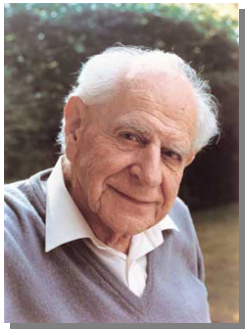
Steady-State Studies

Scientific Background
Regulatory Requirements
Current Discussions / Open Issues

To bear in Remembrance...

Whenever a theory appears to you as the only possible one, take this as a sign that you have neither under-stood 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!

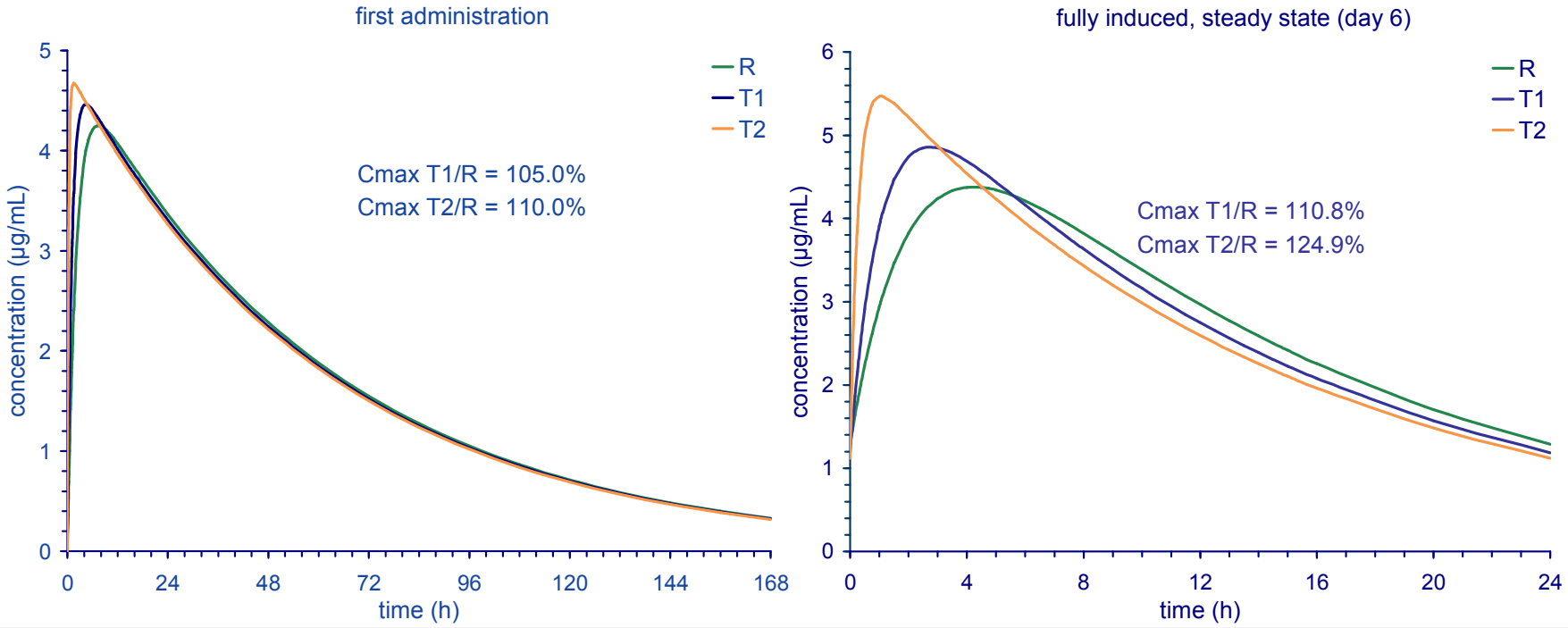
Leslie Z. Benet

Background of Designs in BE

- Design should be able to detect potential differences between formulations
  - Most sensitive condition
    - Highest dose (unless nonlinear PK and saturable absorption)
    - Generally parent drug
    - Fasting and/or fed state
    - Single dose and/or steady state
  - PK metrics which allow appropriate characterization of profiles
  - Accurate and unbiased estimation possible
    - Sampling schedule (esp. for C_{max})
    - If estimation of λ_z required, sampling for $\geq 3 \times t_{½}$
    - In crossover designs washout $\geq 5 \times t_{½}$ (preventing carry-over)
    - In parallel designs similar anthropometric properties of groups (sex, age, BMI, …); geno-/phenotyping if polymorphism known

