weighted inpact factor 3.37 (1.24 – 6.45)

Empiric Type I Error assessed at $\exp(\pm\theta_s \cdot s_{wR})$

1. Tóthfalusi L, Endrényi L, García-Arieta A. Evaluation of bioequivalence for highly variable drugs with scaled average bioequivalence. Clin Pharmacokinet. 2009; 48(11): 725–43.
2. Haidar SH, Makhlouf F, Schuirmann DJ, Hyslop T, Davit B, Conner D, Yu LX. Evaluation of a Scaling Approach for the Bioequivalence of Highly Variable Drugs. AAPS J. 2008; 10(3): 450–4.
3. Endrényi L, Tóthfalusi L. Regulatory and Study Conditions for the Determination of Bioequivalence of Highly Variable Drugs. J Pharm Pharmaceut Sci. 2009; 12(1): 138–49.
4. Karalis V, Symillides M, Macheras P. On the leveling-off properties of the new bioequivalence limits for highly variable drugs of the EMA guideline. Europ J Pharm Sci. 2011; 44(4): 497–505.
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7. 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.
8. Tóthfalusi L, Endrényi L. An Exact Procedure for the Evaluation of Reference-Scaled Average Bioequivalence. AAPS J. 2016; 18(2): 476–89.
9. Tóthfalusi L, Endrényi L. Algorithms for Evaluating Reference Scaled Average Bioequivalence: Power, Bias, and Consumer Risk. Stat Med. 2017; 36(27): 4378–90.
10. Molins E, Cobo E, Ocaña J. Two-Stage Designs Versus European Scaled Average Designs in Bioequivalence Studies for Highly Variable Drugs: Which to Choose? Stat Med. 2017; 36(30): 4777–88.
11. Endrényi L, Tóthfalusi L. Bioequivalence for highly variable drugs: regulatory agreements, disagreements, and harmonization. J Pharmacokin Pharmacodyn. 2019; 46(2): 117–26.
12. Deng Y, Zhou XH. Methods to control the empirical type I error rate in average bioequivalence tests for highly variable drugs. Stat Methods Med Res. 2019; 29(6): 1650–67.
13. Ocaña J, Muñoz J. Controlling type I error in the reference-scaled bioequivalence evaluation of highly variable drugs. Pharm Stat. 2019; 18(5): 583–99.
14. Schütz H, Labes D, Wolfsegger MJ. Critical Remarks on Reference-Scaled Average Bioequivalence. J Pharm Pharmaceut Sci. 2022; 25: 285–96.
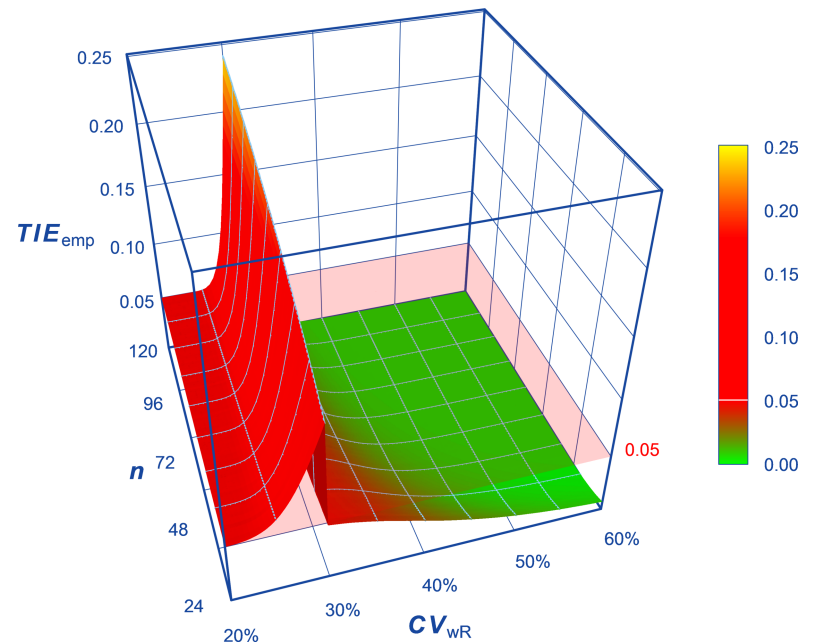
Consumer risk in SABE

