (*i.e.*, formulation-specific) *and*
  - the rate of (distribution and) elimination (*i.e.*, drug-specific)
    - In linear PK according to the superposition principle  
 $AUC_{0-t}$  (steady state) =  $AUC_{0-\infty}$  (single dose)
    - However, due to drug- and regimen-specific accumulation the difference between products in their maximum concentrations is reduced in steady state
- $C_{max}$  (SD) is more sensitive to detect differences in the rate of absorption than  $C_{ss,max}$  (MD)
- Prolonged (a.k.a. sustained, controlled, extended) release products
  - Generally flip-flop PK ( $k_a < k_{el}$ )
  - $C_{min}$  more dependent on the rate of absorption than on elimination

# Minimum concentration

## History

- Was never a *primary* PK metric in any regulation
- Alternative PK metrics for MR products were explored in the mid 1990s;  $C_{min}$  was none of them (likely due to its high ISCV)
- As a primary PK metric
  - The EMA's IR draft (2008)
    - $C_{T,SS}$  (termed  $C_{min,SS}$ ); dropped in the final GL (2010)
  - The EMA's MR draft (2013)
    - $C_{T,SS}$ ; widening of the acceptance criteria possible
  - The EMA's MR GL (2014)
    - Prolonged release products and multiphasic modified release products
      - » With accumulation:  $C_{T,SS}$ ; widening of the acceptance criteria possible
      - » With no risk of accumulation or those intended exclusively for once only use: MD not required

# Minimum concentration (EMA's terminology)

## IR GL (draft 2008)

- $C_{min,ss}$ : minimum plasma concentration at steady state

## IR GL (comments on the draft 2010)

- “By  $C_{min,ss}$  we mean the concentration at the end of the dosage interval, i.e.  $C_{trough}$ .”



## IR GL (final 2010)

- $C_{min,ss}$  removed from required steady state PK metrics

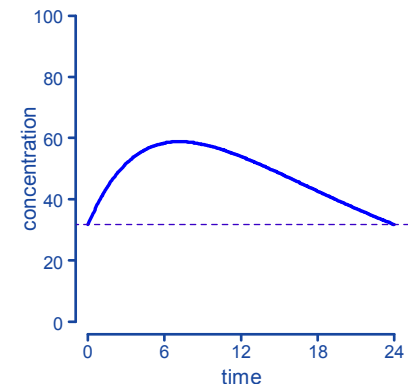
## MR GL (2014)

- New formulations
  - $C_{min,ss}$  (minimum concentration anywhere within the profile)
- Abridged applications (generics)
  - $C_{r,ss}$
  - $C_r$  (together with partial AUCs) might waive MD if low accumulation

# Minimum concentration (problems)

## $C_T$ and $C_{T,ss}$

- Not to be confused with the last concentration >LLOQ ( $C_z$  or  $C_{last}$ )
- Might require intra- or extrapolation if
  - the sample is missing (e.g., vial broken in centrifugation)
  - deviation from scheduled sampling at  $\tau$
- Might not be supported in standard NCA software
  - Only implemented in the current release of Phoenix/WinNonlin (Certara 2017)
- As a single point metric high ISCV expected
  - Esp. for products with low to moderate accumulation the highest ISCV of the entire profile
  - Reference-scaling possible even within a single profile (two values of  $C_{T,ss}$ )
    - Model with two sequences: TTRR | RRTT



# EMA: Waiving of MD studies (generics)

**MD study not required for delayed release products**

**MD study might be waived for prolonged and multiphasic modified release products**

- **Conditions**
  - SD with the highest strength performed
  - Low accumulation expected
    - Mean  $AUC_{0-\tau}$  covers at least 90%  $AUC_{0-\infty}$ , both for test and reference
  - Additional PK metrics representing the shape of profiles demonstrate BE
    - early and late partial AUC with pre-defined cut-off time
    - cut-off =  $\tau/2$  or other if justified
- **If at least one of the partial AUCs fails to demonstrate BE, the MD has to be performed**
  - If PK metrics in the MD study demonstrate BE, overrules failing one(s) of the SD study



# EMA: Waiving of MD studies (generics)

## Proposal to waive the MD study based on BE of the additional PK metric $C_r$ in the SD study \*

- Three models (each with/without lag-time)
  - Matrix type formulation (three absorption rate constants)
  - Osmotic pump (zero- and first-order)
  - Biphasic product (IR fraction first-order, MR fraction zero-order)
- Simulations
  - Crossover
  - 12 – 48 subjects
  - Parameters' CV 10, 15, 20%
  - SD and MD

