MEDICAL UNIVERSITY OF VIENNA

Comparative Bioavailability Studies Fundamentals and Common Pitfalls

Helmut Schütz

Center for Medical Data Science of the Medical University of Vienna
Faculty of Pharmacy, Universidade de Lisboa, Lisbon
BEBAC, Vienna

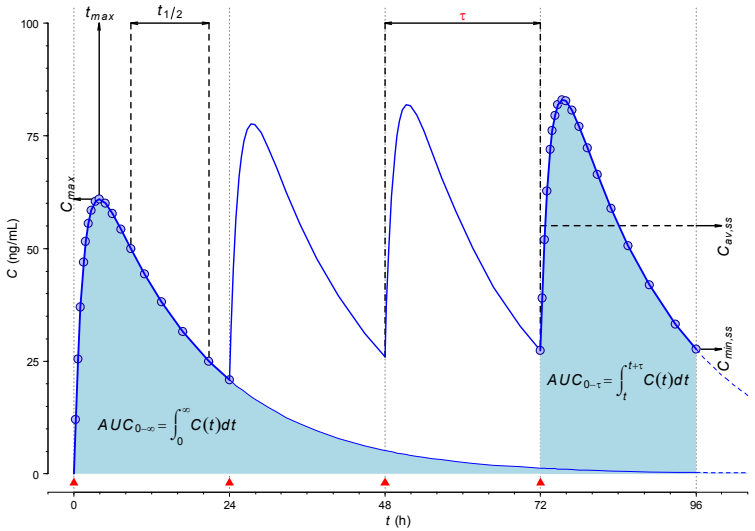
Refresher: Fundamentals of PK

- ***AUC* is the Integral of the Concentration-time Curve**
  - **Example: One compartment, extravascular dose, single dose**

$$C(t) = \frac{f \cdot D \cdot k_a}{V(k_a - k_e)}\left(e^{-k_e \cdot t} - e^{-k_a \cdot t}\right)$$

$$AUC_{0-\infty} = \int_0^{\infty} C(t)\,dt = \frac{f \cdot D}{CL}$$

C	Concentration
t	time
f	fraction absorbed
D	Dose
V	Volume of distribution
k_a, k_e	absorption, elimination rate constants
CL	Clearance



Superposition Principle* of linear PK

$AUC_{t-\tau} \approx AUC_{0-\infty}$

* Dost FH. *Der Blutspiegel: Kinetik der Konzentrationsabläufe in der Kreislaufflüssigkeit*. Leipzig: Thieme-Verlag; 1953. p. 244.

Terminology

1971 ‘Biologic Availability’ → Bioavailability (BA)

1975 Bioequivalence (BE) coined

1979 MeSH term ‘Biological Availability’ introduced

The extent to which the active ingredient of a drug dosage form becomes available at the site of drug action or in a biological medium believed to reflect accessibility to a site of action

- **BE was never a scientific concept in the Popperian sense but an *ad hoc* solution to pressing problems in the 1970s**
  - **Especially with formulations of Narrow Therapeutic Index Drugs (NTIDs) like phenytoin, digoxin, warfarin, theophylline, primidone**

1 Vitti TG, Banes D, Byers TE. *Bioavailability of Digoxin.* N Engl J Med. 1971; 285(25): 1433–4. https://doi.org/10.1056/NEJM197112162852512

2 DeSante KA, DiSanto AR, Chodos DJ, Stoll RG. *Antibiotic Batch Certification and Bioequivalence.* JAMA. 1975; 232(13): 1349–51. https://doi.org/10.1001/jama.1975.03250130033016

Bioavailability

- Absolute: AUC_{EV} / AUC_{IV}
- Relative:
  - $AUC_{Formulation}$ / $AUC_{Solution}$
    Influence of excipients on absorption
  - AUC_{Test} / $AUC_{Comparator}$
    Investigation of Bioequivalence
    - Test — to be marketed Formulation
      Comparator — Formulation used in Phase III
    - Drug-Drug Interactions
    - Line Extensions (*e.g.*, lower / higher doses than already approved)
    - Major Variations (*e.g.*, manufacturing process, site changes)
    - Food Effects
    - Test — Generic
      Comparator — Innovator

Innovators

Generics

BE is the desired result of a Comparative BA study
'Bioequivalence Study' is sloppy terminology

Comparative BA: Terminology

- BA is based in classical PK *solely* on $AUC_{0-\infty}$
- In 1975 the U.S. FDA introduced two terms[1]
  - The 'Extent of BA' or 'Total Exposure', measured by *AUC*
    - For a given formulation it depends only on *D* and *f* (*V* or *CL* and k_e are drug-specific and thus, not relevant)
  - The 'Rate of BA' or 'Peak Exposure', measured by C_{max}
    - C_{max} is a *surrogate* of the formulation-specific k_a but it is a *composite*[2] PK metric (depending also on *AUC*)

$$t_{max} = \frac{\log_e\left(k_a / k_e\right)}{k_a - k_e}, \quad C_{max} = \frac{f \cdot D \cdot k_a}{V(k_a - k_e)}\left(e^{-k_e \cdot t_{max}} - e^{-k_a \cdot t_{max}}\right)$$

Hence, C_{max} *is not* an unbiased estimator of k_a

1. Skelly JP. *Bioavailability and Bioequivalence.* J Clin Pharmacol. 1976; 16(10/2): 539–45. https://doi.org/10.1177/009127007601601013
2. Tóthfalusi L, Endrényi L. *Estimation of C_{max} and T_{max} in Populations After Single and Multiple Drug Administration*. J Pharmacokin Pharmacodyn. 2003; 30(5): 363–85. https://doi.org/10.1023/b:jopa.0000008159.97748.09

Comparative BA: Regulatory Approaches

- PK Modeling is at the time being not acceptable
  - PK models require exhaustive validation and documentation
  - The *same data set* does not necessarily give the *same results* with *different software*
- PK metrics have to be calculated by Noncompartmental Analyses (NCA)*
  - Independent from software; paper, pencil, brain…
  - Planned methods have to be described in the protocol
  - Unlikely that one is able to observe the true C_{max}/t_{max} in every subject → frequent sampling around t_{max} mandatory
  - *At least* three samples required to obtain a reliable estimate of the apparent elimination λ_z

* International Council for Harmonisation. *Bioequivalence for Immediate-Release Solid Oral Dosage Forms. M13A.* Geneva. 23 July 2024. https://database.ich.org/sites/default/files/ICH_M13A_Step4_Final_Guideline_2024_0723.pdf

