

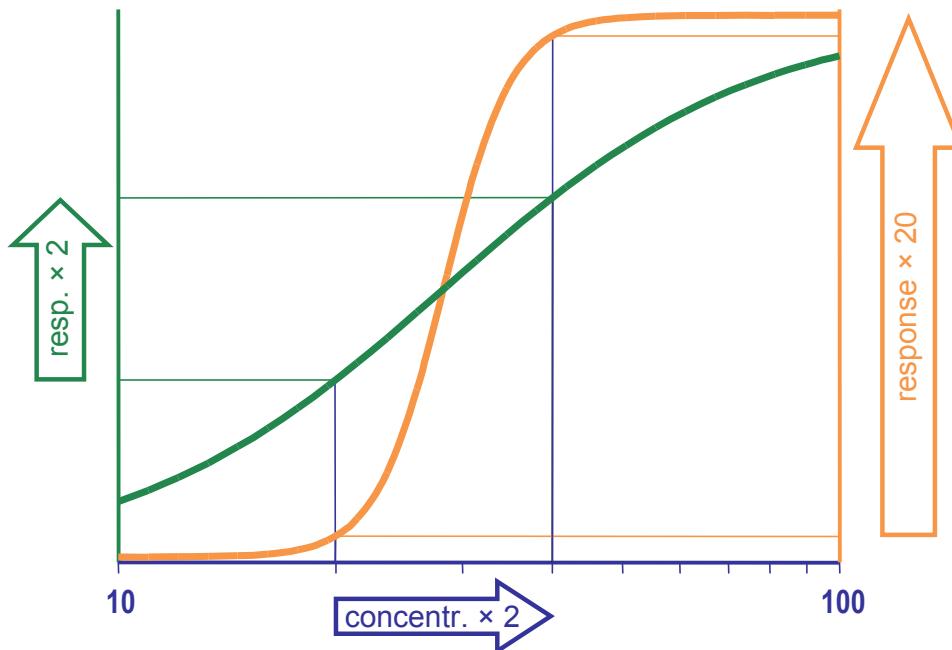
Critical Remarks on Reference-Scaled Average Bioequivalence

«Жизненный путь лекарственных средств: простые и сложные задачи»
«Вопросы статистической обработки, датаменеджмент, IT-технологии в исследованиях лекарственных средств»

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)

$$H_0: \frac{\mu_T}{\mu_R} \ni \{\theta_1, \theta_2\} \text{ vs } H_1: \theta_1 < \frac{\mu_T}{\mu_R} < \theta_2,$$

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)

$$H_0: \frac{\mu_T}{\mu_R} / \sigma_{wR} \ni \{\theta_{s_1}, \theta_{s_2}\} \text{ vs } H_1: \theta_{s_1} < \frac{\mu_T}{\mu_R} / \sigma_{wR} < \theta_{s_2},$$

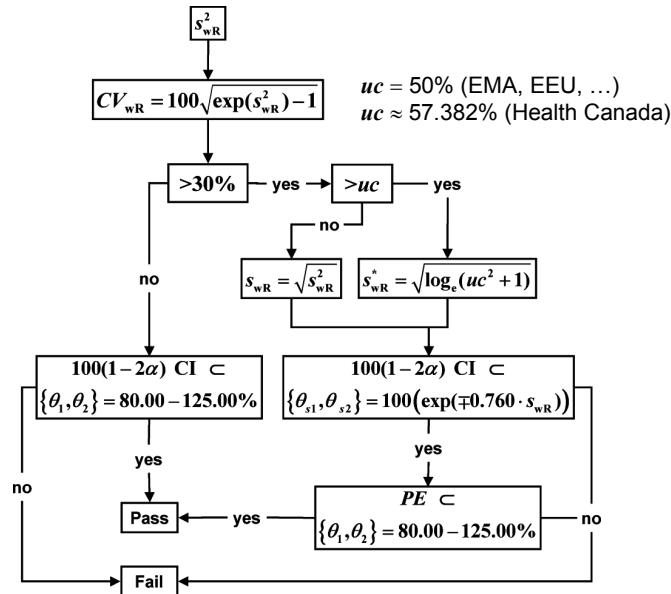
where σ_{wR} is the standard deviation of the reference and the scaled limits $\{\theta_{s_1}, \theta_{s_2}\}$ of the acceptance range depend on conditions given by the agency



