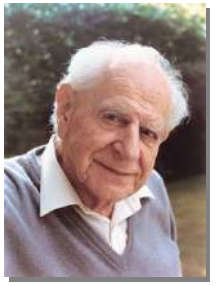
# Steady-state Studies

Scientific Justification
Regulatory Requirements
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 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!

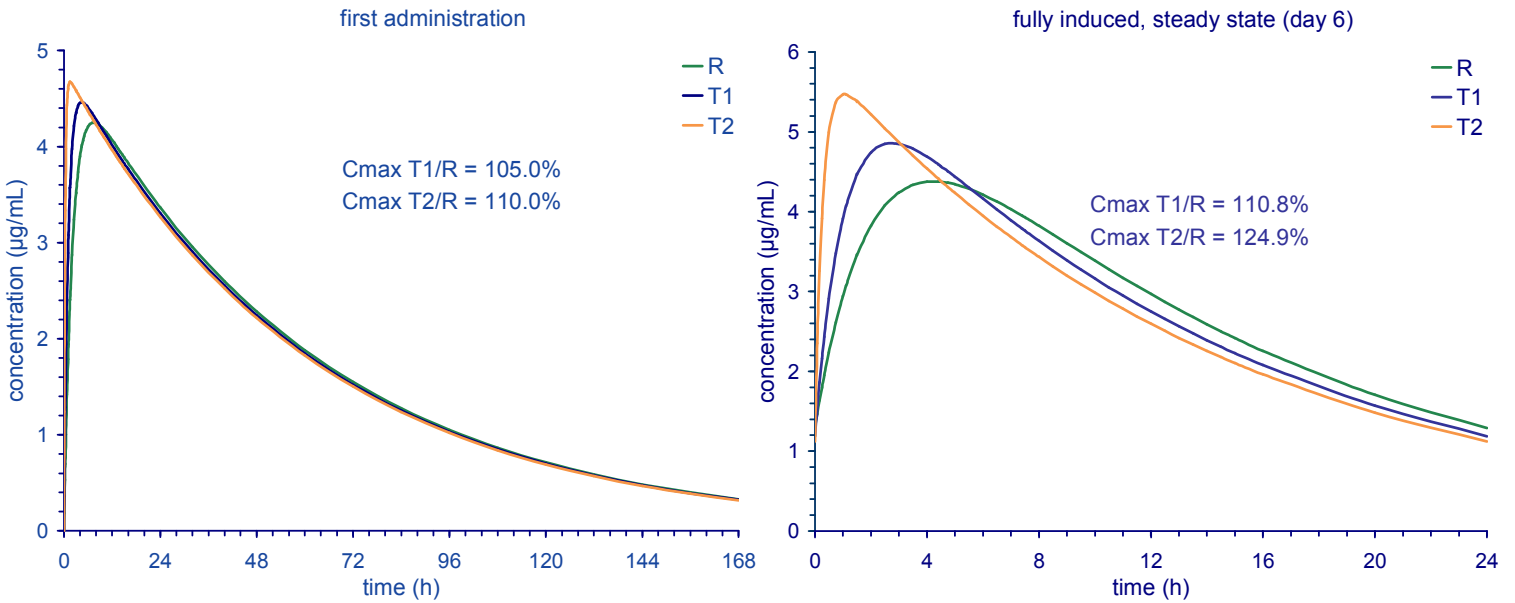
Leslie Z. Benet

# 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 $\lambda_z$ 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

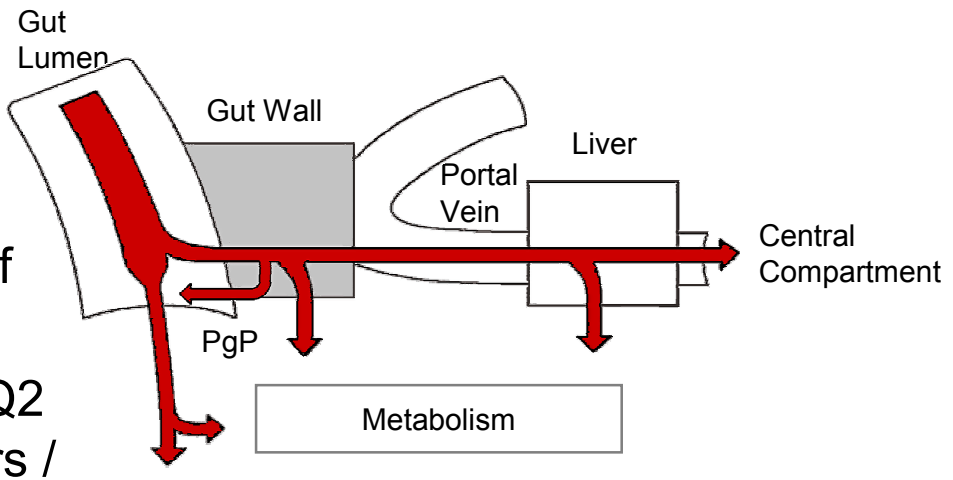
# Background of Designs in BE

- Most sensitive condition
  - Carbamazepine ($k_{a(R)}$ 0.472 $h^{-1}$, $k_{a(T1)}$ 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) 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 strange requirements
  - Carbamazepine possibly is a narrow therapeutic index drug and 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