Sampling time points

- **Recommendations**
  - Equally spaced in the absorption phase up to two times of the anticipated t_{max}
    - For IR products at $2 \times t_{max}$ absorption is practically complete*
    - Avoid "first point C_{max}" – a pilot study is helpful
  - Never plan based on an *average* $t_{½}$ reported in literature
    - The $t_{½}$ of some subjects might be substantially slower or faster
    - The extrapolated part ($AUC_{t-\infty}$) should cover ≥ 80% of $AUC_{0-\infty}$
    - Based on that, define the last sampling time point t and confirm that the bioanalytical method is sufficiently accurate and precise
  - Geometric progression of sampling time points from $2 \times t_{max}$ to t
  - Calculated sampling schedule adjusted according to clinical practicalities

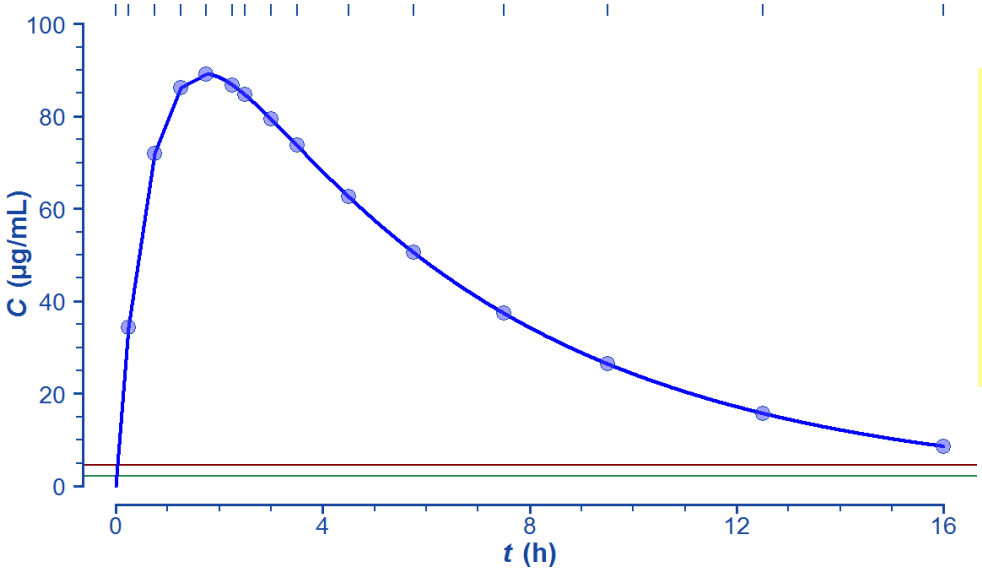
* Scheerans C, Derendorf H, Kloft C. *Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs*. Biopharm Drug Dispos. 2008; 29(3): 145–57. https://doi.org/10.1002/bdd.596

Sampling time points: Example

- Analgesic PO; $f = 0.9$, $D = 400$ mg, $V = 3$ L, $t_{½,a} = 30$ min ($k_a = 1.3863$ h^{-1}), $t_{½,e} = 4$ h ($k_e = 0.1733$ h^{-1})
  - Targets
    - Last sampling time at 16 h, 15 Sampling time points (7 after administration to $2 \times t_{max}$, 7 to t_{last})
    - Extrapolated $AUC \leq 20\%$ of $AUC_{0-\infty}$
  - Sampling schedule and required Lower Limit of Quantification?
  - Calculated
    - C_{max} (t_{max}) 89.16 µg/mL (1.71 h = 1:42 h), C_{last} 8.57 µg/mL
    - Linear pre-dose, 0:25, 0:51, 1:17, 1:42, 2:08, 2:34, 3:00, 3:25 h
    - Geometric 4:25, 5:43, 7:24, 9:43, 12:22, 16:00 h
  - Final schedule pre-dose, 0:15, 0:45, 1:15, 1:45, 2:15, 2:30, 3:00, 3:30, 4:30, 5:45, 7:30, 9:30, 12:30, 16:00 h

Sampling time points: Example (cont'd)

- Analgesic PO; with the practical sampling schedule
  - $\lambda_z = 0.1733\ h^{-1}$ ($t_{½} = 4.00$ h) based on *max*(R^2_{adj}) estimated from 9:30 to 16:00 h; $n = 3$ (guideline ≥ 3)
  - $AUC_{t-\infty}/AUC_{0-\infty} = 7.17\%$ of $AUC_{0-\infty}$ (guideline $\leq 20\%$)
  - LLOQ 4.5 µg/mL (≈ 5% of C_{max}), 2.25 µg/mL (≈ 2.5% of C_{max})



Bias (NCA vs. PK model)

C_{max}	–0.015%
t_{max}	+2 min
AUC_{0-t}	–0.458%
$AUC_{0-\infty}$	–0.425%

Problems with the GL's "first point C_{max}" unlikely

Remarks about *AUC*

- The ‘linear trapezoidal method’[1,2] should have been thrown into the scientific trash can with the introduction of scientific pocket calculators more than 50 years ago
  - Systematically overestimates *AUC* in the distribution / elimination phase → only of historical interest
- With few exceptions drugs follow first-order elimination, *i.e.*, an exponential decrease

$$C(t) = \frac{f \cdot D \cdot k_a}{V(k_a - k_e)} \left(e^{-k_e \cdot t} - e^{-k_a \cdot t} \right)$$

  - Can be approximated by the ‘linear-up / logarithmic-down trapezoidal method’[2]

1 Skelly JP. *A History of Biopharmaceutics in the Food and Drug Administration 1968–1993*. AAPS J. 2010; 12(1): 44–50. https://doi.org/10.1208/s12248-009-9154-8

2 Yeh KC, Kwan KC. *A Comparison of Numerical Integrating Algorithms by Trapezoidal, Lagrange, and Spline Approximation. J Pharmacokin Biopharm*. 1978; 6(1): 79–98. https://doi.org/10.1007/BF01066064

Remarks about *AUC* (cont'd)

- **Linear-up / logarithmic-down trapezoidal method**
  - Sections with *increasing or equal* concentrations ($C_{i+1} \geq C_i$) are calculated by the linear trapezoidal method

$$AUC_{t_i \to t_{i+1}} \simeq \frac{C_{i+1} + C_i}{2}\left(t_{i+1} - t_i\right)$$

  - Sections with *decreasing* concentrations ($C_{i+1} < C_i$) are calculated by the logarithmic-linear trapezoidal method

$$AUC_{t_i \to t_{i+1}} \simeq \frac{C_{i+1} - C_i}{\log_e \frac{C_{i+1}}{C_i}}\left(t_{i+1} - t_i\right)$$

  - Implemented in software since 1993 (!!)
  - Suitable for IV (bolus, infusion) and any EV administration

Design Considerations

- **Fundamental Assumption of BE**
  The similarity in concentrations observed in the circulation (PK) is reflected in the site of action (PD = effects), allowing for the extrapolation of results to the patient population(s)
- **Always in the condition which is most sensitive to detect potential differences in formulations**
  - Commonly single dose, highest strength
  - Sometimes in steady state (*e.g.*, the auto-inducer carbamazepine)
- **If ever possible, studies in healthy volunteers in a cross-over design order to decrease variability**
- **If not possible (extremely long half-life or AEs in healthy volunteers), studies in a parallel design**

