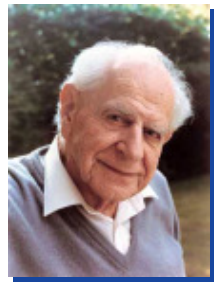
Primary and secondary PK metrics for evaluation of steady state studies, C_{min} *vs.* C_{τ}, relevance of C_{min}/C_{τ} or fluctuation for bioequivalence assessment

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

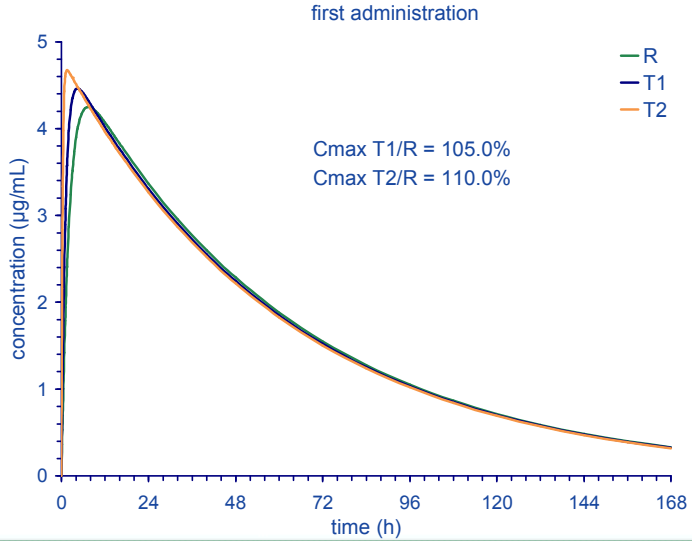
Even though it's *applied* science we're dealin' with, it still is – *science*!

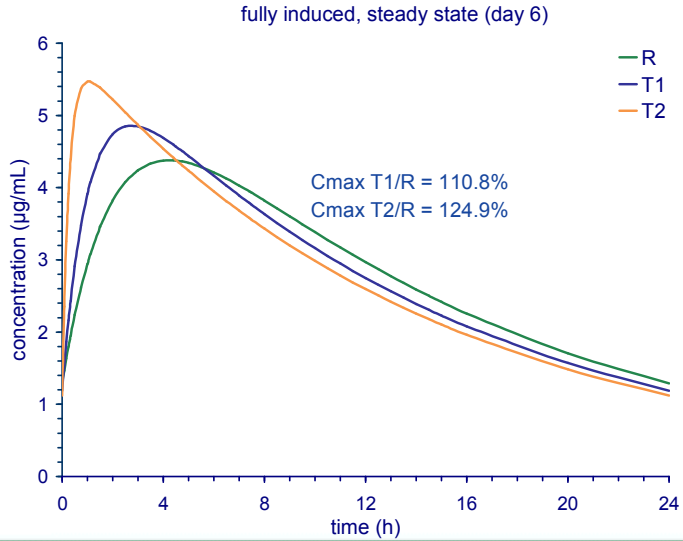
Leslie Z. Benet

Regulatory demands for study design in BE

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

- Carbamazepine ($k_{a(R)}$ 0.472 h^{-1}, $k_{a(T1)}$ 0.94 h^{-1}, $k_{a(T2)}$ 3.6 h^{-1}).
  - $t_{½}$ after first administration 43 h (↘ 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
      $AUC_{0-\tau}$ (steady state) = $AUC_{0-\infty}$ (single dose)
    - However, due to drug- and regimen-specific accumulation the difference between products in their maximum conentrations 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)
    - $C_{\tau,ss}$ (termed $C_{min,ss}$); dropped in the final GL (2010)
  - The EMA's MR draft (2013)
    - $C_{\tau,ss}$; widening of the acceptance criteria possible
  - The EMA's MR GL (2014)
    - Prolonged release products and multiphasic modified release products
      - » With accumulation: $C_{\tau,ss}$; 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

