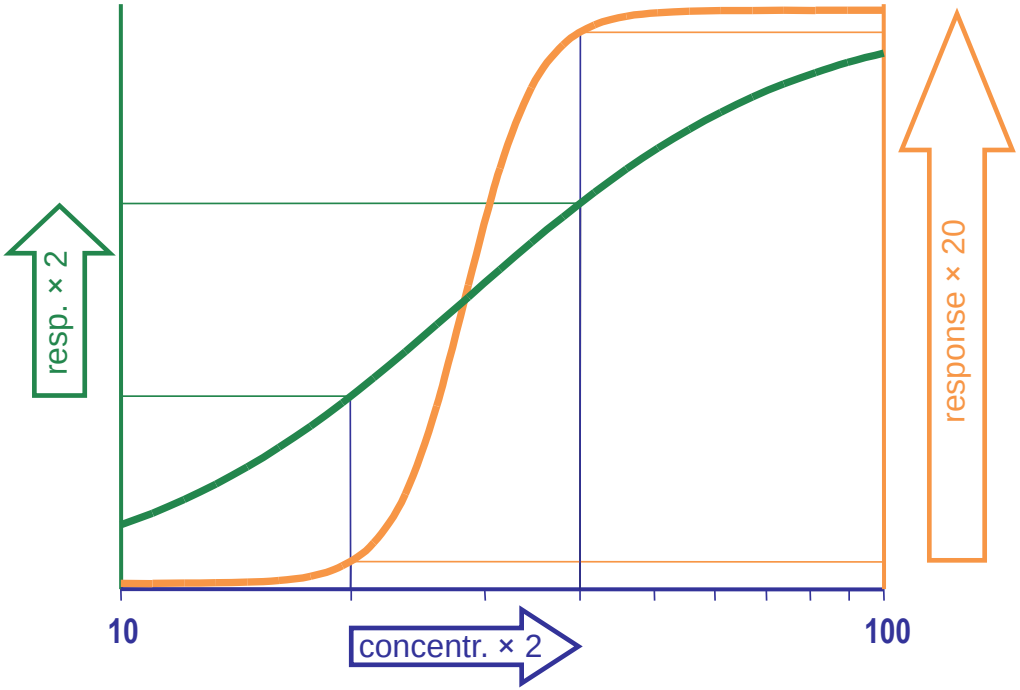
Critical Remarks on Reference-Scaled Average Bioequivalence

Yaroslavl, 22 October 2021

Highly Variable Drugs / Drug Products

- Clinically not relevant difference Δ?
  - Based on pharmacokinetics but extrapolated to similarity of safety and efficacy in the patient population
    - Δ depends on the dose-response curves: HVD (flat), NTID (steep)



Statistical Hypotheses

- Average Bioequivalence (ABE)

  $H_0 : \frac{\mu_T}{\mu_R} \in \{\theta_1, \theta_2\}$ *vs* $H_1 : \theta_1 < \frac{\mu_T}{\mu_R} < \theta_2$,

  where the – fixed – limits $\{\theta_1, \theta_2\}$ of the acceptance range depend on the clinically not relevant difference Δ by

  $\theta_1 = 1 - \Delta,\ \theta_2 = (1 - \Delta)^{-1}$

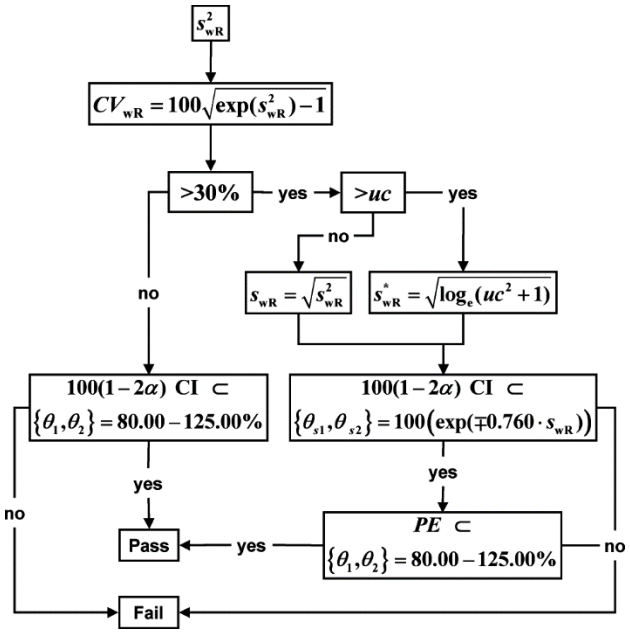
- Scaled Average Bioequivalence (SABE)