Design Considerations (cont'd)

- In crossover designs treatment periods have to be separated by a sufficiently long washout-period ($\geq 5\, t_{1/2}$)
  - In later period(s) subjects have to be in the *same physiological* state than in the drug-naïve first
  - In multiple dose studies the washout of the first treatment can overlap with the saturation phase of the next treatment
- ICH E9 (1998)

  The number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed
- ICH M13A (2024)

  The number of subjects […] should be based on an appropriate sample size determination to achieve a pre-specified power and […] type 1 error

Design Considerations (cont'd)

- The more complex a design is, the more information can be extracted, which leads to a lower sample size
- Hierarchy of designs

  Full replicate (TRTR | RTRT or TRT | RTR)

  Partial replicate (TRR | RTR | RRT)

  2×2×2 crossover (TR | RT)

  Parallel (T | R)

- Variances which can be estimated

Parallel	*total* (pooled of *between* + *within* subjects)
2×2×2 crossover	+ *between*, *within* subjects
Partial replicate	+ *within* subjects (of R only)
Full replicate	+ *within* subjects (of R *and* T)

Design Considerations (cont'd)

- The sample size depends on
  - the clinically not relevant deviation Δ
    - For most drugs $\Delta = 20\%$, leading to BE limits of $100\{1 - \Delta, 1 / (1 - \Delta)\} = \{80\%, 125\%\}$
    - For Highly Variable Drugs / Drug Products $\Delta > 20\%$ and $\leq 50\%$, leading in most jurisdictions to expanded BE limits of up to {69.84%, 143.19%}
    - For NTIDs $\Delta = 10\%$, leading in most jurisdictions to narrower BE limits of $100\{1 - \Delta, 1 / (1 - \Delta)\} = \{90.00\%, 111.11\%\}$
  - the desired power π (where the producer's risk $\beta = 1 - \pi$)
  - the acceptable consumer risk α (fixed by the authority)
  - the assumed deviation of the Test formulation to the Comparator
  - the assumed variability (generally expressed as *CV*)
  - the study design (the more complex, the less subjects)

$\Delta = 20\%$ is arbitrary (as is any other) However, we have decades of empiric evidence that it is suitable

PK metrics follow a log-normal distribution
BE limits are symmetrical in log-scale but asymmetrical after back-transformation, *e.g.*, ± 0.2231
$e^{-0.2231} = 0.80$, $e^{+0.2231} = 1.25$

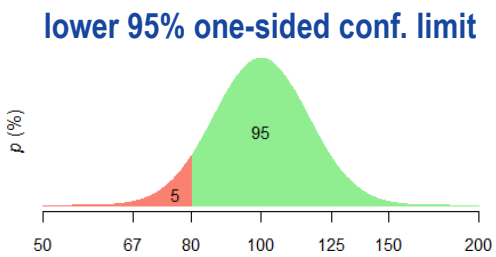
Hypotheses in BE

- The Null Hypothesis H_0 – we hope to *reject* – is Bioinequivalence ($\mu_T \neq \mu_R$)
- The Alternative Hypothesis H_a – we hope to *accept* – is Bioequivalence ($\mu_T \cong \mu_R$)
- All formal decisions are subjected to two Types of Error
  - α = Probability of Type I Error (a.k.a. Risk Type I)
  - β = Probability of Type II Error (a.k.a. Risk Type II)

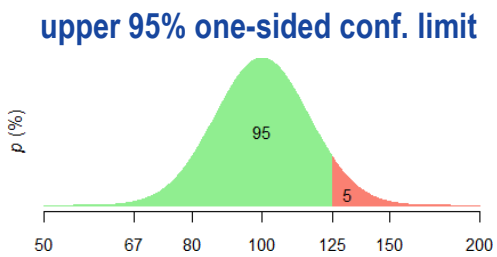
Decision	H_0 is *true*	H_0 is *false*
H_0 rejected	Patient's risk (α)	Correct (BE)
H_0 not rejected	Correct (not BE)	Producer's risk (β)

Type I Error

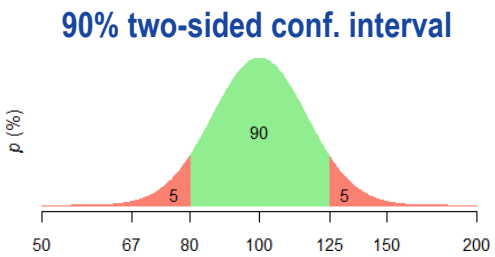
- $\alpha =$ **Patient's risk to be treated with an inequivalent formulation (H_0 *falsely* rejected)**
  - **BA of the Test compared to Reference in a *particular* patient is considered to be risky *either below* 80% *or above* 125%**
    - **If we keep the risk of *particular* patients at α 0.05 (5%), the risk of the entire *population* of patients (where BA < 80% *and* > 125%) is 2α (10%) – expressed as a confidence interval: $100(1 - 2\alpha) = 90\%$**
    - **However, since in a patient BA cannot be < 80% and > 125% *at the same time*, the patient's risk from a 90% CI is still only 5%**



5% of patients <80%



5% of patients >125%



90% of the patient population within 80 – 125%

Type II Error

- β = **Producer's risk that an equivalent formulation is not approved (*H_1 falsely* not accepted)**
  - **Fixed in study planning to $10 \approx \leq 20\%$, where power $\pi = 1 - \beta = \geq 80 \approx 90\%$**
  - **If all assumptions in the sample size estimation turn out to be correct and power was fixed at 80%,**
    one out of five studies will fail by pure chance

α 0.05	BE
not BE	β 0.20

1 / 5

  - ***Post hoc* (*a posteriori*, retrospective) power * is irrelevant; the outcome of a comparative BA study is dichotomous – *either* it passed BE *or* it failed**

* WHO. *Frequent deficiencies in BE study protocols*. Geneva. November 2020. https://extranet.who.int/prequal/sites/default/files/document_files/Frequent-Deficiencies_BE-Protocols_Nov2020.pdf

Sample Size Estimation: Basics*

- Never – *ever* – assume perfectly equal formulations ($\mu_T/\mu_R = 100\%$)
  - Base the T/R-ratio on the measured content but
    - the analytical method is not perfectly accurate/precise and
    - validated only for the Test formulation
- Take reported variability (esp. from the literature) with a grain of salt
  - Better the *CV* of an own pilot study
  - Best an own *failed* study…
  - Always assume a larger variability (be conservative)
- Targeting power > 90% may raise concerns from the IEC

* Schütz H. *Power Calculation and Sample Size Estimation*. Vienna. 2024. https://bebac.at/articles/index.phtml#power_sample_size

