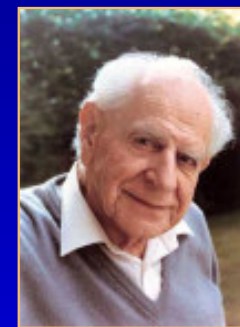


Design and Interpretation of Bioequivalence Studies – Current and Future Issues

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!*

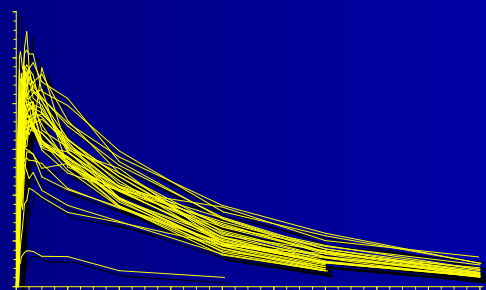
Leslie Z. Benet



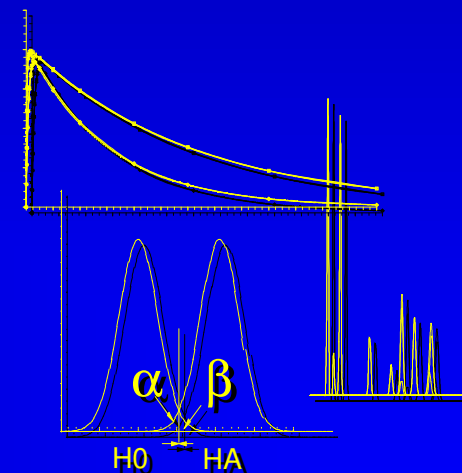
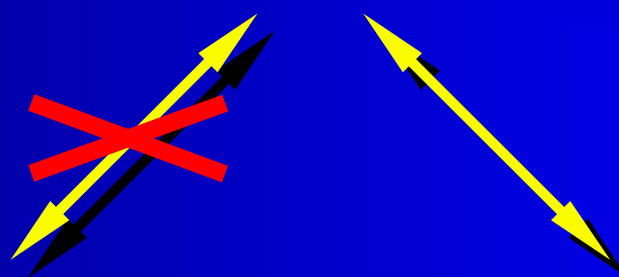
Assumptions



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 Guinea pigs 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 Guinea pigs 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.

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



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?