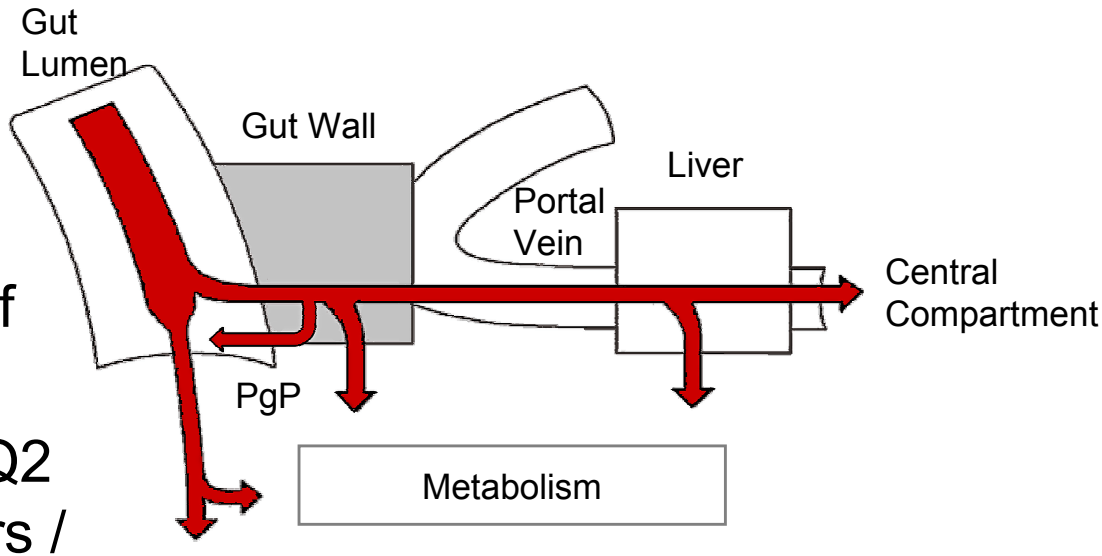
Background of Designs in BE

- Most sensitive condition
  - Carbamazepine ($k_{a(R)}$ 0.472 h^{-1}, $k_{a(T_1)}$ 0.94 h^{-1}, $k_{a(T_2)}$ 3.6 h^{-1})
    - $t_{½}$ after first administration 43 h ($\rightarrow$ 10 h after full auto-induction)
    - A – rare – example where a multiple dose study is more sensitive to detect differences in the rate of absorption than a single dose study



Background of Designs in BE

- Most sensitive condition
  - Only Steady-State can capture the impact of time dependent non-linearity (note: this should not be relevant if products are Q1/Q2)
  - If products are not Q1/Q2 and gut wall transporters / metabolism are involved in the time dependent non linearity, then different excipients may interact differently, having a potential impact on the systemic exposure of the API and/or the metabolite at steady state



* Zhang W, Li Y, Zou P, Wu M, Zhang Z, Zhang T. *The Effects of Pharmaceutical Excipients on Gastrointestinal Tract Metabolic Enzymes and Transporters—an Update*. AAPS J. 2016; 18(4): 830–43. doi:10.1208/s12248-016-9928-8.

Regulatory Demands for Steady-State Studies

- Sometimes agencies have peculiar requirements
  - Carbamazepine possibly is a narrow therapeutic index drug and is subjected to auto-induction
  - The FDA requires two single dose studies (fasting/fed) with Reference-Scaling…
- Prolonged release * products
  - EMA, WHO, …, partly ANVISA (№ 760.20)
    - Steady-State studies generally required
    - but can be waived under certain conditions

* a.k.a. controlled release (CR), extended release (ER/XR), long-acting (LA)