  $H_0 : \frac{\mu_T}{\mu_R} \Big/ \sigma_{wR} \in \{\theta_{s_1}, \theta_{s_2}\}$ *vs* $H_1 : \theta_{s_1} < \frac{\mu_T}{\mu_R} \Big/ \sigma_{wR} < \theta_{s_2}$,

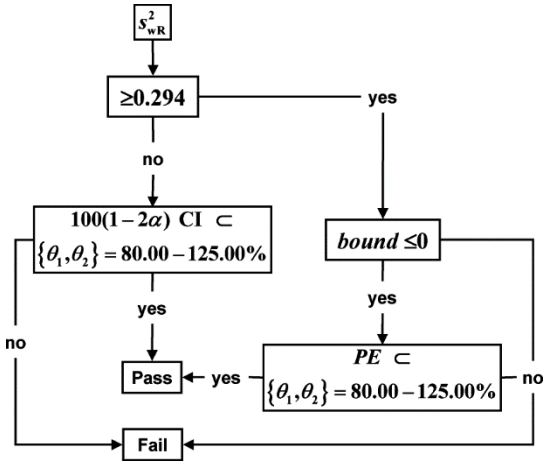
  where σ_{wR} is the standard deviation of the reference and the scaled limits $\{\theta_{s1}, \theta_{s2}\}$ of the acceptance range depend on conditions given by the agency

Frameworks

- Implemented



Average **B**ioequivalence with **E**xpanding **L**imits «ABEL» (EMA, EEU, …)



Reference-**S**caled **A**verage **B**ioequivalence «RSABE» (FDA, CDE)

Lack of Harmonization

- $\Delta > 20\%$
  - GCC 25% → BE-limits 75.00 – 133.33% (C_{max} only)
  - EMA, EEU Scaled based on CV_{wR} (C_{max} only)
  - WHO Like EMA (if justified, also *AUC*)
  - HC Like EMA (*AUC* only)
  - FDA Scaled based on CV_{wR} (*AUC* and C_{max})

EMA, EEU, WHO, …	
CV_{wR}	BE limits (%)
≤30	80.00 – 125.00
35	77.23 – 129.48
40	74.62 – 143.02
45	72.15 – 138.59
≥50	69.84 – 143.19

Health Canada	
CV_{wR}	BE limits (%)
≤30	80.0 – 125.0
35	77.2 – 129.5
40	74.6 – 143.0
45	72.2 – 138.6
50	69.8 – 143.2
≥57.4	66.7 – 150.0