Sample Size Estimation: Examples

- **All targeted for 80% power**
  - **Parallel design, limits 80 – 125%**
    - **T/R-ratio 0.90, CV_{total} 40%: 266**
  - **2×2×2 crossover design, limits 80 – 125%**
    - **T/R-ratio 0.90, CV_{within} 40%: 134**
    - **T/R-ratio 0.95, CV_{within} 30%: 40**
  - **2×2×2 crossover design, limits 90.00 – 111.11% (NTID)**
    - **T/R-ratio 0.95, CV_{within} 15%: 96**
    - **T/R-ratio 0.975, CV_{within} 15%: 46**
  - **2×2×4 full replicate design, limits 80 – 125%**
    - **T/R-ratio 0.90, CV_{within} 40%: 68**
    - **T/R-ratio 0.95, CV_{within} 30%: 20**
  - **2×2×4 full replicate design, limits 69.84 – 143.19% (HVD)**
    - **T/R-ratio 0.90, CV_{wR} 50%: 28**

Labes D, Schütz H, Lang B. *PowerTOST: Power and Sample Size Based on Two One-Sided t-Tests (TOST) for (Bio)Equivalence Studies*. 2024; Version 1.5-6. https://cran.r-project.org/package=PowerTOST

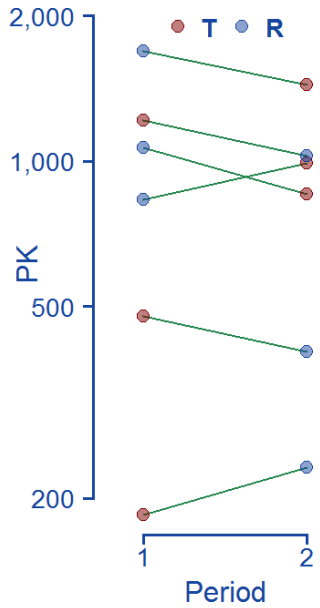
Evaluation: 100(1 – 2α) CI within BE limits

- Parallel design
  - Equal variances of groups *must not* be assumed
    - The conventional *t*-test or an ANOVA are wrong (liberal)
    - The Welch-Satterthwaite test adjusts for unequal variances and/or unequal group sizes (due to dropouts)
- Crossover (including replicate) designs
  - All effects fixed (ANOVA), except
  - for the FDA, Health Canada, and China's CDE – requiring a mixed effects model (subjects as a random effect, all others fixed)
- Reference-scaling for HVD(P)s
  - If $CV_{wR} > 30\%$ (EMA, …) or $s_{wR} > 0.294$ (FDA, CDE), the BE limits can be expanded if clinically not problematic
  - Additionally, the point estimate (PE) has to lie within 80 – 125%

Evaluation: Example (2×2×2 crossover)

- **Spreadsheets are not acceptable[1] – difficult to validate[2]**

Subject	Period	Sequence	Treatment	PK	$\log_e$(PK)	PK_T/PK_R
1	1	TR	T	185	5.220	0.797
1	2	TR	R	232	5.447	
2	1	RT	R	1,068	6.974	0.801
2	2	RT	T	856	6.752	
3	1	RT	R	831	6.723	1.194
3	2	RT	T	992	6.900	
4	1	TR	T	1,213	7.101	1.183
4	2	TR	R	1,025	6.932	
5	1	RT	R	1,689	7.432	0.854
5	2	RT	T	1,442	7.274	
6	1	TR	T	478	6.170	1.189
6	2	TR	R	402	5.996	



1. EMA (CHMP). *Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP).* London. 19 November 2015.
2. Schütz H, Labes D, Fuglsang A. *Reference Datasets for 2-Treatment, 2-Sequence, 2-Period Bioequivalence Studies.* AAPS J. 2016; 16(6): 1292–7. https://doi.org/10.1208/s12248-014-9661-0

Evaluation: Example (2×2×2 crossover)

- Simplified output based on $\log_e$–transformed data (Phoenix WinNonlin, Certara 2023)

