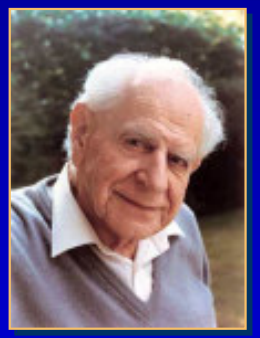
Design and Interpretation of Bioequivalence Studies – Current and Future Issues

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.



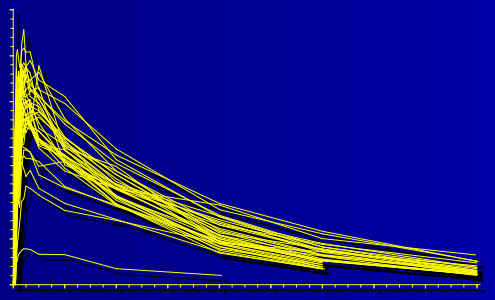
Karl R. Popper

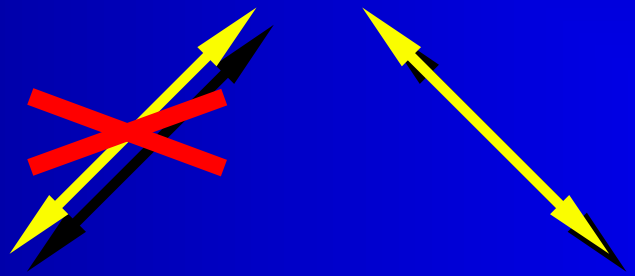
Even though it's *applied* science we're dealin' with, it still is – *science!*

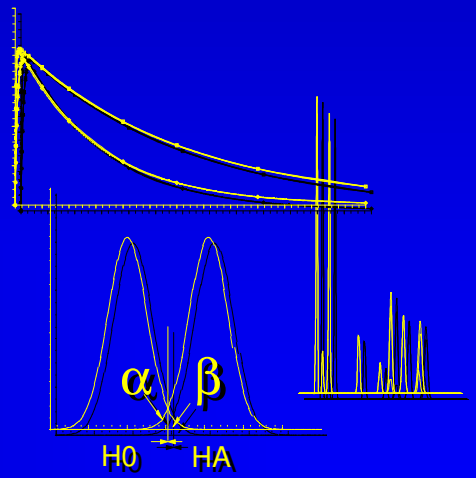
Leslie Z. Benet

Assumptions

World *'Reality'*







Model *'Data'*

Theory *'Truth'*

A Reminder

Rose
is a rose
is a rose
is a rose.

Gertrude Stein (1913)

Guidelines
are guidelines
are guidelines.

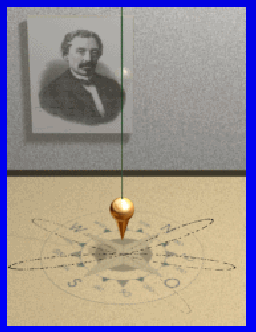
Henrike Potthast (ca. 2004)

In advanced engineering, you expected failure; you learned as much from failures as from successes – indeed if you never suffered a failure you probably weren't pushing the envelope ambitiously enough.

Stephen Baxter; Transcendent, Chapter 36 (2006)

History

- Bioequivalence
  - Surrogate of clinical equivalence (1985+)
    - Studies in steady state in order to reduce variability
    - Studies based on active metabolite
    - Wider acceptance range if clinical justifiable (not FDA!)
  - Measure of pharmaceutical quality (2000+)
    - Single dose studies preferred
    - Generally parent drug
    - Widening of acceptance range exceptional



Human Guineapigs I

- BE studies as a surrogate for clinical efficacy / safety ('essential similarity')
  - We want to get unbiased estimates, *i.e.*, the point estimate from the study sample …

$$PE = \frac{\hat{X}_{Test}}{\hat{X}_{Reference}}$$

  - … should be representative for the population of patients.