ABEL (EMA and others)
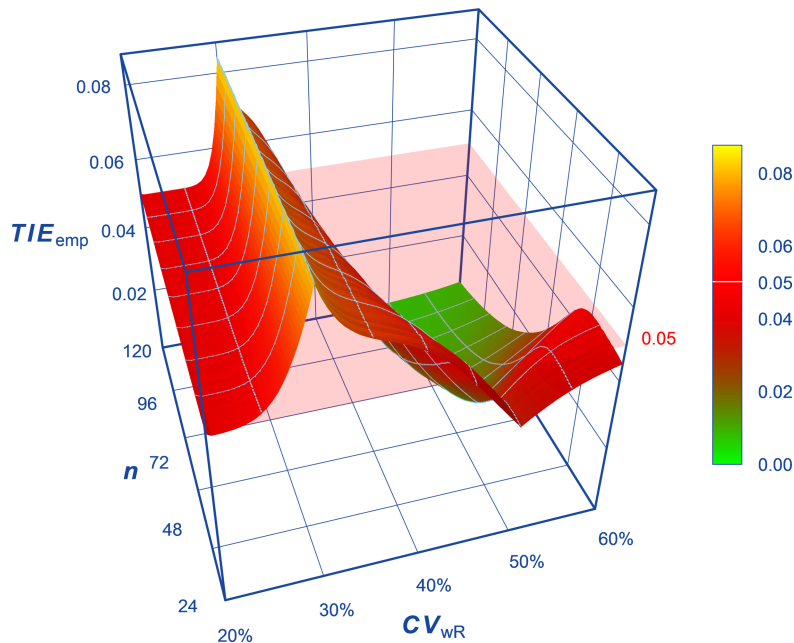
TIE_{emp} at CV_{wR} 30%; *n* 24: **0.0804**, *n* 120: **0.0838**

RSABE (FDA 'implied limits')

TIE_{emp} at CV_{wR} 30%; *n* 24: **0.1335**, *n* 120: **0.2418**

2-sequence 4-period full replicate design, $CV_{wT} = CV_{wR}$

Consumer risk in the FDA's RSABE

Haidar *et al*. (2008), Section 'Results and Discussion'

> » Furthermore, a σ_{w0} of 0.25 results in a lower inflation of Type I error compared to a σ_{w0} value of 0.294. Type I error, defined as the risk of concluding two products are bioequivalent when in fact they are not, is 0.05 (or 5%) for average BE. **It is undesirable for any new method to significantly deviate from this value.** «

- 100 runs of 10^6 simulations with random seeds ($CV_{wT} = CV_{wR} = 30\%$, partial replicate design, $n = 36$), passing studies with GMR = 1.25:

  - minimum   13.15%
  - median   13.24%
  - maximum   13.90%

- **Does $\approx 13\%$ significantly deviate from 5%?**
  Yes, it does.

- **Does RSABE <u>as implemented</u> show such an undesirable property?**
 **Yes, indeed.**

The FDA's 'desired consumer risk model'

Empiric Type I Error assessed at

- **0.8000 or 1.2500** if $s_{wR} \leq 0.25$
- $\exp(\pm\theta_s \cdot s_{wR})$ if $s_{wR} > 0.25$

Davit *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. https://doi.org/10.1208/s12248-012-9406-x

Section 'Controversies'