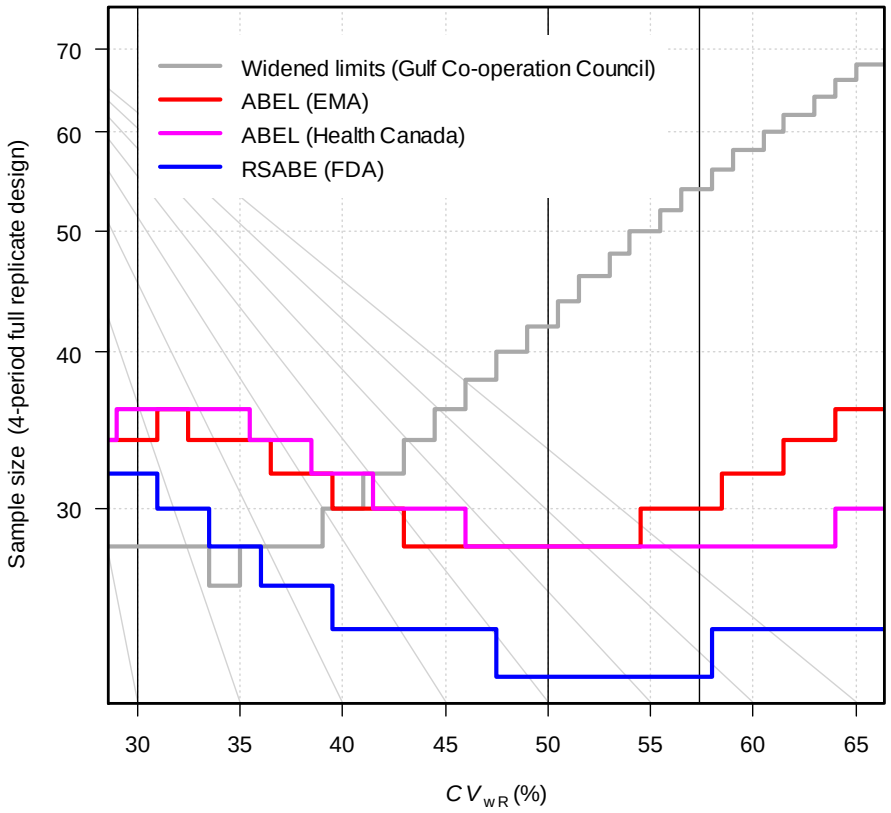
$100\exp(\mp 0.760 \cdot s_{wR})$

FDA, CDE	
CV_{wR}	BE limits (%)
≤30	80.00 – 125.00
35	73.83 – 135.45
40	70.90 – 141.04
45	68.16 – 146.71
50	65.60 – 152.45
60	60.96 – 164.04

$100\exp(\mp 0.8925742 \cdot s_{wR})$

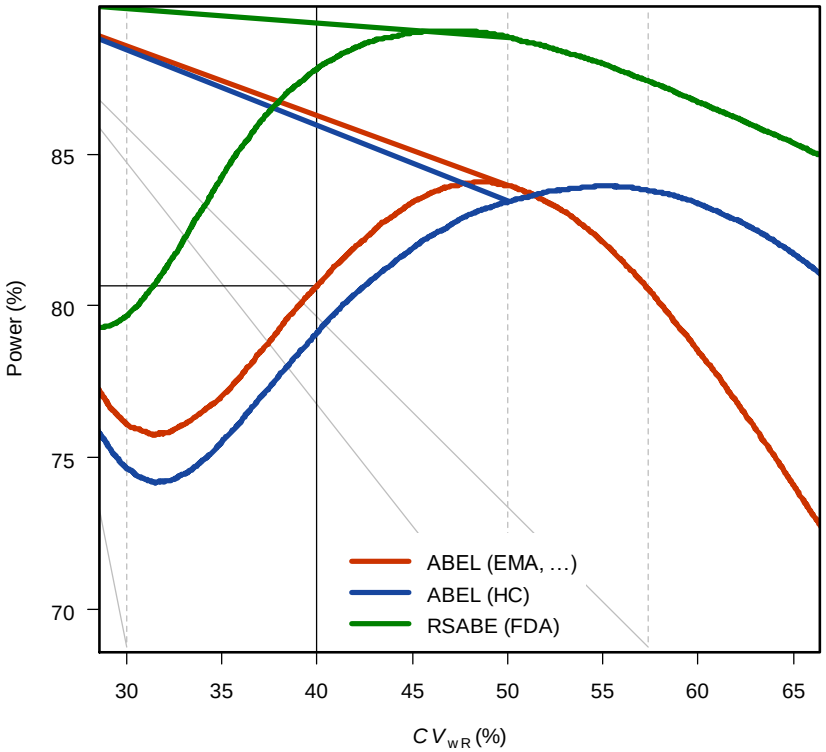
Sample Sizes

- Example TRTR | RTRT
  - Assumed T/R-ratio = 0.90
  - Target power ≥ 80%
- RSABE requires smaller sample sizes for target (desired) power than the ABEL variants