Regulatory Demands for Steady-State Studies

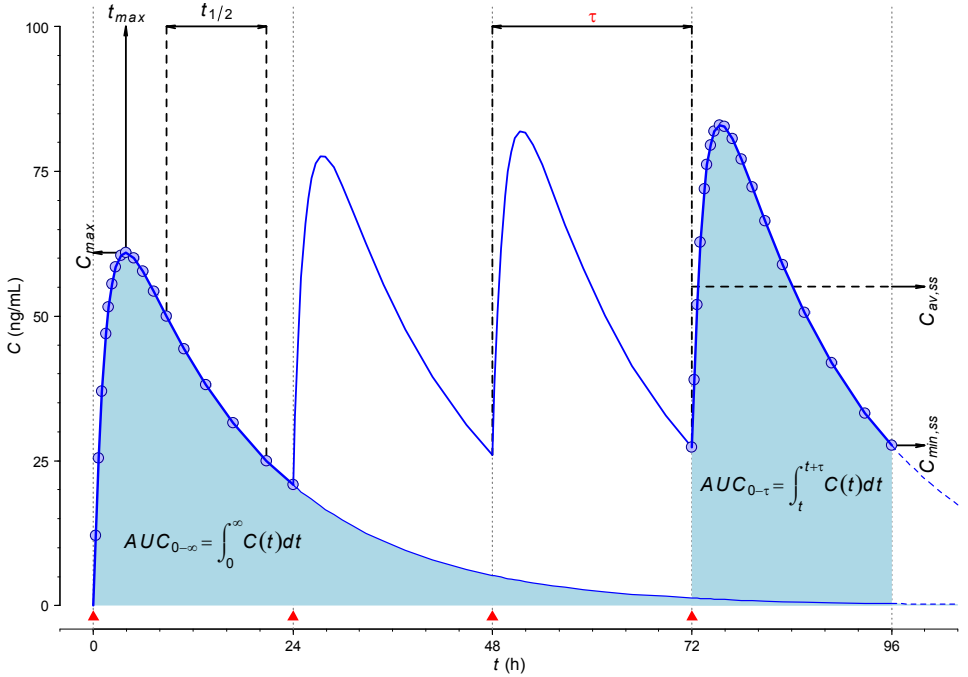
- Prolonged release products
  - EMA
    - Steady-State studies can be waived if
      - single dose studies performed with the highest strength (fasting/fed);
      - no ‘risk’ of accumulation (extrapolated *AUC* in SD study ≤10% of $AUC_{0-\infty}$);
      - additional PK metrics representing the shape of profiles demonstrate BE
        - » Early and late partial *AUC* with pre-defined cut-off time
        - » Cut-off time $\tau/2$ (or other if justified)
    - If at least one of the partial *AUC*s fails to demonstrate BE, steady-state studies have to be performed
      - Highest strength, fasting and fed state
      - If all conventional PK metrics in the steady-state study demonstrate BE, the failed one(s) of the SD study are overruled
      - No reason for an authority to reject the application

Regulatory Demands for Steady-State Studies

- Prolonged release products
  - FDA: Steady-State studies (with few exceptions) not required
  - In linear PK the superposition principle

    $AUC_{0-\tau}$ (MD) = $AUC_{0-\infty}$ (SD)

    holds, *i.e.*,
    - difference in the extent of absorption will be the same (though with lower variability)
    - difference in the rate of absorption will be lower (due to accumulation)
  - Generall lower variability in Steady-State than after a single dose



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Regulatory Demands for Steady-State Studies

- Prolonged release products
  - For almost thirty years Canada required Steady-State studies only if *AUC* in the single dose study >20% of $AUC_{0-\infty}$ (Steady-State studies not more required since 2010)
  - Given all that
    - *Scientifically* Steady-State studies are not justified (less sensitive to detect differences between formulations than SD)
    - Pharmacovigilance is not very sensitive but no problems with safety or efficacy were evident for decades even in countries with a high market share of generic products like the USA and Canada
    - Provocative question

      Where are the dead people lying in the streets?

PK Metrics in Steady-State

- Extent of Absorption, Total Exposure (FDA)
  - $AUC_{0-\tau}$ *AUC* covering the dosing interval τ or
  - AUC_{0-24} if chronopharmacological variation and $>$ o.a.d.
  - No extrapolation of *AUC* in any case
- Rate of Absorption, Peak Exposure (FDA)
  - $C_{max,ss}$
- Minimum Concentration
  - EMA, …
    - $C_{min,ss}$ lowest concentration within the profile (originators)
    - $C_{\tau,ss}$ concentration at the end of the dosing interval (generics)
  - ANVISA
    - C_{min} concentration at the end of the dosing interval

PK Metrics in Steady-State

- *PTF* (Peak-to-Trough Fluctuation, Degree of Fluctation)
  - $(C_{max,ss} - C_{min,ss}) / C_{av,ss}$, where $C_{av,ss} = AUC_{0-\tau}/\tau$
    $C_{av,ss}$ is termed C^* by the ANVISA
- *Swing*
  - $(C_{max,ss} - C_{min,ss}) / C_{min,ss}$
    Mentioned in some GLs but practically obsolete due to its extreme variability esp. in case of low accumulation
- $t_{75\%}$, *POT*-25
  - Plateau Time, Peak Occupancy Time 25:
    time span where $C(t) \geq 75\%\ C_{max}$ (mandatory in Russia for controlled release products)
- *HVDu*, *POT*-50
  - Half Value Duration, Peak Occupancy Time 50:
    time span where $C(t) \geq 50\%\ C_{max}$ (more stable than *POT*-25)