$$F_{Pop} = \frac{\mu_{Test}}{\mu_{Reference}}$$

Human Guineapigs II

- BE studies as a special case of documented pharmaceutical quality
  - The *in vivo* release in the biostudy …

$$PE = \frac{\hat{X}_{Test}}{\hat{X}_{Reference}}$$

  - … should be representative for the *in vitro* performance.

$$f_2 = 50 \cdot \log\left[\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{t=n}\left[\bar{R}(t)-\bar{T}(t)\right]^2}{n}}}\right]$$

Science → Regulations

- We can't study bioequivalence in the entire population of patients
  - Scientific Reductionism (based on assumptions)
    - 'Similar' concentrations in healthy subjects will lead to 'similar' effects in patients
    - Equal doses and inter-occasion clearances

$$\frac{F_T \cdot AUC_T}{D_T \cdot CL_T}, \frac{F_R \cdot AUC_R}{D_R \cdot CL_R}$$

$$D_T = D_R, CL_T = CL_R$$

Highly Variable Drugs?

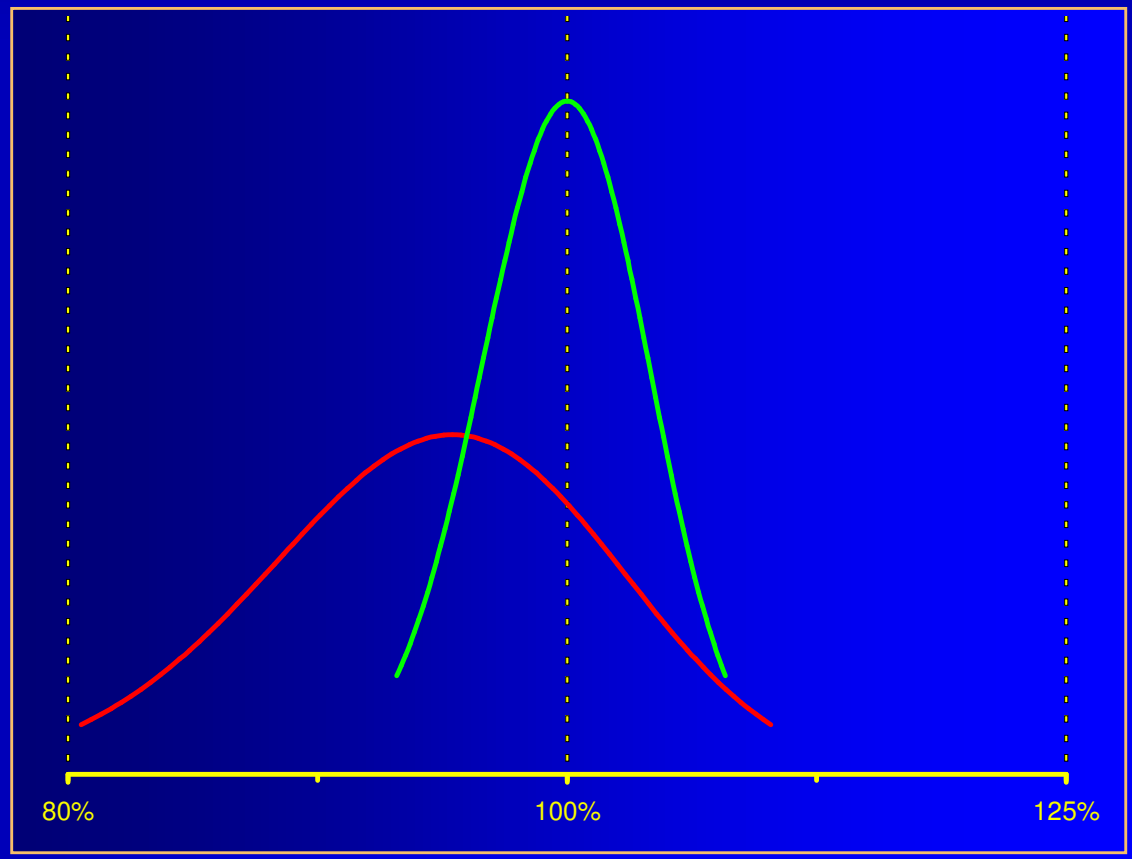
$$F_{rel}(BA) = \frac{AUC_T}{AUC_R}$$

Science → Regulations

- Scientific Reductionism (cont'd)
  - Independent Identically Distribution (IDD)