\* An alternative single dose parameter to avoid the need for steady-state studies on oral extended-release drug products. Eur J Pharmaceut Biopharmaceut. 2012;80(2):410–7. [doi:10.1016/j.ejpb.2011.11.001](https://doi.org/10.1016/j.ejpb.2011.11.001)

# EMA: Waiving of MD studies (generics)

## Proposal to waive the MD study based on BE of the additional PK metric $C_T$ in the SD study

- Results
  - ISCV
    - Conventional PK metrics 20 – 30%
    - $C_T$  (SD) and  $C_{T,SS}$  (MD) 30 – 40%
  - Inclusion of  $C_T$  in the required PK metrics of the SD study is predictive of MD performance
  - Higher sample size in the SD study required in order to maintain power
- AAPS Clinical Pharmacology and Translational Research Section's  
*Outstanding Manuscript Award  
in Modeling and Simulation (2012)*



# EMA: Waiving of MD studies (generics)

## Proposal challenged based on real data \*

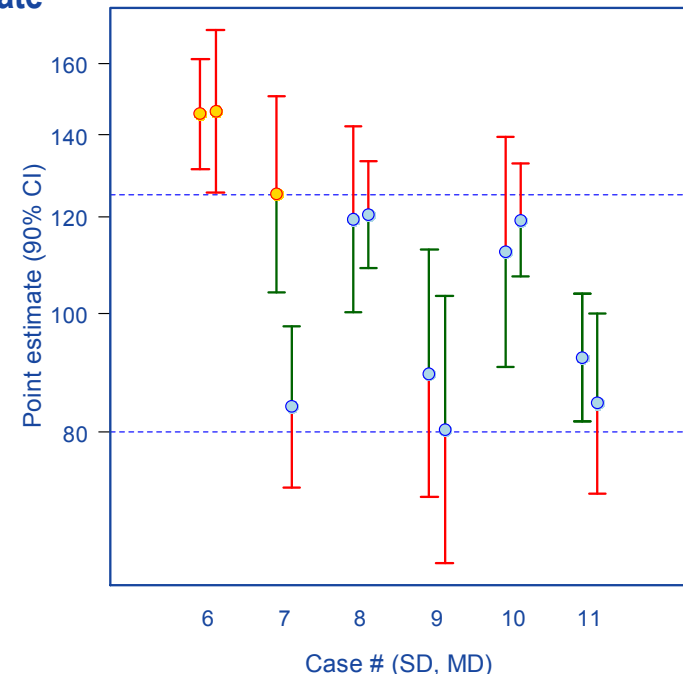
- Review of all studies of prolonged release products submitted to the Spanish Agency since 2000
  - Outcome (SD and MD) of six cases where the MD study *failed* on  $C_{min,ss}$
  - Authors concluded that  
[...] in [...] six cases [...] the multiple dose study was the only design able to detect the differences and, therefore, it was essential when comparing the *in vivo* performance of prolonged release products.  
Regarding the predictive value of  $C_T$ , one case [...] shows that it is predictive of the bioequivalence failure of  $C_{min,ss}$  but in the other five cases, the results are not predictive or as sensitive as  $C_{max,ss}$  or  $C_{min,ss}$ .

\* Investigation on the need of multiple dose bioequivalence studies for prolonged-release generic products. Int J Pharm. 2012;423(2):321–5. [doi:10.1016/j.ijpharm.2011.11.022](https://doi.org/10.1016/j.ijpharm.2011.11.022)

# EMA: Waiving of MD studies (generics)

## Proposal challenged based on real data

- Critical review of the review
  - Cases where the MD study passed on  $C_{min,ss}$  were not reported
    - Impossible to assess the false positive rate
  - Outcome (SD and MD) of six cases where the MD study *failed* on  $C_{min,ss}$ 
    - In five of six cases  $C_r$  (SD) *correctly* predicted the result of  $C_{min,ss}$
    - In cases 6 and 11 the ISCV after MD increased – which is uncommon
    - In case 7 both SD and MD failed but the deviation of the PE from 100% reversed (SD 125%, MD 84%). Coding error?
    - None of the studies were sufficiently powered to show BE of  $C_r$  and  $C_{min,ss}$  (median 11.84%, quartiles 3.25 – 13.35%)