Hypothesis	DF	SS	MS	F	p
Sequence	1	2.24242	2.24242	91.1313	0.0007
Sequence*Subject	4	3.20154	0.800386	32.5275	0.0026
Treatment	1	0.00063226	0.00063226	0.0256948	0.8804
Period	1	0.0083987	0.0083987	0.341322	0.5904
Error	4	0.0984257	0.0246064		
Sequence as Error Term:					
Sequence*Subject	4	3.20154	0.800386	0.35693	0.8305

```
     Test LSMean = 6.569433 GeoLSM = 712.9655
Reference LSMean = 6.583950 GeoLSM = 723.3913

Difference =  -0.0145, SE (Diff) = 0.0906, df = 4
Ratio(%R)  =  98.5588
CI 90%     = (81.2558, 119.5463)
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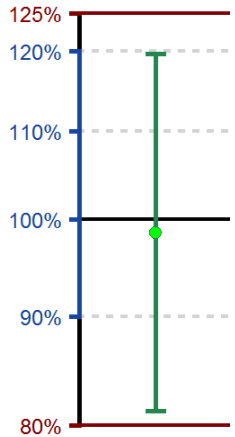

Evaluation: Example (2×2×2 crossover)

- 'By hand'…

$$df = n_{TR} + n_{RT} - 2,\ \alpha = 0.05$$

$$\log_e 90\%\,CI = (\log_e LSM_T - \log_e LSM_R) \mp t_{df,\alpha}\sqrt{\frac{MSE}{2}\left(\frac{1}{n_{TR}} + \frac{1}{n_{RT}}\right)}$$

$$\log_e 90\%\,CI = (6.569443 - 6.583950) \mp 2.131847\sqrt{\frac{0.0246064}{2}\left(\frac{1}{3} + \frac{1}{3}\right)}$$

$$PE = 100 \times \exp(6.569443 - 6.583950) \approx 98.56\%$$

$$\log_e 90\%\,CI = (-0.207589,\ +0.178555)$$

$$90\%\,CI = 100 \times \exp(-0.207589,\ +0.178555) \approx (81.25\%,\ 119.55\%)$$

An all too common Misconception

- **Skeptical physician**
  - » *Given the BE limits of 80 – 125%, there is currently a market presence of formulations with BA differences of up to 45%; I don't trust in generics and will not prescribe any …* «
- **The 90% CI has to lie within 80 – 125%, not only the PE**

  Average difference of generic to innovator products reported in a review* of 2,070 studies by the FDA:
  - ***AUC*** **(3.56 ± 2.58)%**
  - C_{max} **(4.35 ± 3.54)%**
- **Charlie DiLiberti (GBHI Conference, Rockville 2016)**