Power

- Example TRTR | RTRT
  - Designed for ABEL
    - Assumed $CV_{wR} = 40\%$
    - Assumed T/R-ratio = 0.90
    - Target power ≥ 80%
  - $n = 30$ (80.7% power)
- For any given sample size the ABEL variants are less powerful than RSABE
- Hypothetical situation
  - The *same* study is submitted to *different* agencies
  - Might *pass* for one and *fail* for another



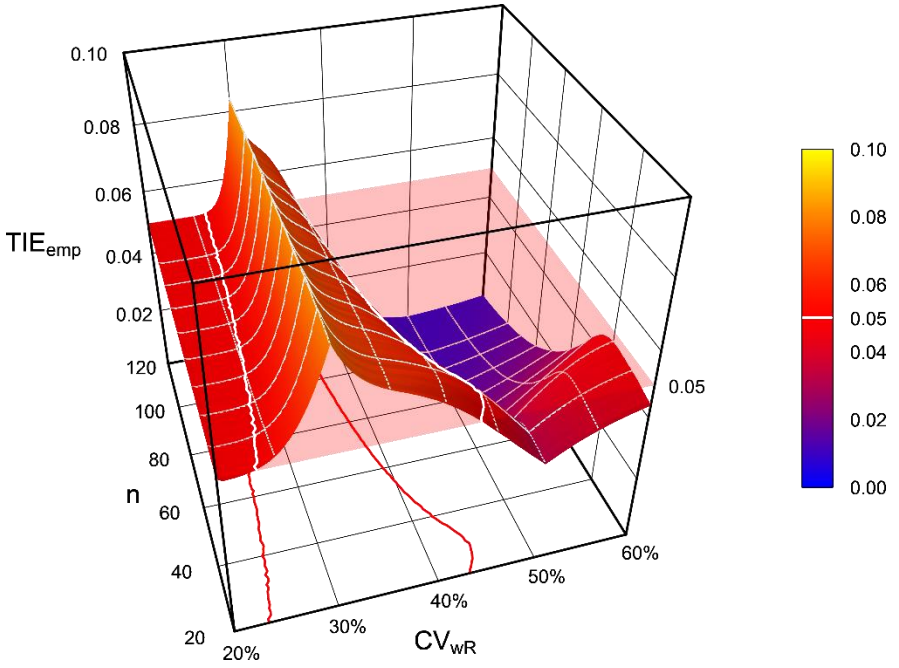
Inflation of the Type I Error

- SABE as implemented by agencies in …
  - ABEL
  - RSABE
- … are frameworks, where the acceptance limits are random variables depending on the observed variability
  - Strictly speaking, Δ is not defined beforehand
  - The *model* is based on the true – but unknown – population parameter σ_{wR}, whereas the *study* is assessed based on the sample s_{wR}
  - This may lead to a misclassification, *i.e.*,
    - the limits are scaled (because $CV_{wR} > 30\%$), although the drug is *not* highly variable and hence,
    - the chance to pass increases, compromising the patient's risk [1,2]

1. Labes D, Schütz H. *Inflation of Type I Error in the Evaluation of Scaled Average Bioequivalence, and a Method for its Control*. Pharm Res. 2016: 33(11); 2805–14. doi:10.1007/s11095-016-2006-1.
2. Schütz H, Labes D. *Critical remarks on reference-scaled average bioequivalence*. Manuscript submitted 2021.