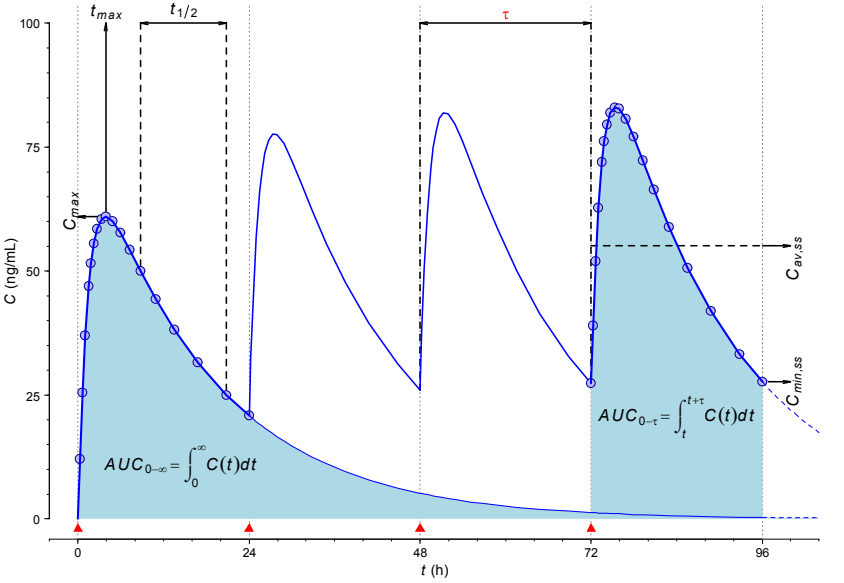
- Prolonged release products
  - EMA
    - Steady-state studies can be waived if
      - single dose studies performed with the highest strength (fasting/fed);
      - no 'risk' of accumulation (extrapolated *AUC* in SD study ≤ 10% of $AUC_{0-\infty}$);
      - additional PK metrics representing the 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 $AUC_{0-\infty}$ (no more required since 2010)
  - Given all that
    - Scientifically steady-state studies are not justified (less sensive to detect differences between formulations)
    - 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 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 $\tau$ 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

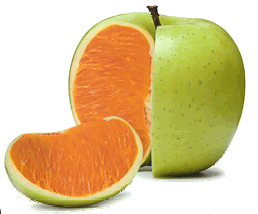
- *PTF* (Peak-to-Trough Fluctuation, Degree of Fluctation)
  - $(C_{max,ss} - C_{min,ss}) / C_{av,ss}$, where $C_{av,ss} = AUC_{0-\tau} / \tau$
    Note that $C_{av,ss}$ is termed $C^*$ by ANVISA
- *Swing*
  - $(C_{max,ss} - C_{min,ss}) / C_{min,ss}$
    Mentioned in some GLs but practically obsolete due to its extreme variability esp. in case of low accumulation
- $t_{75\%}$, *POT*-25
  - Plateau Time, Peak Occupancy Time 25; time span where $C(t) \geq 75\%\ C_{max}$ (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
  - Additionally 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, OROS formulations of methylphenidate)
- Delayed release products
  - Steady-state studies not required

# Computational Issues

- $C_\tau$ (single dose) and $C_{min,ss}$, $C_{\tau,ss}$ (steady-state)
  - $C_\tau$ and $C_{\tau,ss}$ are the concentrations at the end of the intended dosing interval
    - Must not be confused with the last *measurable* concentration $C_{tlast}$
    - If $t_{last} \neq \tau$ (due to time deviation, BLQ, missing sample), a comparison of $C_{tlast}$ would be biased and increase the intra-subject variability
  - Only $C_{tlast}$ and $C_{min,ss}$ are implemented in NCA software
  - *Estimated* $C_\tau$ 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*. 2019; R package version 0.9.1. 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 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 $C_\tau$ (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 $C_\tau$ – help?