PK Metrics in Steady-State

- Multiphasic release products
  - Additional to common PK metrics
    - Partial *AUC*s $pAUC_{0-t1}$, …, $pAUC_{tn-1,tn}$
    - EMA: C_{max} within each interval
    - Cut-off time(s) $t_1,\ldots,t_n$ pre-specified in the protocol
      - Based on PK/PD-relationship (FDA, *e.g.*, early onset and maintainance of effect)
      - Based solely on PK of the reference product (EMA, Health Canada)
        - » Difficult, if only mean data in the public domain
        - » Sometimes no clear-defined trough between phases (*e.g.*, zolpidem, osmotic pump formulations of methylphenidate)
- Delayed release products
  - Steady-state studies not required

Computational Issues

- C_τ (single dose) and $C_{min,ss}$, $C_{\tau,ss}$ (Steady-State)
  - C_τ and $C_{\tau,ss}$ are the concentrations at the end of the intended dosing interval
    - Must not be confused with the last *measurable* concentration C_{last}
    - If $t_{last} \neq \tau$ (due to time deviation, BLQ, missing sample), a comparison of C_{last} would be biased and increase the intra-subject variability
  - Only C_{last} and $C_{min,ss}$ are implemented in NCA software
  - *Estimated* C_τ and $C_{\tau,ss}$ are only implemented in some newer software versions
    - Phoenix WinNonlin 8.0+ (Certara 2017)
    - R-package PKNCA 0.8+ (Denney *et al*. 2017) [1,2]

1. Denney WS, Duvvuri S, Buckeridge C. *Simple, Automatic Noncompartmental Analysis: The PKNCA R Package*. J Pharmacokin Pharmacodyn. 2015; 42(1): 11–107, S65. doi:10.1007/s10928-015-9432-2.
2. Denney WS, Buckeridge C, Duvvuri S. *PKNCA: Perform Pharmacokinetic Non-Compartmental Analysis*. 2020; R package version 0.9.4. https://cran.r-project.org/package=PKNCA.

Achievement of Steady-State

- Previous approaches
  - Linear regression of at least three pre-dose contrations
    - If the slope differs significantly from zero (or zero is not contained in the CI) → exclude the subject because not in Steady-State
    - Problematic
      Will almost always conclude Steady-State if highly variable and exclude many subjects if slightly variable
  - Multivariate analysis (Health Canada)
    - Results in a yes|no decision; possibly discard the entire study
- Current
  - At least three pre-dose concentrations are measured
    - Presented in tables together with geometric means / *CV*
    - Plots
    - No fixed decision rules but common sense!

Development of the EMA's GL

- Steady-State was required in Note for Guidance (1999)
- During development of the immediate release guideline (2007–2010)
  - Concerns about problems with concentrations at the end of the dosing interval (oxycodone)
  - Steady-State and/or comparison of C_τ (SD) considered (draft 2008) but did not make it to the final IR GL
- Concerns whether *AUC* and C_{max} – alone – will be sufficient to compare prolonged release products
  - Shape of profiles can be different
  - Could an additional PK metric – like C_τ – help?

Differences in the Rate of Absorption

- C_{max} and C_{min} are <u>composite</u> metrics, depending on
  - the rate of absorption (*i.e.*, formulation-specific) and
  - the rate of (distribution and) elimination (*i.e.*, drug-specific)
  - Due to drug- and regimen-specific accumulation the difference between products in their maximum / minimum concentrations decreases in Steady-State (*i.e.*, less sensitive than SD)
- Prolonged release products
  - Generally flip-flop PK ($k_a \leq k_{el}$), *i.e.*, the *late* part of the profile represents mainly absorption
  - C_{min} more dependent on the rate of absorption than C_{max}
  - That's good because we are interested in detecting differences between products

Differences in the Rate of Absorption

- Proposal to waive the MD study based on BE of the additional PK metric C_τ in the SD study *
  - Three models (each with and without lag time)
    - Matrix type formulation (three absorption rate constants)
    - Osmotic pump (zero- and first-order)
    - Biphasic product (IR fraction first-order, ER fraction zero-order)
  - Simulations
    - Crossover
    - 12 – 48 subjects
    - Parameters' *CV* 10, 15, 20%
    - Single dose and multiple dose

* Paixão P, Gouveia LF, Morais JAG. *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.