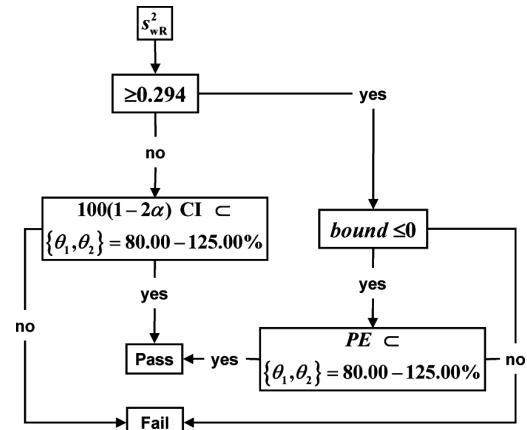
Frameworks



- Implemented



Average Bioequivalence
with Expanding Limits
«ABEL» (EMA, EEU, ...)



Reference-Scaled
Average Bioequivalence
«RSABE» (FDA, CDE)

Lack of Regulatory 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, ...		Health Canada		FDA, CDE	
CV_{wR}	BE limits (%)	CV_{wR}	BE limits (%)	CV_{wR}	BE limits (%)
≤ 30	80.00 – 125.00	≤ 30	80.0 – 125.0	≤ 30	80.00 – 125.00
35	77.23 – 129.48	35	77.2 – 129.5	35	73.83 – 135.45
40	74.62 – 143.02	40	74.6 – 143.0	40	70.90 – 141.04
45	72.15 – 138.59	45	72.2 – 138.6	45	68.16 – 146.71
≥ 50	69.84 – 143.19	50	69.8 – 143.2	50	65.60 – 152.45
		≥ 57.4	66.7 – 150.0	60	60.96 – 164.04