  - » *Ask ten physicians what BE is and eleven will get it wrong.* «

* Davit BM, Nwakama PE, Buehler GJ, Conner DP, Haidar SH, Patel DT, Yang Y, Yu LX, Woodcock J. *Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration.* Ann Pharmacother. 2009; 43(10): 1583–97. https://doi.org/10.1345/aph.1M141

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Helmut Schütz

Center for Medical Data Science

MEDICAL UNIVERSITY OF VIENNA

1090 Vienna, Austria

helmut.schuetz@muv.ac.at

Faculty of Pharmacy, Universidade de Lisboa

1649-004 Lisbon, Portugal

helmut@edu.ulisboa.pt

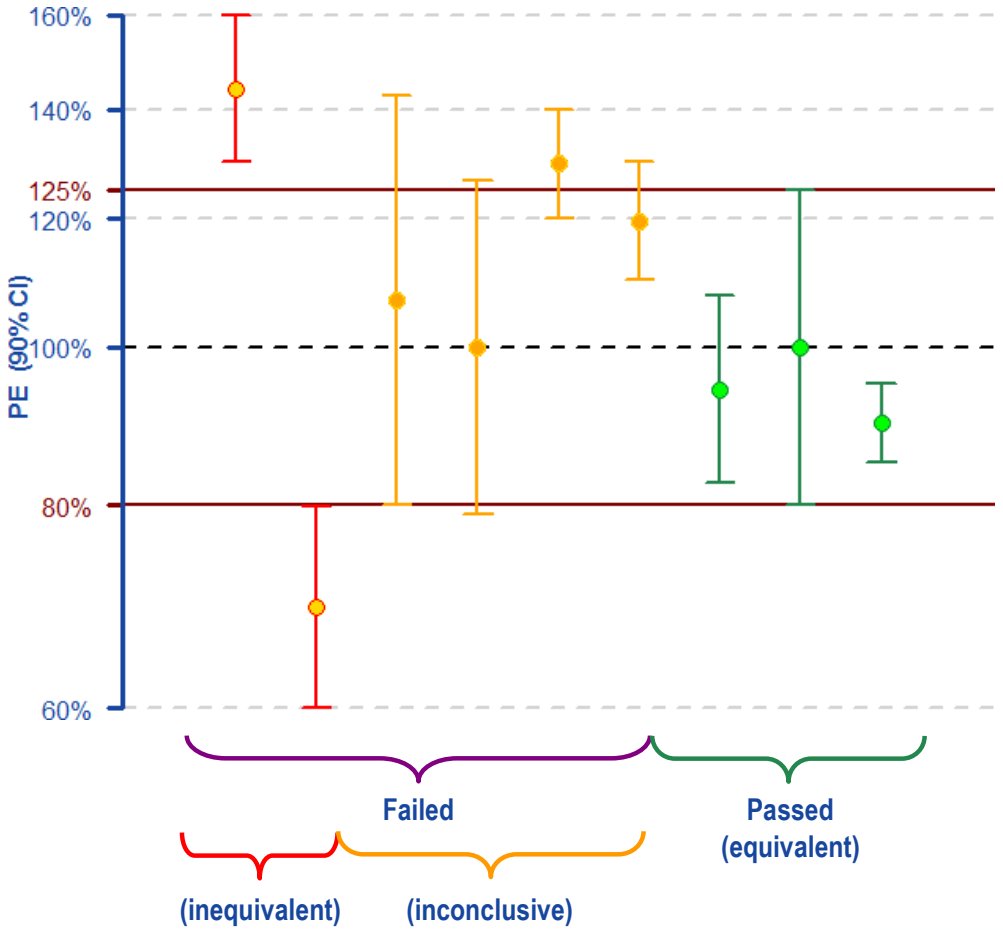
BEBAC

1070 Vienna, Austria

helmut.schuetz@bebac.at

Further information and examples
https://bebac.at/articles/

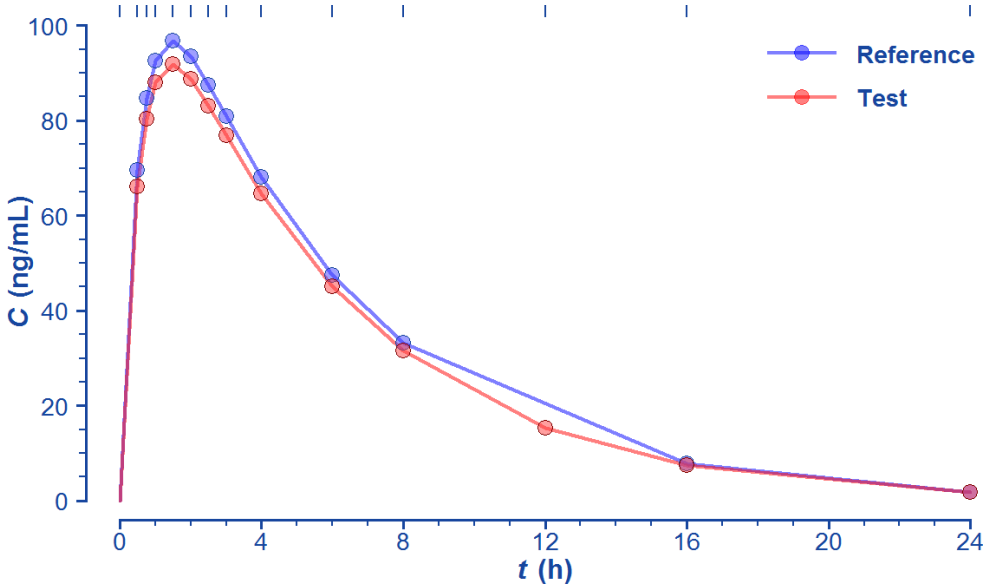
Backup: Typical results of Comparative BA



- **Studies which failed BE**
  - If the CI lies entirely outside the BE limits → reformulate
  - If wide CI and the PE is – *well* – within the BE limits, overly optimistic (too small) sample size and/or *CV* larger than assumed → repeat the study in a larger sample size size
  - If narrow CI and the PE lies close to one of the limits, repeating the study is risky (consider reformulation)
- **Studies which passed BE**
  - If the CI lies exactly at the limits, you were extremely lucky…
  - If the CI is very narrow, consider to perform the *next* study in a smaller sample size (*CV* smaller than assumed)

Backup: Missing sample and linear trapezoidal method

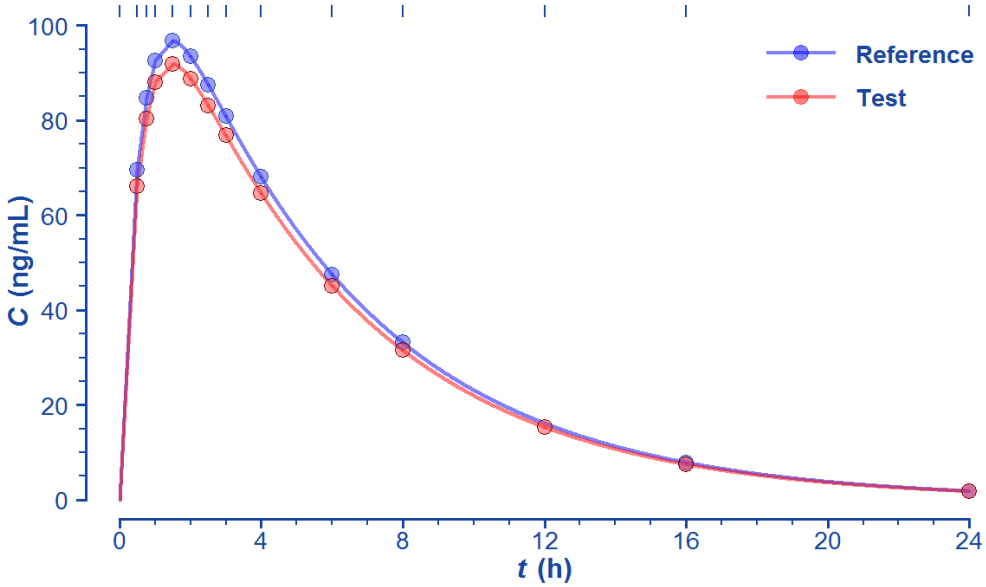
- Simulated profiles (true T/R 0.95), 12 h sample after R is missing



$AUC_{0-\infty}$ (T)	671 h×ng/mL
$AUC_{0-\infty}$ (R)	725 h×ng/mL
T/R	0.925
Bias	–2.60%

Backup: Missing sample and linear-up / logarithmic-down trapezoidal method