Differences in the Rate of Absorption

- Proposal to waive the MD study …
  - Results
    - Intra-subject *CV*
      - Conventional PK metrics 20 – 30%
      - C_{τ} (SD) and $C_{\tau,ss}$ (MD) 30 – 40%
    - Inclusion of C_{τ} in the required PK metrics of the SD study <u>is predictive</u> 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)

Differences in the Rate of Absorption

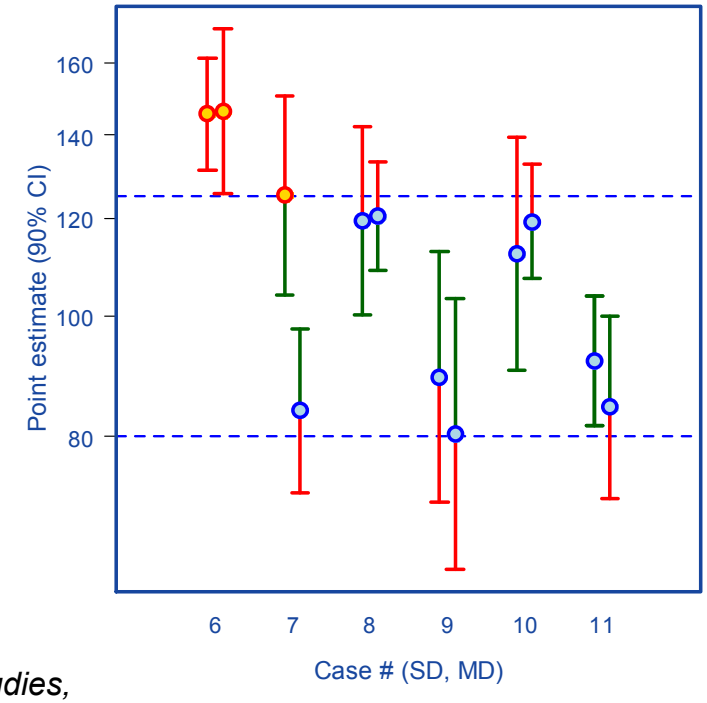
- Proposal challenged based on real data *
  - Review of all studies of prolonged release products submitted to the Spanish Agency since 2000
    - Outcome (SD and MD) of six cases where the MD study *failed* on $C_{min,ss}$
    - The authors concluded that

      […] *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_{τ}*, 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* $C_{min,ss}$.

* García-Arieta A, Morales-Alcelay S, Herranz M, de la Torre-Alvarado JM, Blázquez-Pérez A, Suárez-Gea ML, Alvarez C. *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.

Differences in the Rate of Absorption

- 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 of six cases where the MD study *failed* on $C_{min,ss}$
      - In five of six cases C_τ (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 PE reversed (SD 125%, MD 84%); acc. to the main author not a coding error
      - Studies were not adequately powered to show BE of C_τ or $C_{min,ss}$ ($\tilde{x}$ 11.84%, quartiles 3.25–13.35%)



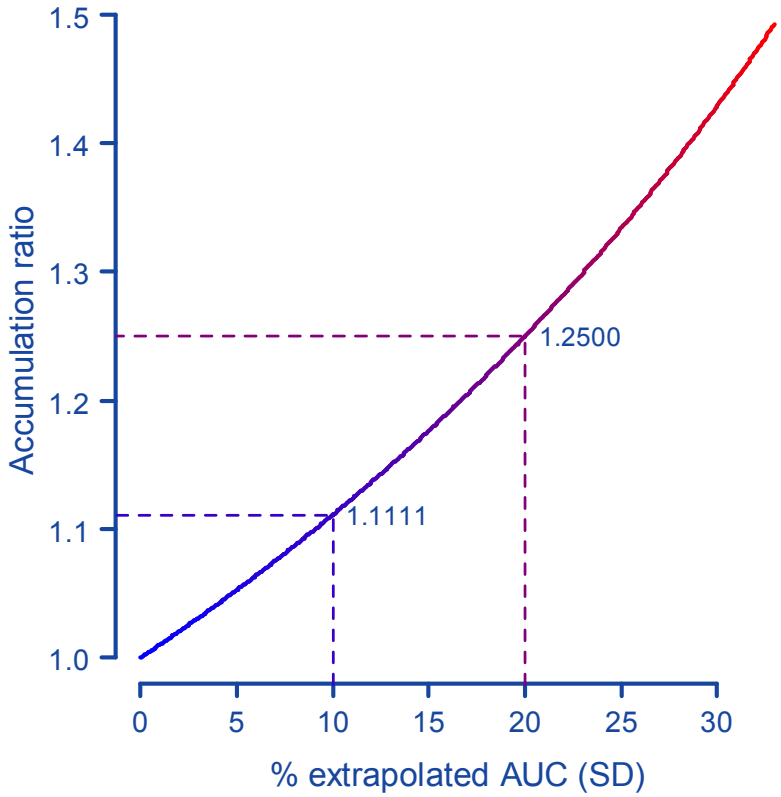
* Schütz H. *Primary and secondary PK metrics for evaluation of steady state studies, C_{min} vs. C_τ, relevance of C_{min}/C_τ or fluctuation for bioequivalence assessment*. Amsterdam: GBHI 3rd Workshop; 12 Apr 2018.