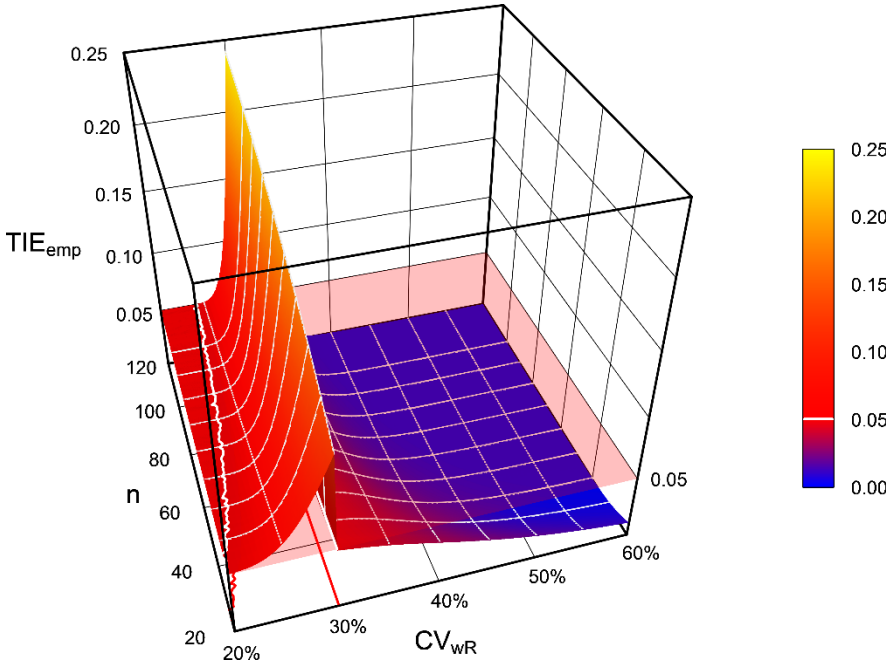
Inflation of the Type I Error

- Example TRTR | RTRT



ABEL

Inflated *TIE* with CV_{wR} ~24 – ~42%
low dependency on sample size
($n = 20$: 0.0800, $n = 120$: 0.0838)