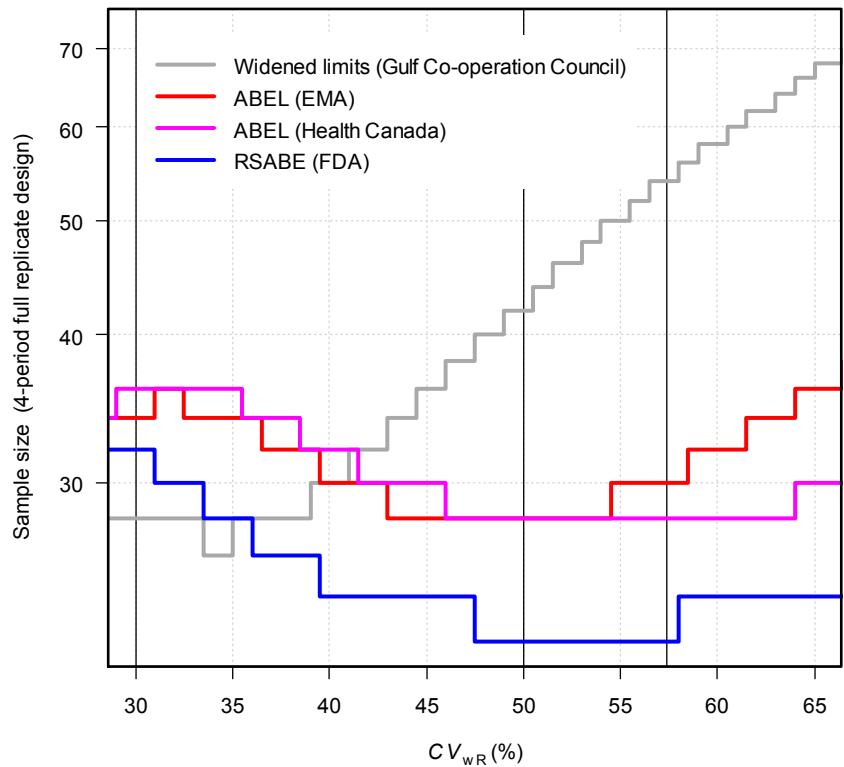
$$100 \exp(\mp 0.760 \cdot s_{wR})$$

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



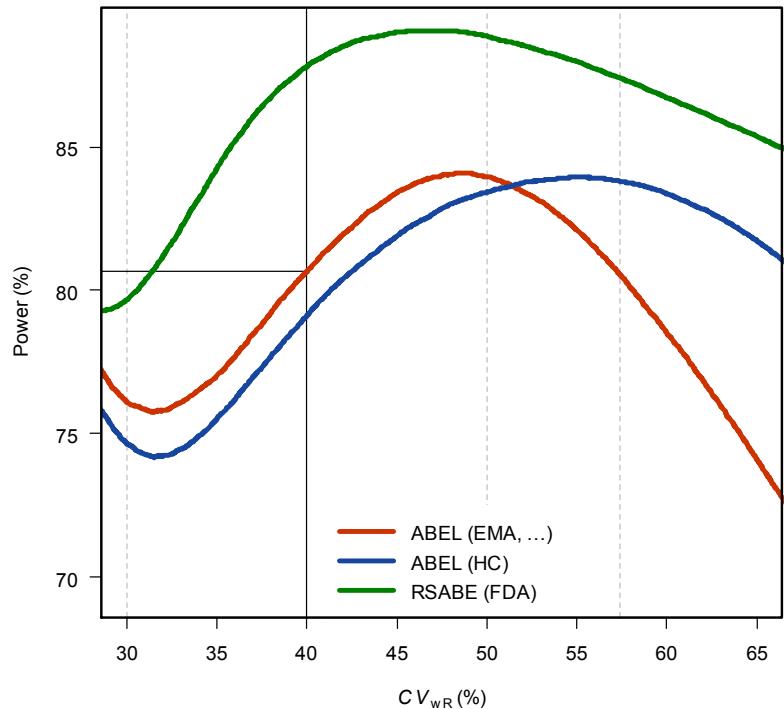
Sample Sizes

- Example TRTR | RTRT
 - Assumed T/R-ratio = 0.90
 - Target power $\geq 80\%$
- 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 $\geq 80\%$
 - $n = 30$ (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 regulatory 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 probability to pass increases, compromising the patient's risk^{1,2}

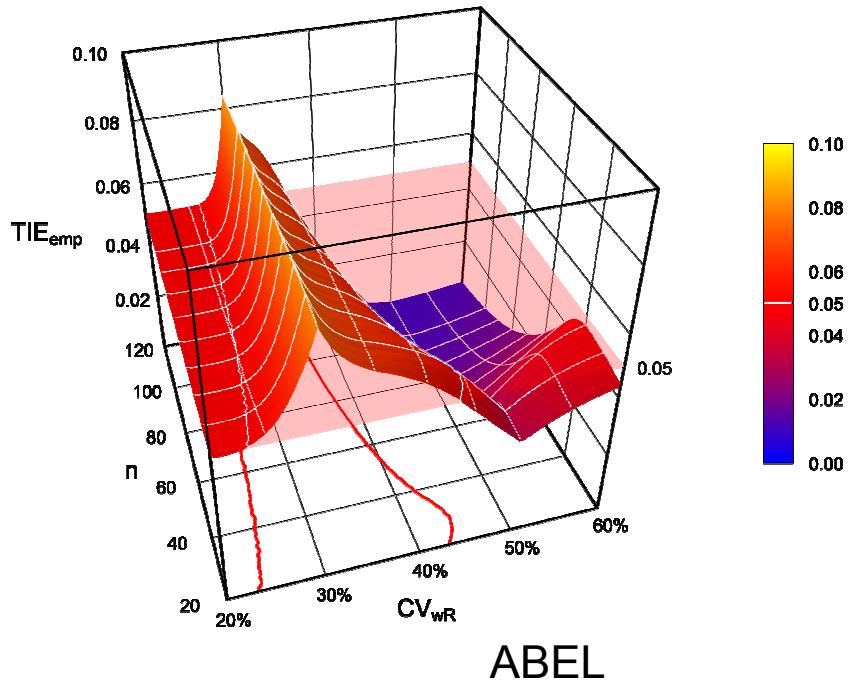
1. Labes D, Schütz H. *Inflation of Type I Error in the Evaluation of Scaled Average Bioequivalence, and a Method for its Control*. Pharm Res. 2016; 33(11); 2805–14. doi:10.1007/s11095-016-2006-1.