» Results of simulations conducted by members of the HV Drug Working Group support the position that using a cutoff value of 0.294 for s_{wR} maintains an acceptable type I error rate relative to FDA's desired consumer risk model. «
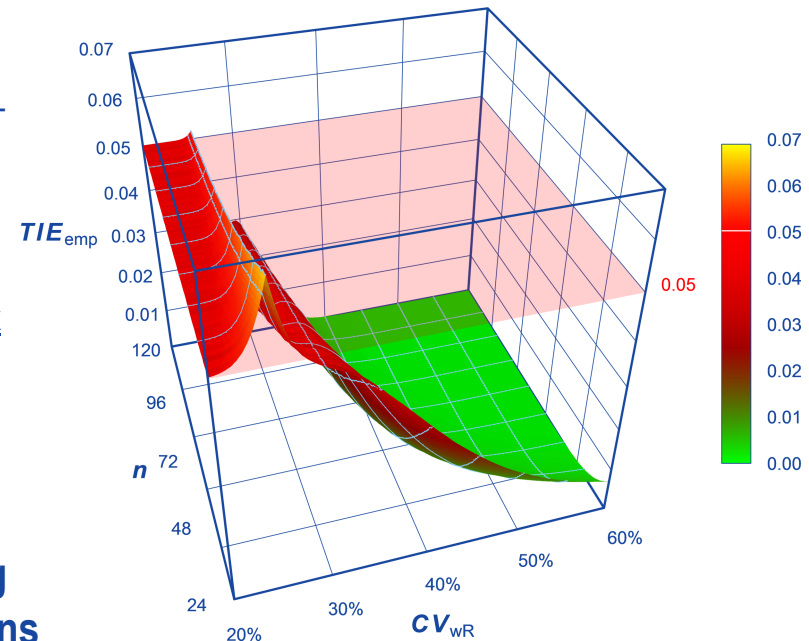

TIE_{emp} at $CV_{wR} \approx 25.396\%$ (s_{wR} 0.25); *n* 24: **0.0663**, *n* 120: 0.0501

The FDA's proposal for harmonization

The EMA and Health Canada should implement Howe's approximation[1] while keeping their current regulatory conditions[2]

- **Regulatory constant $k = 0.760$**

- **Cap of scaling**
  - **EMA $CV_{wR} = 50\%$ max TIE_{emp} 0.0686**
  - **HC $CV_{wR} \approx 57.382\%$ max TIE_{emp} 0.0690**

1. Howe W.G. Approximate Confidence Limits on the Mean of $X + Y$ Where X and Y Are Two Tabled Independent Random Variables.
   J Am Stat Assoc. 1974; 69(347): 789–94.
   https://doi.org/10.2307/2286019