- Simulated profiles (true T/R 0.95), 12 h sample after R is missing



$AUC_{0-\infty}$ (T)	658 h×ng/mL
$AUC_{0-\infty}$ (R)	694 h×ng/mL
T/R	0.949
Bias	–0.15%

Backup: Why $\log_e$–transform the data? I

- If we want to compare bioavailabilities of two treatments (f_T, f_R) we arrive based on the fundamental equation of PK

$$\frac{f_T}{f_R} = \frac{AUC_T \cdot D_T}{CL} \Big/ \frac{AUC_R \cdot D_R}{CL}$$

only with $D_T = D_R$ and $CL = const$ at $\frac{f_T}{f_R} = \frac{AUC_T}{AUC_R}$

  - This is a *ratio* and thus, we have to use a *multiplicative* model
  - However, in the statistical models we need *additive* effects
  - Since f_T / f_R is the point estimate we are interested in, we can rewrite/transform the equation and use *e.g.*, an ANOVA

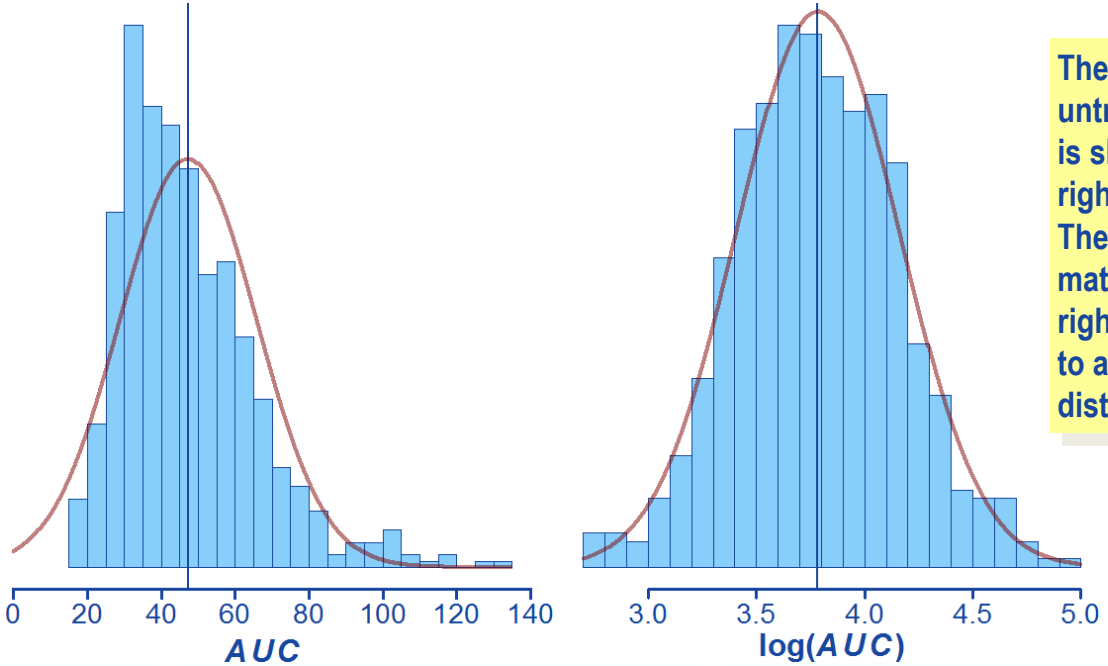
$$\log_e PE = \log_e f_T - \log_e f_R = \log_e AUC_T - \log_e AUC_R$$

and finally $PE = \exp(\log_e PE)$

Backup: Why $\log_e$–transform the data? II

- **PK metrics are *not* normally distributed but follow a lognormal distribution**
  - **Drug X ($n = 608$)**
    Arithmetic mean = 47.2 h×ng/mL, geometric mean = 44.0 h×ng/mL

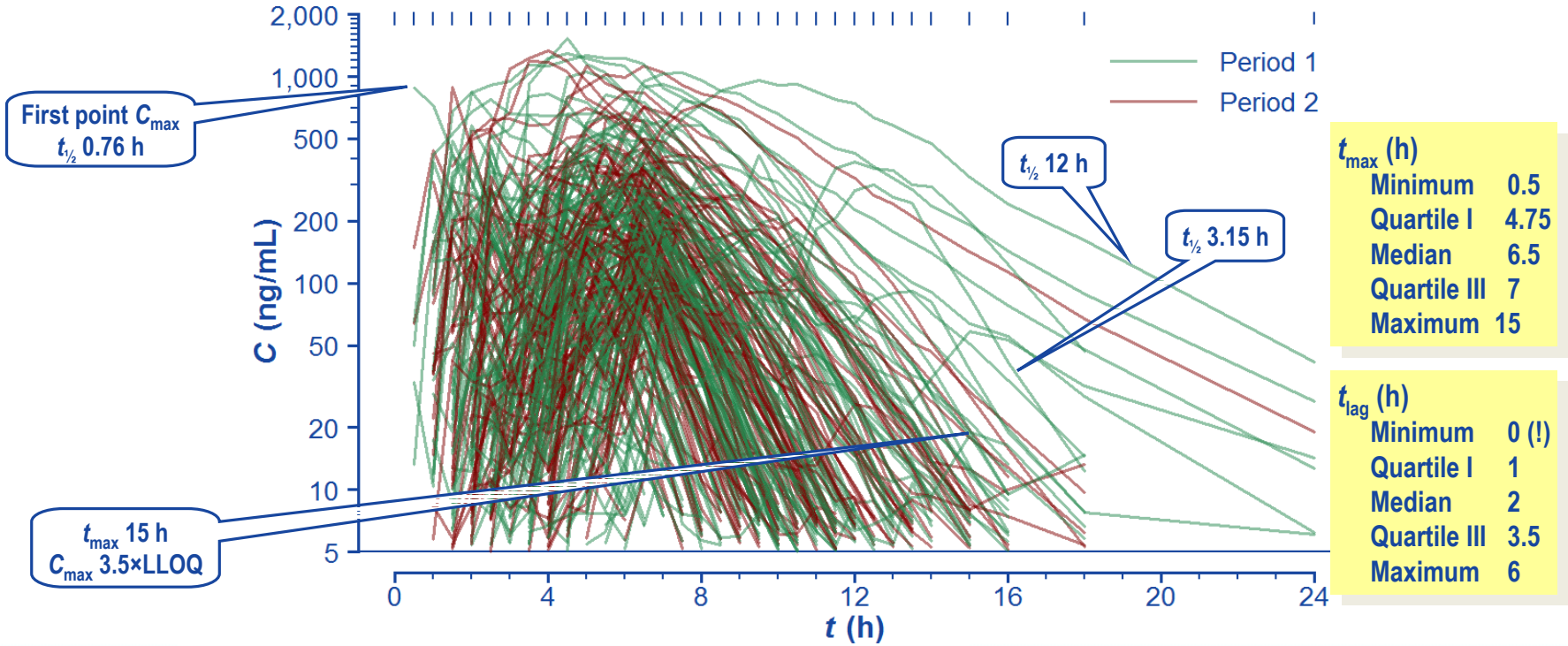
Strictly speaking, not the PK metrics *per se* have to be normally distributed after $\log_e$-transformation but the model residuals (estimates of ε). However, when exploring large data sets (without and after transformation), we see that the latter are closer to normally distributed.



The distribution of untransformed data is skewed to the right.
The $\log_e$-transformation pulls the right tail in, leading to a symmetrical distribution.

Backup: Sampling Schedule Problems

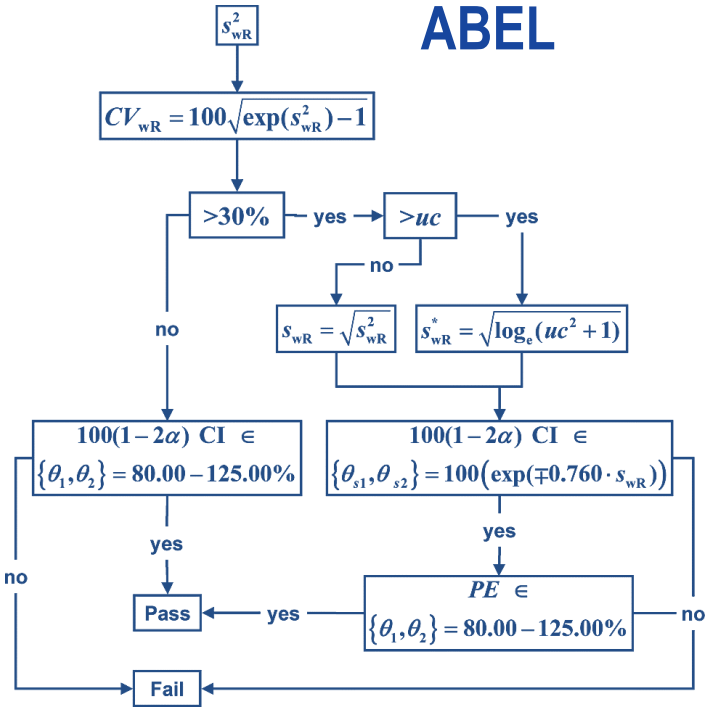