2. Schütz H, Labes D. *Critical remarks on reference-scaled average bioequivalence*. Manuscript submitted 2021.

Inflation of the Type I Error

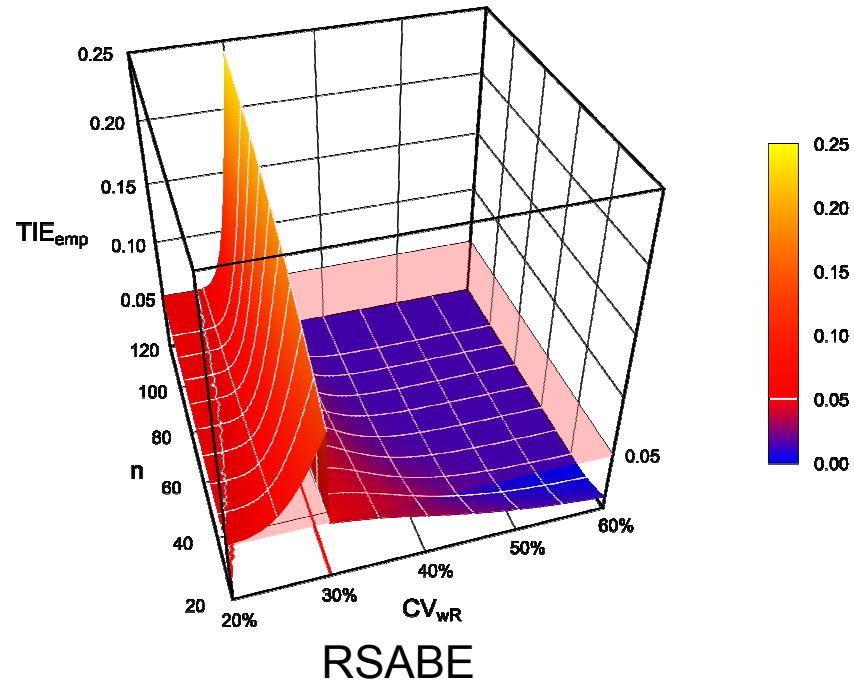


- Example TRTR | RTRT



Inflated T/E with $CV_{wR} \sim 24 - \sim 42\%$
low dependency on sample size
($n = 20$: 0.0800, $n = 120$: 0.0838)