2. Muñoz J, Alcaide D, Ocaña J. Consumer's risk in the EMA and FDA regulatory approaches for bioequivalence in highly variable drugs.
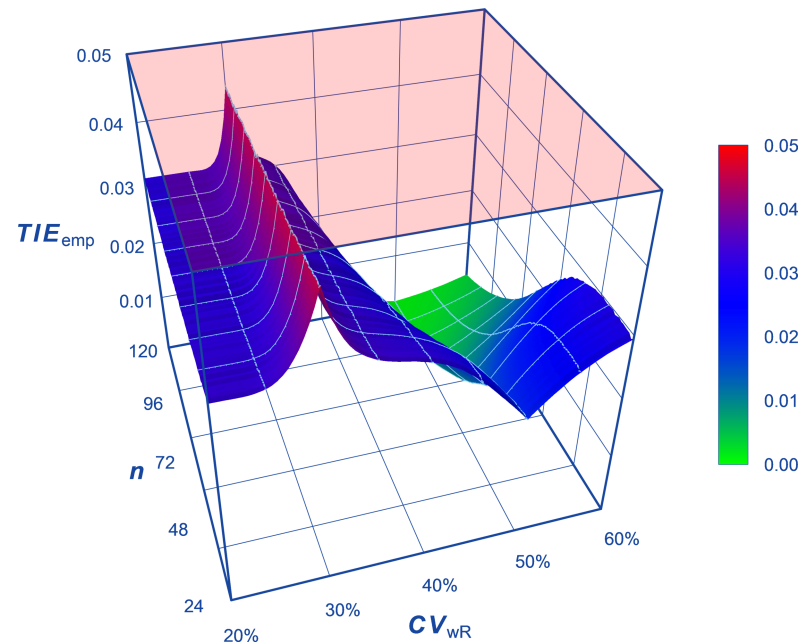   Stat Med. 2016; 35(12): 1933–43.
   https://doi.org/10.1002/sim.6834
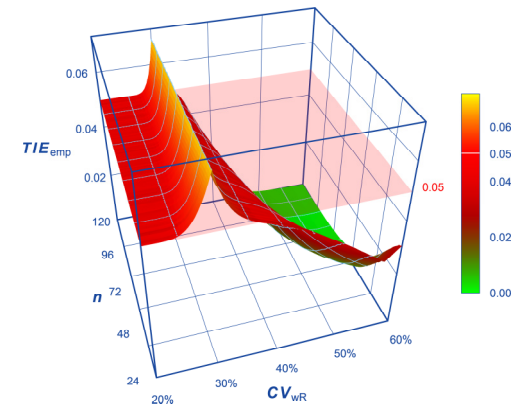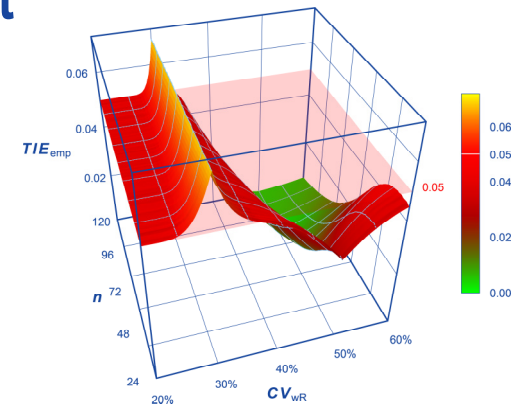
Alternative: Iteratively adjusted α

Molins *et al.* (2017)
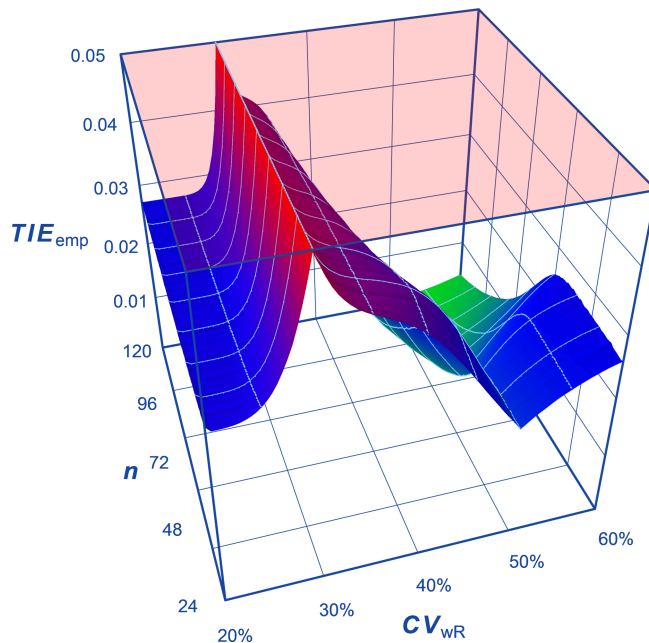
Ocaña *et al.* (2019)

*TIE*emp at *CV*wR 30%: 0.0500 ✓

*TIE*emp at *CV*wR 30%; *n* 24: 0.0430, *n* 120: 0.0456 ✓

2-sequence 4-period full replicate design, $CV_{wT} = CV_{wR}$ (evaluation for the EMA's ABEL)