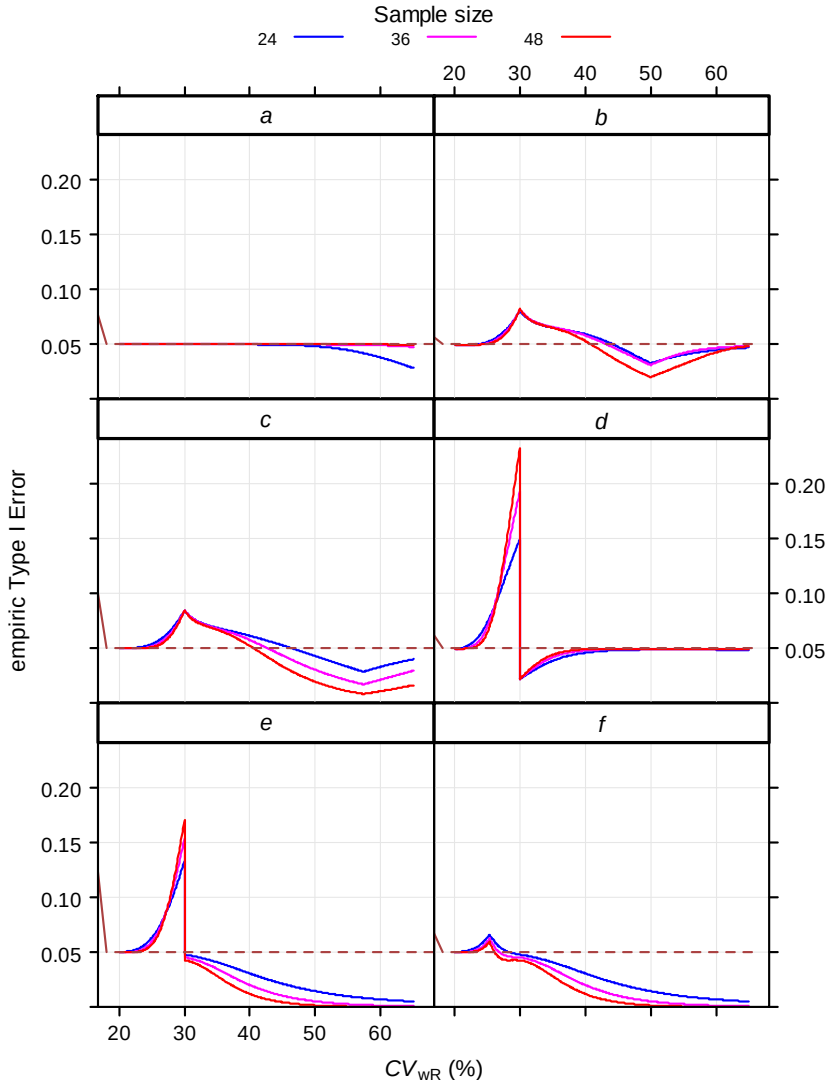
RSABE

Inflated *TIE* with CV_{wR} <30%
high dependency on sample size
($n = 20$: 0.1251, $n = 120$: 0.2421)

Maximum empiric *TIE* at true $CV_{wR} = 30\%$

Inflation of the Type I Error

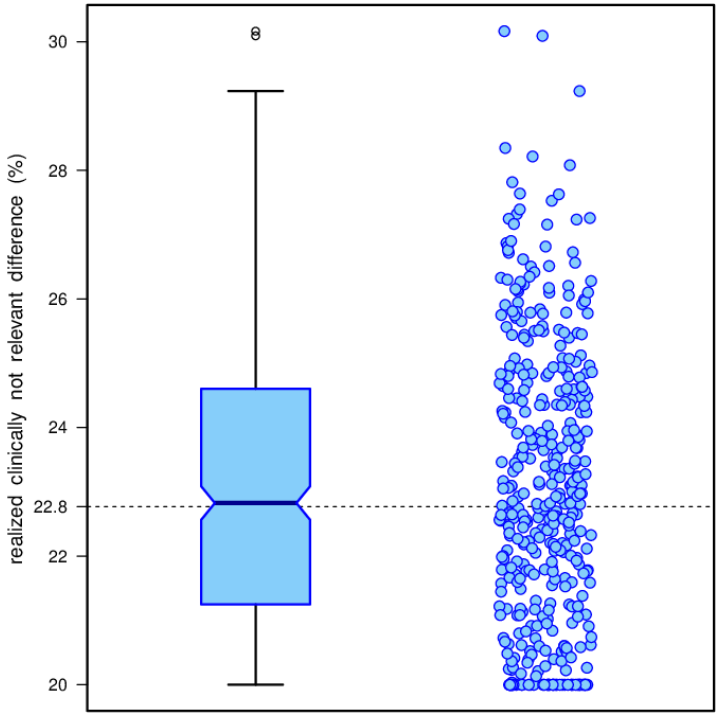
- Example TRTR | RTRT
  - 10^6 simulated [1] studies
  - $n = 24, 36, 48$
  - True $CV_{wR} = 20 – 65\%$
  - True T/R-ratio $= \theta_{s2}$
    - *a* Conventional ABE
    - *b* ABEL (EMA, EEU, and others)
    - *c* ABEL (Health Canada)
    - *d* ABEL (GCC)
    - *e* RSABE (implied limits) [2]
    - *f* RSABE (desired consumer risk model) [2]



1. No exact method exists for power and hence, the *TIE* in the implemented regulatory frameworks. Therefore, extensive simulations under the Null are required.
2. Davit BM *et al*. *Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration*. AAPS J 2012; 14(4): 915–24. doi:10.1208/s12248-012-9406-x.

Realized Δ_r

- Example TRTR | RTRT
  - 500 studies simulated for ABEL
  - $n = 34$ (81.2% power)
  - True $CV_{wR} = 35\%$ ($\Delta = 22.77\%$)
  - True T/R-ratio = 0.90
    - 417 studies passed (83.4%)
    - Realized CV_{wR} 22.30 – 51.25% (Δ_r 20.00 – 30.16%)



- Every study sets its own rules, awarding ones with high CV_{wR}
  - Without access to the study report, Δ_r is unknown to physicians, pharmacists, and patients alike
  - This is an unsatisfactory situation – we put the cart before the horse

Critical Remarks on Reference-Scaled Average Bioequivalence

Thank You!
Благодарю вас!

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