Maximum empiric Type I Error at true $CV_{wR} = 30\%$



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

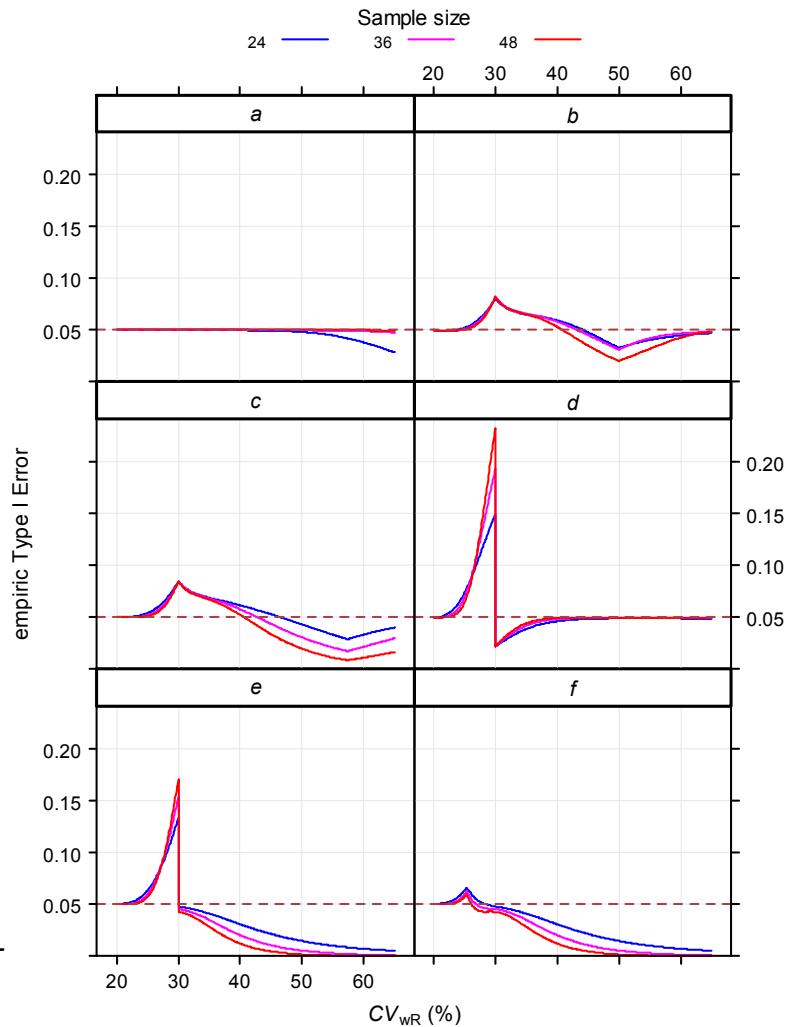
Inflation of the Type I Error



- Example TRTR | RTRT

- 10^6 simulated ¹ studies
- $n = 24, 36, 48$
- True $CV_{wR} = 20 - 65\%$
- True T/R-ratio = θ_{s_2}
 - 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

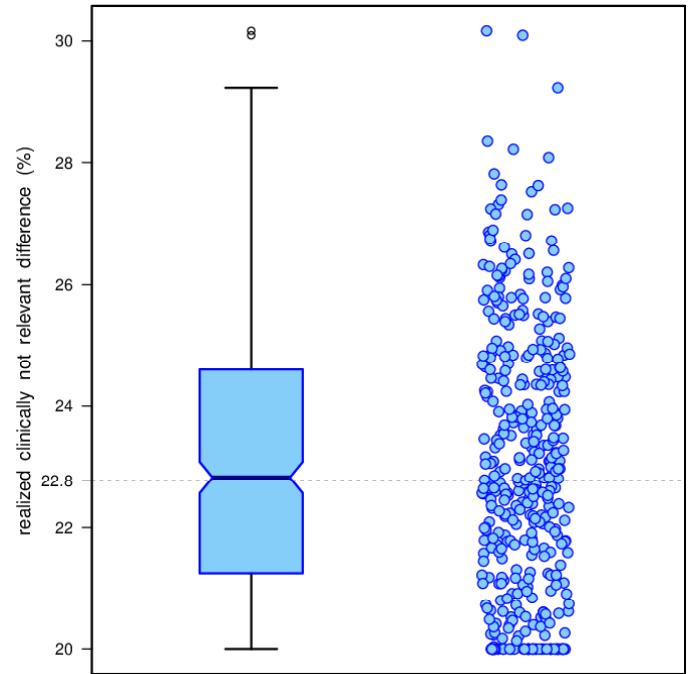
1. No exact method exists for power and hence, the *T/I/E* in the implemented regulatory frameworks. Therefore, extensive simulations under the Null Hypothesis are required.
2. Davit BM et al. *Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products 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!
Спасибо!



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