What if…

$$\sigma_T \neq \sigma_R$$



Regulations = Science?

FDA 2010, EMA 2010

ln-Transformation (based on PK, analytics)

Parametric Evaluation (*e.g.*, ANOVA)

Data and Residuals normally distributed ?

yes

Parametric Evaluation (*e.g.*, ANOVA)

no

Nonparametric Evaluation (*e.g.*, bootstrap)

ICH E9 1998
Canada Draft 2009

Global Harmonization?

- In almost all regulations two metrics are necessary to demonstrate BE, namely
  - extent (AUC_t *or* AUC_∞) and
  - rate (C_{max}) of exposure.
- One exception: US-FDA (where AUC_∞ *and* AUC_t must demonstrate extent of BE)
  - Although stated in the GL, such a requirement is statistically flawed.
    - Multiplicity issues (what is the patient'
    - Impossible α-adjustment (interdepend

There can be only one!

Global Harmonization?

- Traps are set…
  - AUC truncated at 72 hours
    - EMA 2010: All IR formulations (irrespective of $t_{½}$)
    - WHO 2006: as above; truncation at $3 \times t_{max}$ (ref.) if sensitivity problems
    - NIHS 2006: drugs with extremely long half-life
    - ANVISA 2006: drugs with long half-life (>24 h)
    - MCC 2007: drugs with long half-life (>24 h). For moieties demonstrating high inter-subject variability in distribution and clearance the use of AUC truncation warrants caution. In these circumstances sampling periods beyond 72 hours may be required.

Global Harmonization?

- Traps (cont'd)
  - Highly Variable Drugs / Drug Products
    - CV_{intra} >30%
      (BioInternational Conference, Toronto 1989)
    - If assumption of IDD does not hold, a 'good' test will be penalized for a 'bad' reference
    - Reference is known to be safe and efficacious despite the high variability
      - Arbitrary widening of acceptance range (*e.g.*, from 80%–125% to 75%–133%)
      - Widening of the acceptance range based on the intra-subject variance of the reference ('scaling')