- **Lansoprazole (Proton Pump Inhibitor)**
  Attempt to deal with high variability of C_{max}/t_{max} and lag-times:
  Sampling every 30 minutes up to 14 hours (140 subjects, 7,785 samples)

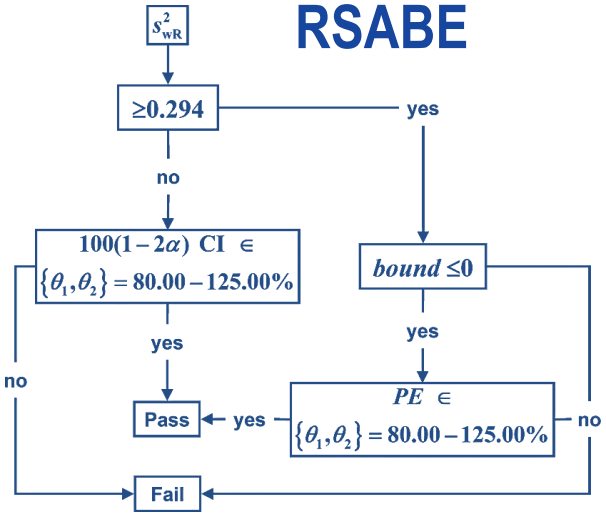


t_{max} (h)	
Minimum	0.5
Quartile I	4.75
Median	6.5
Quartile III	7
Maximum	15

t_{lag} (h)	
Minimum	0 (!)
Quartile I	1
Median	2
Quartile III	3.5
Maximum	6

Backup: Why can the Type I Error in Scaled Average Bioequivalence be inflated?

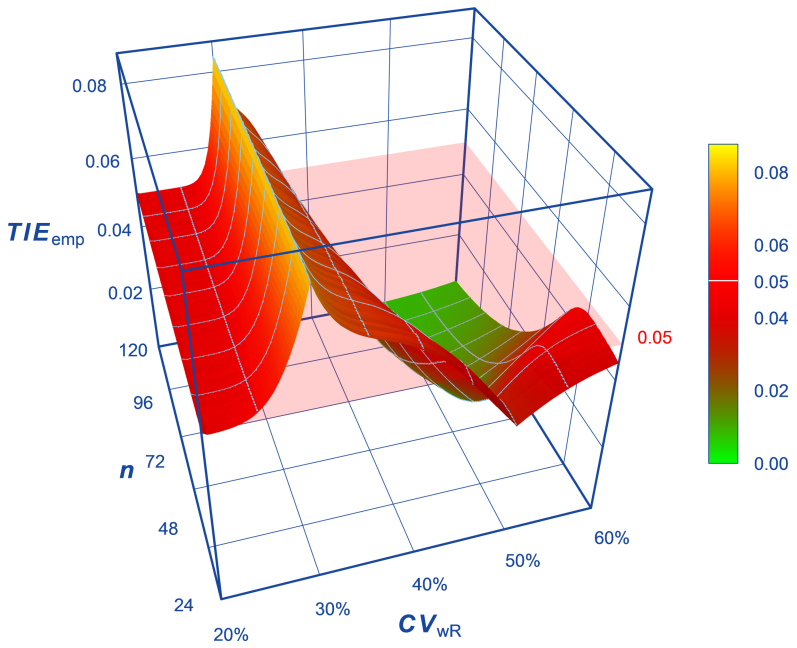




- Implemented SABE approaches are frameworks
  - Limits are random variables dependent on the reference's variance
  - Drugs will be misclassified if the observed CV_{wR} ≠ true CV_{wR}

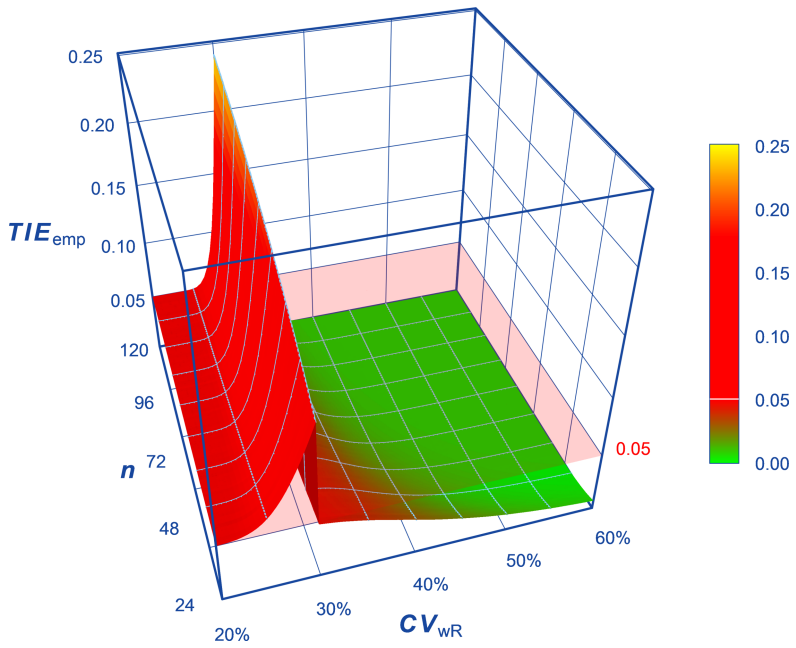
Backup: Empiric Type I Error in SABE

ABEL (EMA and others)



TIE$_{emp}$ at *CV*$_{wR}$ 30%; *n* 24: 0.0804, *n* 120: 0.0838

RSABE (FDA 'implied limits')



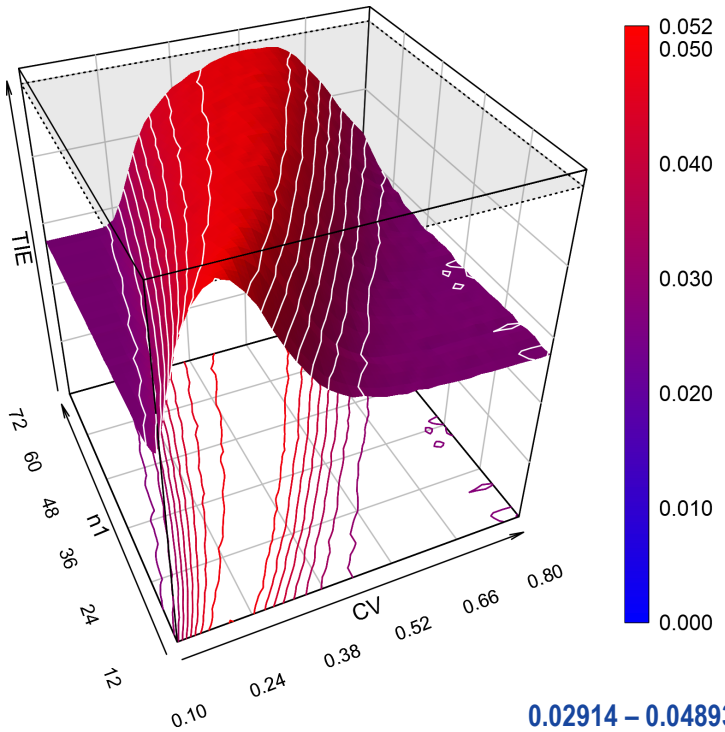
TIE$_{emp}$ at *CV*$_{wR}$ 30%; *n* 24: 0.1335, *n* 120: 0.2418

2-sequence 4-period full replicate design

Backup: Operating Characteristics (simulation-based Type 1 Two-Stage Design)

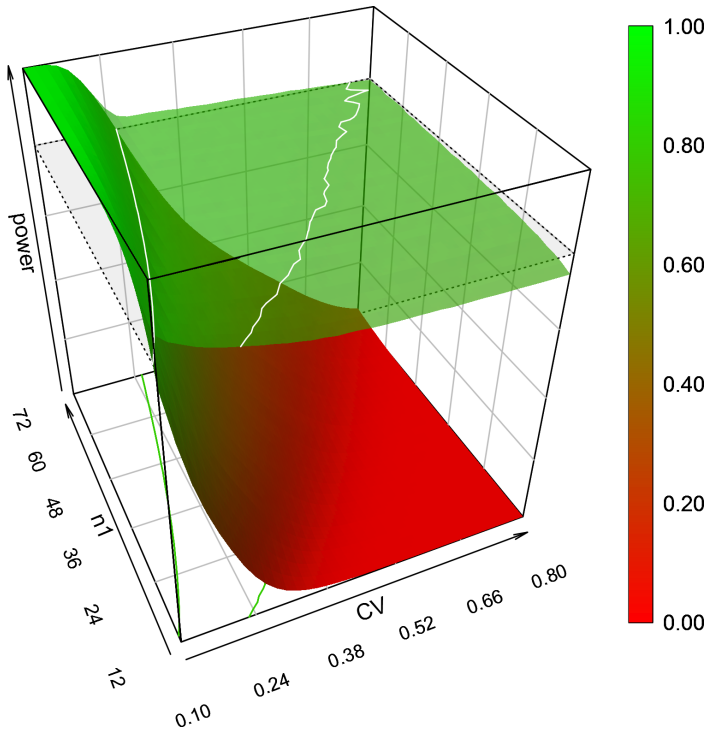
GMR 0.95, power 80%, α_{adj} 0.0294 (Potvin *et al.* 'Method B')

Type I Error



0.02914 – 0.04893

Power



Backup: Operating Characteristics (Exact Method for a Two-Stage Design)

Fixed GMR 0.95 (*CV* 0.1–0.8, n_1 12–72)

No futility rules

Type I Error 0.02598 – 0.04995

Adaptive GMR (*CV* 0.1–0.8, n_1 12–72)

Futility on the CI (outside $0.95 – 0.95^{-1}$)

Type I Error 0.01678 – 0.04523

Adaptive GMR (*CV* 0.1–0.8, n_1 12–72)

Futility on the CI (outside $0.95 – 0.95^{-1}$)

Futility on N_{max} ($> 4 \times n_1$)

Type I Error 0.00006 – 0.03838