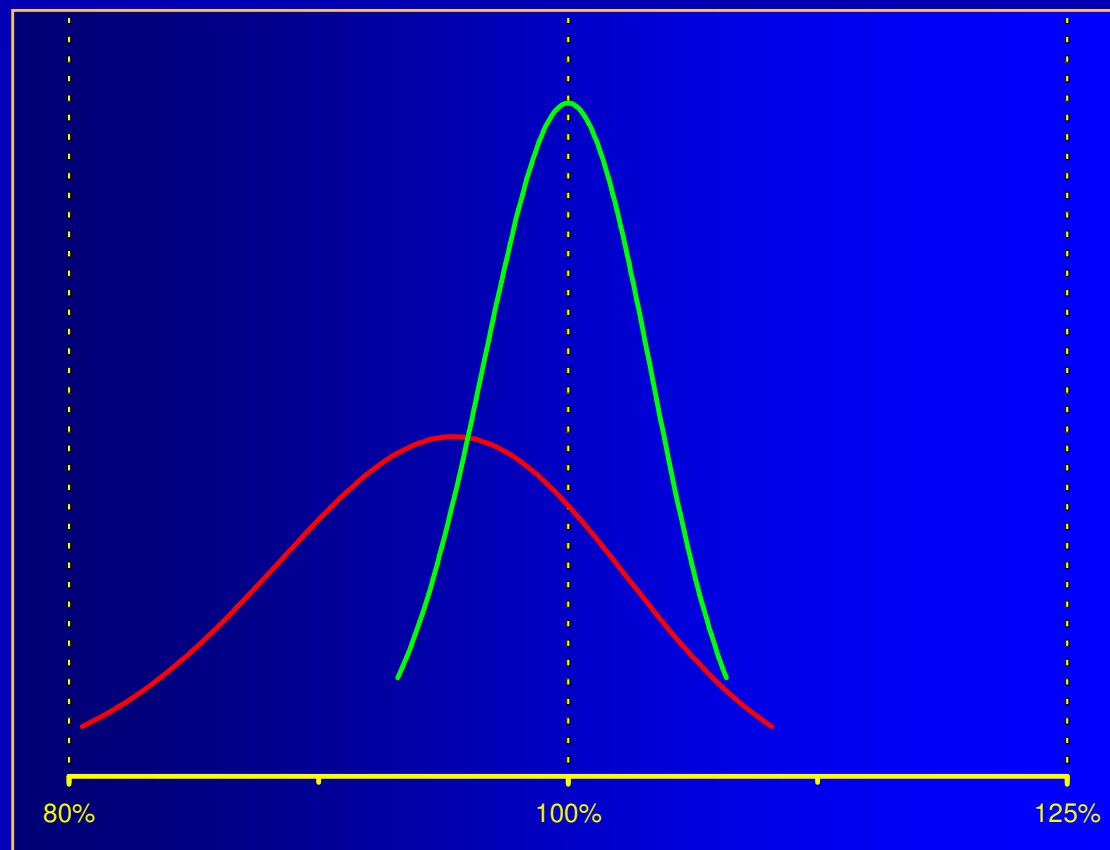
$$F_{rel}(BA) = \frac{AUC_T}{AUC_R}$$

Science → Regulations

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

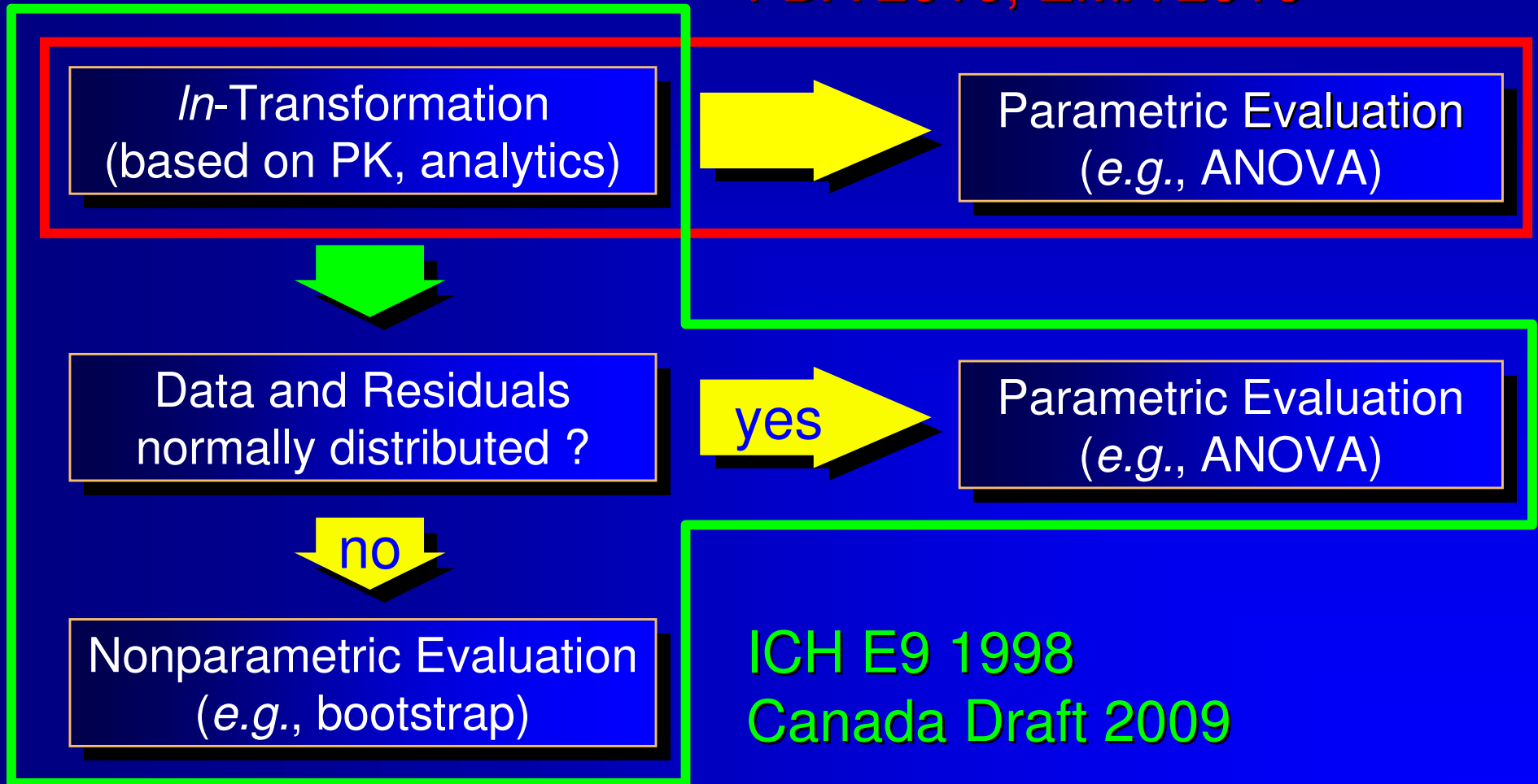
What if...