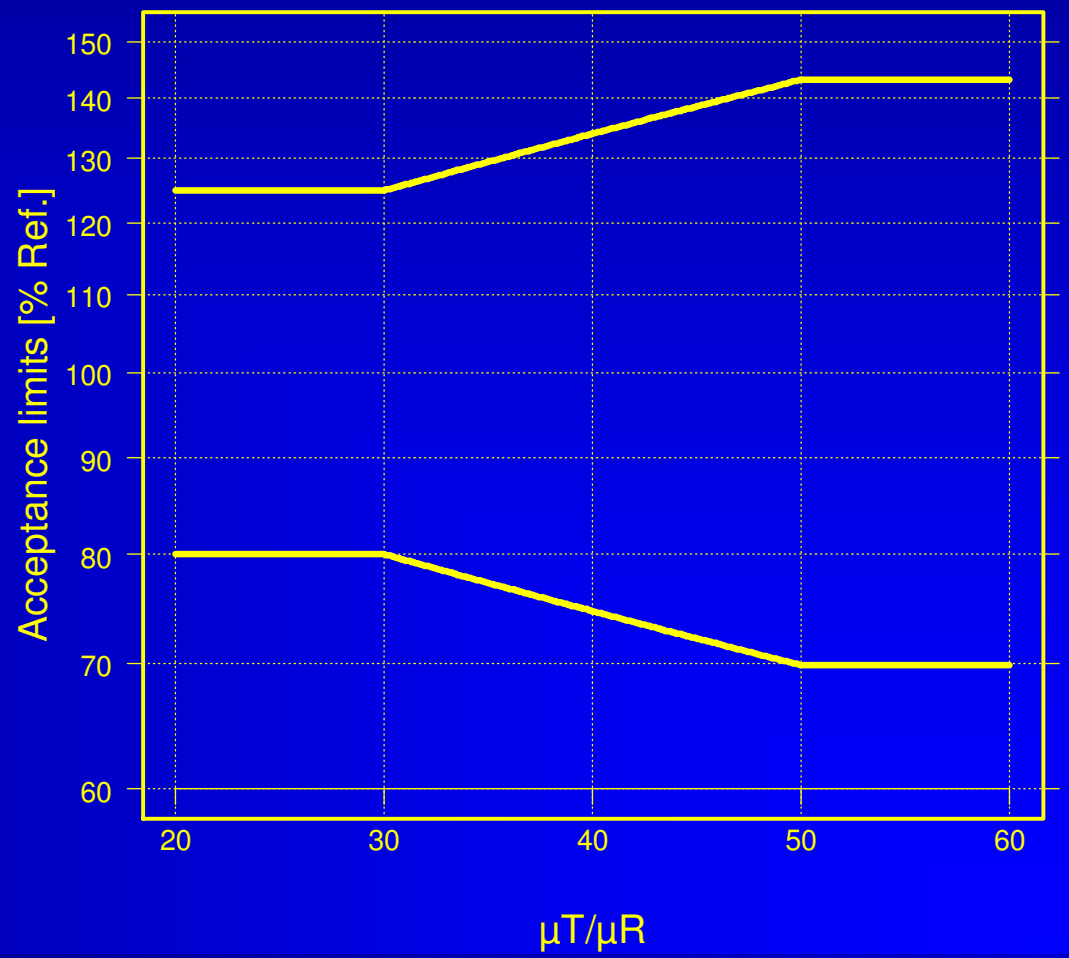
Recent Developments

- Traps (cont'd)
  - Highly Variable Drugs / Drug Products
    - Proof of CV_{intra} >30% of the reference needs a replicate design
    - No literature data, no previous 2×2 studies acceptable
    - FDA individual API-GLs: Widening for C_{max} and AUC acceptable; no specific limit
    - GMR restricted to 80%–125% (nonsense)
    - RSA: Scaling allowed, C_{max} and AUC, no restriction
    - EMA 2010: Widening of AR for C_{max} only; GMR-restriction, cut-off at CV 50%

Recent Developments

- EU GL on BE (2010)

CV%	L%	U%
30	80.00	125.00
32	78.87	126.79
34	77.77	128.58
36	76.69	130.39
38	75.64	132.20
40	74.61	134.02
42	73.61	135.85
44	72.63	137.68
46	71.68	139.52
48	70.74	141.36
50	69.83	143.20