# EMA: Waiving of MD studies (generics)

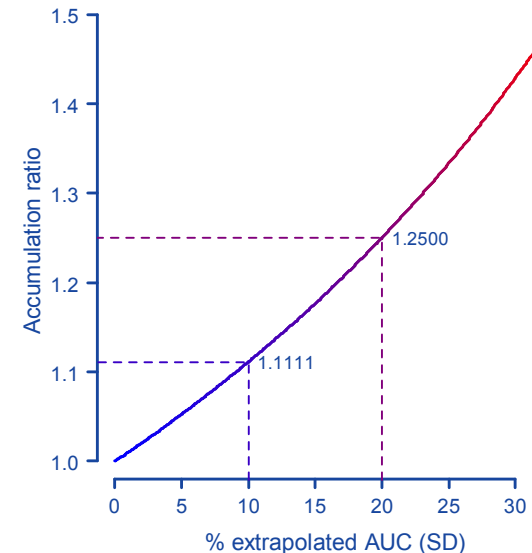
## Proposal supported by real data

- Critical review of the review
  - All studies failing on  $C_{min,ss}$  (MD) failed on  $C_T$  (SD) as well
  - Insufficient power as expected since at the time of submission  $C_{min}$  was not a strict requirement (even if designed for an expected GMR of 95%, only three of the twelve studies would have a power of  $\geq 80\%$ )
  - The one case passing  $C_T$  (SD) and failing  $C_{min,ss}$  (MD) was extremely underpowered in MD and therefore, inconclusive
  - Contrary to their conclusions authors confirmed by real cases that  $C_T$  (SD) is indeed a reliable predictor of multiple dose performance of prolonged release formulations
  - The findings do not refute but rather support the simulation study

# EMA: Waiving of MD studies (generics)

## Harmonisation

- Option to waive the MD study based on low extent of accumulation
  - Health Canada 20% extrapolated *AUC*
  - EMA 10% extrapolated *AUC*  
Accumulation ratio of 1.1111  
very unlikely to meet with prolonged release products \*
- MD studies are generally not required in other jurisdictions
  - Pharmacovigilance is not very sensitive but obviously no problems with safety or efficacy are evident even in countries with a high market share of generic products



\* Proposal for defining the relevance of drug accumulation derived from single dose study data for modified release dosage forms. *Biopharm Drug Dis.* 2015;36:93–103. [doi:10.1002/bdd.1923](https://doi.org/10.1002/bdd.1923)

# Secondary shape metrics

## % Peak-to-Trough Fluctuation (PTF)

- $(C_{max,ss} - C_{min,ss}) / C_{av,ss}$ , where  $C_{av,ss} = AUC_{0-T} / T$ 
  - Variability generally lower than the one of  $C_{max,ss}$

## Swing

- $(C_{max,ss} - C_{min,ss}) / C_{min,ss}$ 
  - Might show extreme variability (esp. if low accumulation)

## Plateau Time ( $t_{75\%}$ ), Peak Occupancy Time (POT-25)

- Time span during which concentrations are within 25% of  $C_{max}$ 
  - Mandatory in Russia and the Eurasian Economic Union

## Half Value Duration (HVD), Peak Occupancy Time (POT-50)

- Time span during which concentrations are within 50% of  $C_{max}$ 
  - More stable than  $t_{75\%}$ /POT-25

# Relevance of additional PK metrics

## Currently limited data available on any

- Proposal at the “EUFEPS Open Discussion Forum on the Revised European Guideline on Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms” (Bonn, June 2013)
  - Science-based regulations
  - Applicants should analyze studies with the suggested new PK metrics in an exploratory (!) manner and submit results to agencies
  - BE should be assessed only by conventional PK metrics like in the previous GL
  - After a limited time frame (e.g., two years) the data could be assessed for their sensitivity and included in the GL if deemed necessary



# Primary and secondary PK metrics for evaluation of steady state studies, $C_{min}$ vs. $C_T$ , relevance of $C_{min}/C_T$ or fluctuation for bioequivalence assessment

## Thank You!



**Helmut Schütz**

**BEBAC**

Consultancy Services for  
Bioequivalence and Bioavailability Studies

1070 Vienna, Austria

[helmut.schuetz@bebac.at](mailto:helmut.schuetz@bebac.at)