$$\sigma_T \neq \sigma_R$$



Regulations = Science?

FDA 2010, EMA 2010



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 (interdependence)



There can be only one!

Global Harmonization?

- Traps are set...
 - AUC truncated at 72 hours
 - EMA 2010: All IR formulations (irrespective of $t_{1/2}$)
 - 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
 - $CV_{\text{intra}} > 30\%$
(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

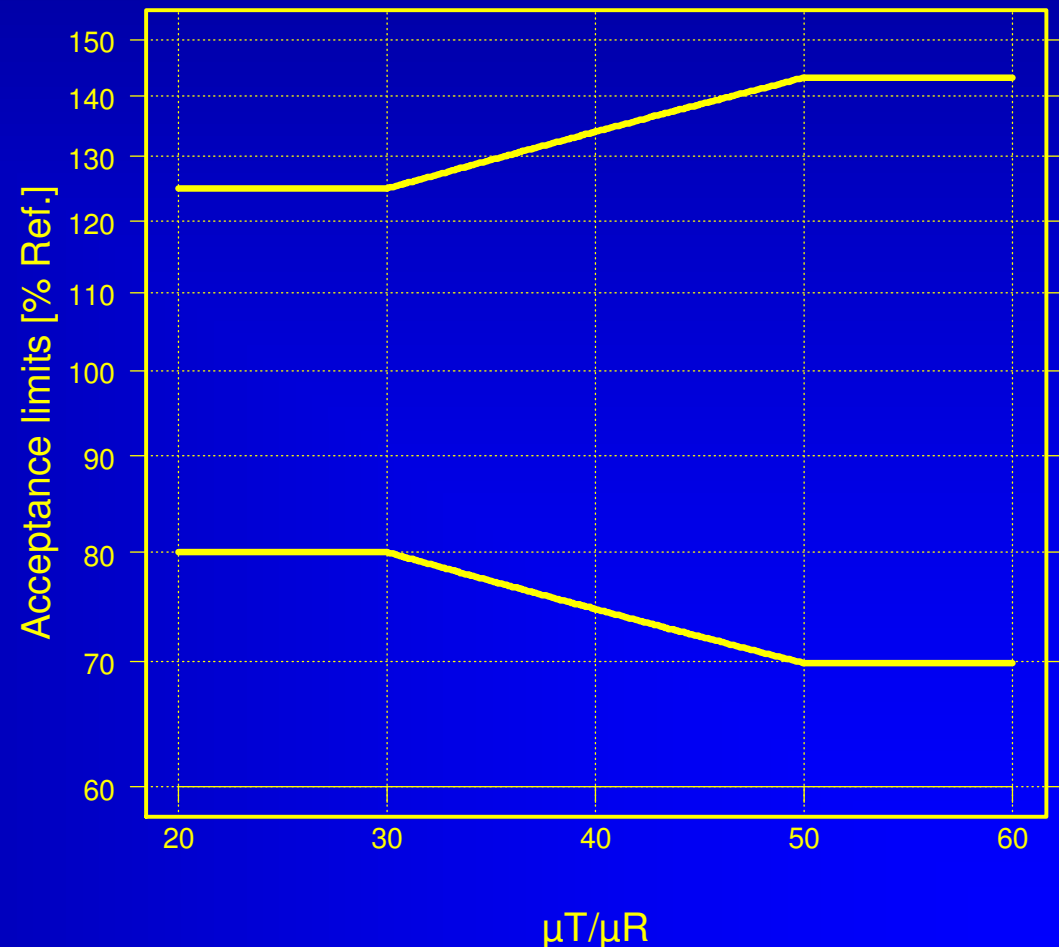
- Traps (cont'd)
 - Highly Variable Drugs / Drug Products
 - ◆ Proof of $CV_{\text{intra}} > 30\%$ of the reference needs a replicate design
 - ◆ No literature data, no previous 2x2 studies acceptable
 - ◆ FDA individual API-GLs: Widening for C_{max} and AUC acceptable; no specific limit
 - ◆ GMR restricted 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