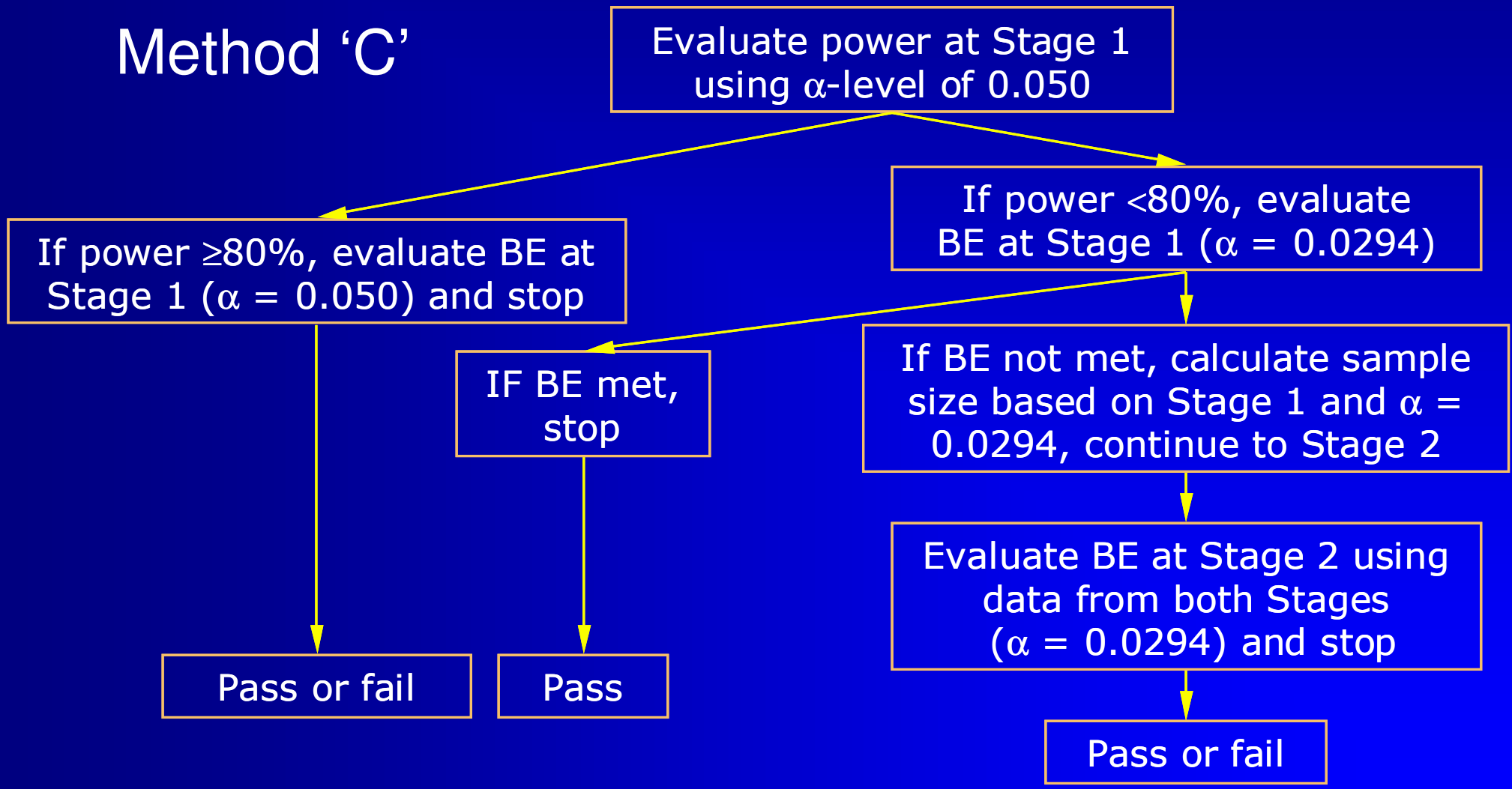


Recent Developments

- Add-On / Two-Stage / Sequential Designs
  - Already acceptable in many countries (Canada, Japan, RSA,…)
  - Not (officially) in the USA, EU
  - New & more specific procedures (Canada Draft 2009, EMA 2010)
    - Canada: LA Gould (1995)
    - EMA: based on SJ Pocock (1977); *e.g.*, D Potvin et al. (2007)

Sequential Design

Method 'C'



Caveats / Suggestions

- BE studies should be based on
  - The pharmacology of the drug
  - The biopharmaceutical properties of test and reference formulations
  - Regulatory requirements
- Keep the order of these three points
  - Avoid guideline-blindness
  - No copy-and-paste protocols
  - If you opt for a scientific advisory meeting, go for a 'difficult' country

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Thank You!

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