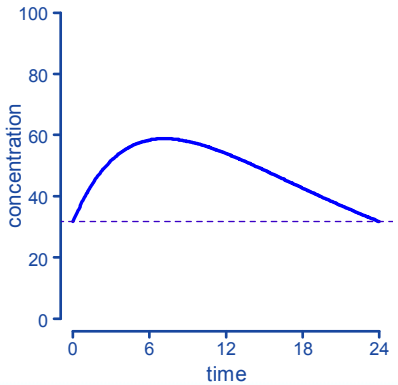
MR GL (2014)

- New formulations
  - $C_{min,ss}$ (minimum concentration anywhere within the profile)
- Abridged applications (generics)
  - $C_{τ,ss}$
  - $C_τ$ (together with partial *AUC*s) 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 τ
- 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 strenght 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 *AUC*s 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_t 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

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

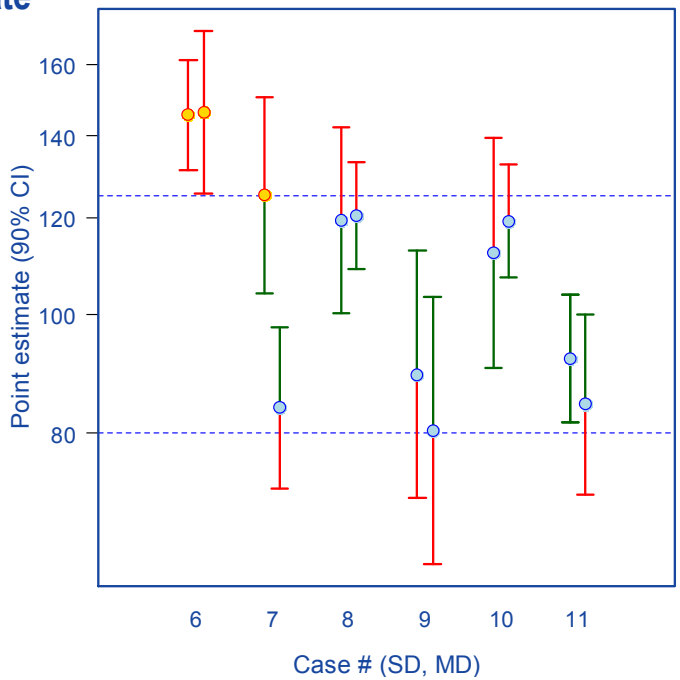
    […] in […] six cases […] the multiple dose study was the only design able to detect the differences and, therefore, it was essential when comparing the *in vivo* performance of prolonged release products.
    Regarding the predictive value of C_t, one case […] shows that it is predictive of the bioequivalence 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

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 the 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_T (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_T and $C_{min,ss}$ (median 11.84%, quartiles 3.25 – 13.35%)



EMA: Waiving of MD studies (generics)

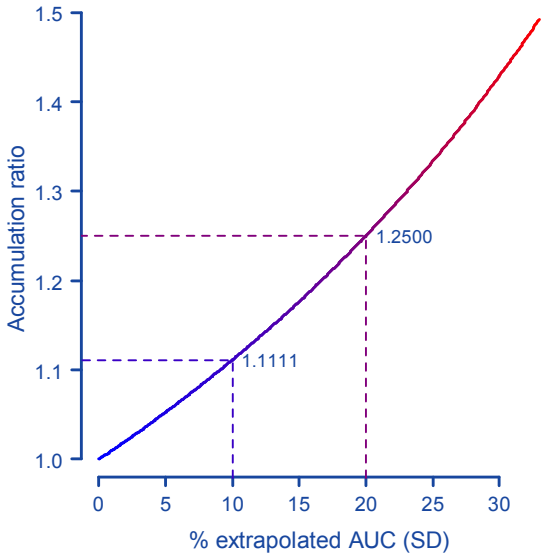
Proposal supported by real data

- 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 ≥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

Secondary shape metrics

% Peak-to-Trough Fluctuation (PTF)

- $(C_{max,ss} - C_{min,ss}) / C_{av,ss}$, where $C_{av,ss} = AUC_{0-\tau} / \tau$
  - 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