EU SABE

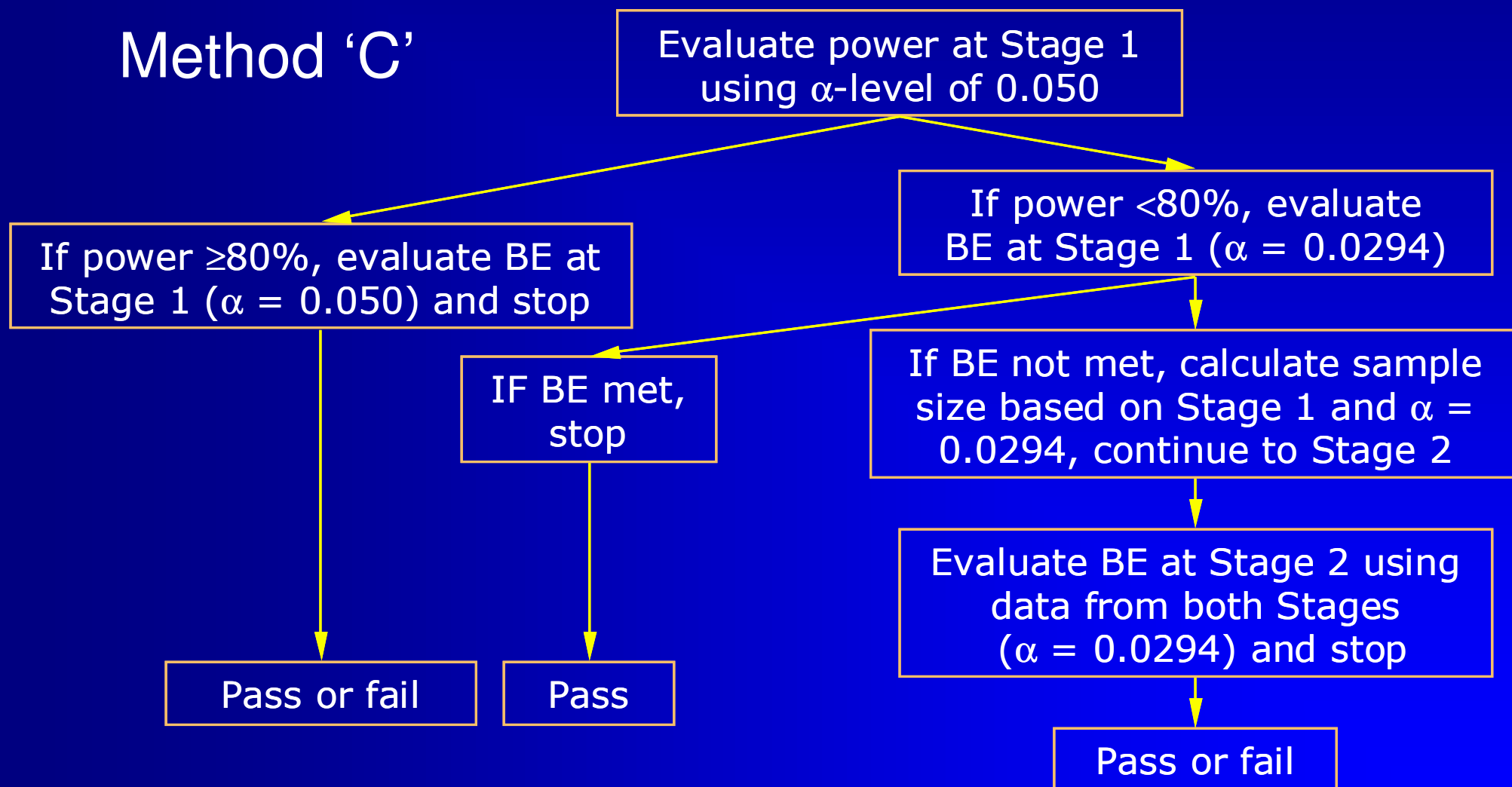


Recent Developments

- 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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