Differences in the Rate of Absorption

- Proposal challenged based on real data
  - Critical review of the ‘review’
    - All studies failing on $C_{min,ss}$ (MD) failed on C_{τ} (SD) as well
    - Insufficient power as expected since at the time of submission C_{min} was not a requirement (even if designed for an expected GMR of 95%, only 3/12 studies would have a power of ≥80%)
    - The one case passing C_{τ} (SD) and failing $C_{min,ss}$ (MD) was extremely underpowered in MD and therefore, inconclusive
    - Contrary to their conclusions authors <u>confirmed</u> by real cases that C_{τ} (SD) is indeed a reliable predictor of multiple dose performance of prolonged release formulations
    - The <u>results</u> do not refute but rather <u>support</u> the simulation study
      - Not only the data base is unclear (selection bias) but – more importantly – the authors’ conclusions *contradicts* their findings
      - If I would peer-review such a manuscript, I would reject it

Waiving MD if no ‘Risk’ of Accumulation

- Health Canada (1992–2010)
  ≤20% extrapolated *AUC*
- EMA, … , ANVISA (№ 760.20)
  ≤10% extrapolated *AUC*
  - This translates into an accumulation ratio of 1.1111…
  - Almost impossible for prolonged release products *



* Scheerans C, Heining R, Mück W. *Proposal for defining the relevance of drug accumulation derived from single dose study data for modified release dosage forms*. Biopharm Drug Dis. 2015; 36(2): 93–103. doi:10.1002/bdd.1923.

Science *vs*. ‘made out of thin air’

- Relevance of proposed new PK metrics (*e.g.*, partial *AUC*s, C_{max} within cut-off times, C_{τ}, …) unclear
  - Proposals at the
    - EUFEPS Open Discussion Forum on the Revised European Guideline on Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms (Bonn, June 2013)
    - Global Bioequivalence Harmonization Initiative (GBHI) 3rd International Workshop (Amsterdam, April 2018)
      - Science based regulations
      - Applicants should analyze studies with suggested new PK metrics in an exploratory (!) manner and submit results to agencies
      - BE should be assessed only by conventional PK metrics according to the previous guideline
      - 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

Current Discussions

- Global Bioequivalence Harmonization Initiative, 3rd International Workshop (Amsterdam, April 2018)
  - Session II: Necessity of Multiple Dose Studies in BE Testing
    - EMA
      - Follow the GL; the option to waive the steady-state is an improvement over the old NfG (MD mandatory)
    - FDA
      - SD sufficient, unless studies in patients where uninterrupted treatment is mandatory
      - Modeling and Simulation sometimes sufficient
      - MD rarely required
    - Industry
      - SD sufficient, unless time dependent nonlinearity and products not Q1/Q2
      - MD as a general requirement questioned
      - Simulations by Paixão *et al*. supported and review by García-Arieta *et al*. criticized
      - Before new PK metrics are introduced, they should be assessed for their relevance

Current Discussions

- GBHI 4th WS (Bethesda, December 2019)
  - Session I: Necessity of Multiple Dose Studies in BE Testing
    - EMA
      - No update of the GL planned in the near future
      - Some members of the PKWP are considering to relax the requirement for Steady-State studies (extrapolated *AUC* in SD study >20% of $AUC_{0-\infty}$)
    - Academia
      - Review by García-Arieta *et al*. criticized
      - More simulations should be performed to explore which PK metrics in SD are suitable to waive the Steady-State study
    - Industry
      - Review by García-Arieta *et al*. – heavily – criticized again

Steady-State Studies

Thank You!

Obrigado!

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