# Differences in the Rate of Absorption

- $C_{max}$ and $C_{min}$ are composite metrics, which depend 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 is reduced in steady-state
- 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 $C_\tau$ 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%
      - $C_\tau$ (SD) and $C_{\tau,ss}$ (MD) 30 – 40%
    - Inclusion of $C_\tau$ 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)

# Differences in the Rate of Absorption

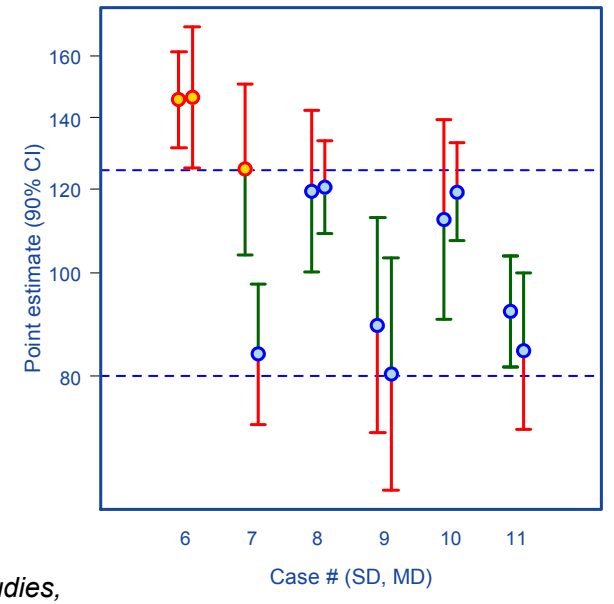
- Proposal challenged based on real data *
  - Review of all studies of prolonged release products submitted to the Spanish Agency since 2000
    - Outcome (SD and MD) of six cases where the MD study *failed* on $C_{min,ss}$
    - The authors concluded that

      *[…] 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 $C_{\tau}$, 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 $C_\tau$ (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 $C_\tau$ or $C_{min,ss}$ ($\tilde{x}$ 11.84%, quartiles 3.25–13.35%)



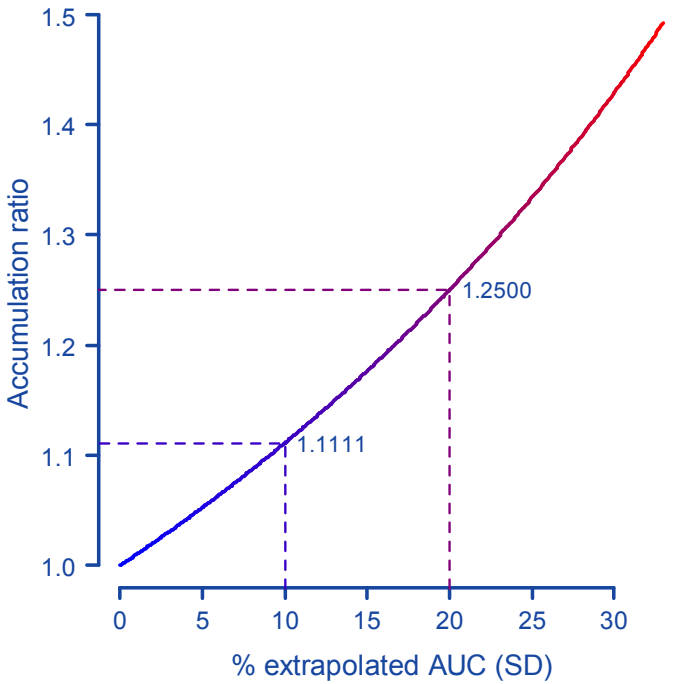

* Schütz H. *Primary and secondary PK metrics for evaluation of steady state studies, $C_{min}$ vs. $C_\tau$, relevance of $C_{min}/C_\tau$ or fluctuation for bioequivalence assessment*. Amsterdam: GBHI 3rd Workshop; 12 Apr 2018.

# 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 $C_{\tau}$ (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 $C_{\tau}$ (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 $C_{\tau}$ (SD) is indeed a reliable predictor of multiple dose performance of prolonged release formulations
    - The results do not refute but rather support the simulation study
      - If I would receive such a manuscript as a reviewer, I would reject it
      - Not only the data base is unclear (selection bias) but – more important – the authors’s conclusion contradicts their findings

# 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, $C_{\tau}$, …) unclear
  - Proposals at
    - the 'EUFEPS Open Discussion Forum on the Revised European Guideline on Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms' (Bonn, Jun 2013)
    - Global Bioequivalence Harmonization Initiative (GBHI) 3rd International Workshop (Amsterdam, Apr 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 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

# Current Discussions

- Global Bioequivalence Harmonization Initiative, 3rd International Workshop (Amsterdam, Apr 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
      – M&S 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*. critized
      – Before new PK metrics are introduced, they should be accessed for their relevance

# Current Discussions

- GBHI 4th WS (Bethesda, Dec 2019)
  - Session I: Necessity of Multiple Dose Studies in BE Testing
    - EMA – No update of the GL planned in the near future (though some members of the PKWP are considering to relax the requirement for steady-state studies to 20%)
    - 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)

**Thank You!**

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