BA/BE design *versus* ‘job creation scheme’

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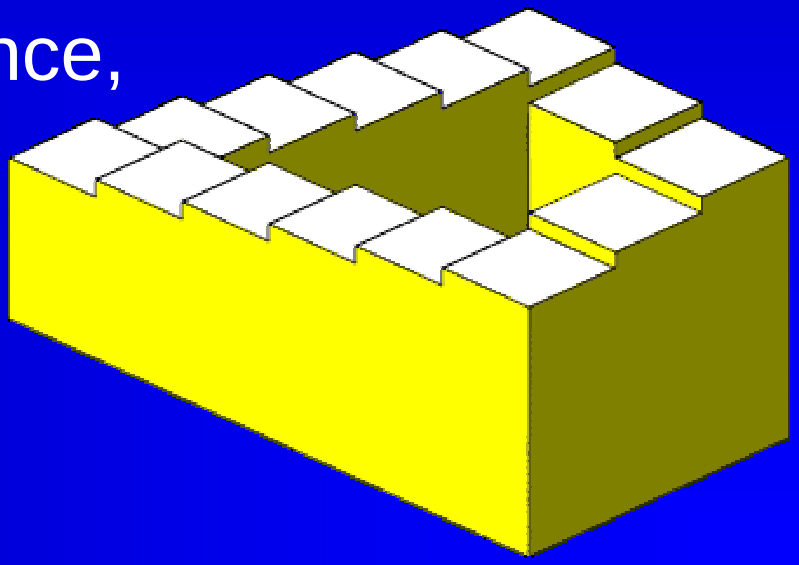
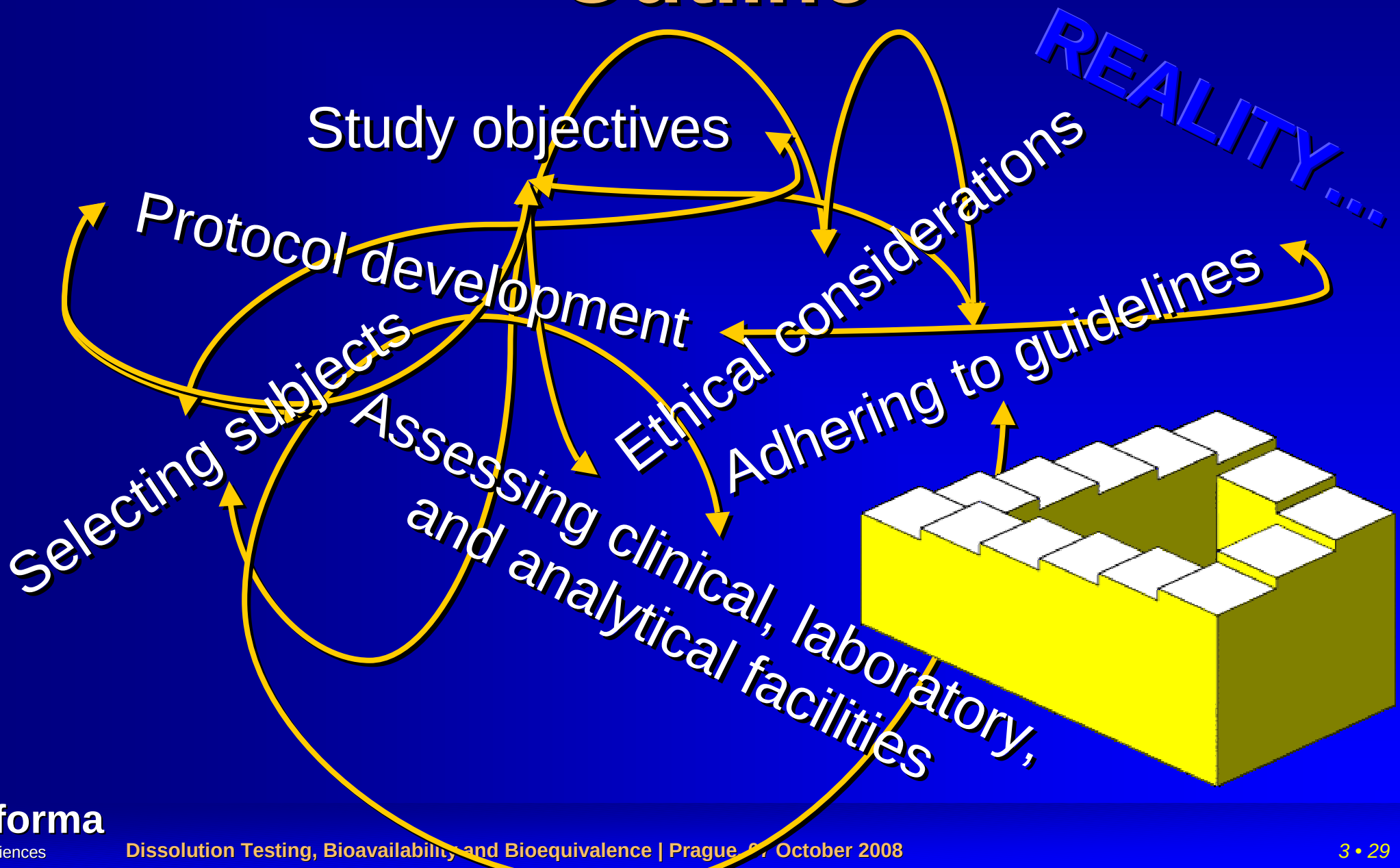
Main Topics

DREAM...

- Designing a suitable pilot study: is it always an end in itself?
- Using the PK profile help demonstrate bioequivalence when a conventional BE study is unsuitable, including practical examples.
- Beyond the bioanalytical guidance, using the latest research to gain regulatory approval.
- Navigating through unclear statistical issues.

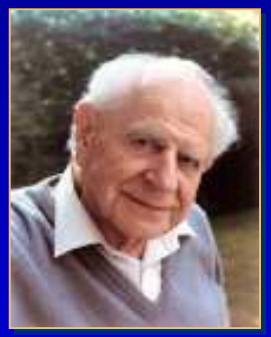


Outline


Study objectives
Protocol development
Selecting subjects
Assessing clinical, laboratory, and analytical facilities
Ethical considerations
Adhering to guidelines
REALITY ...

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.



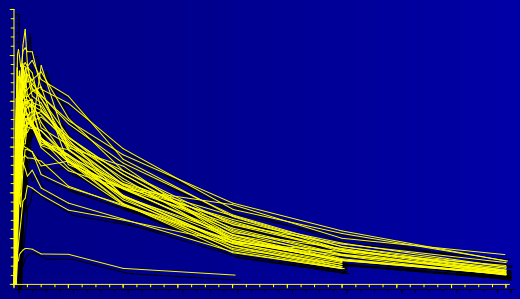
Karl R. Popper

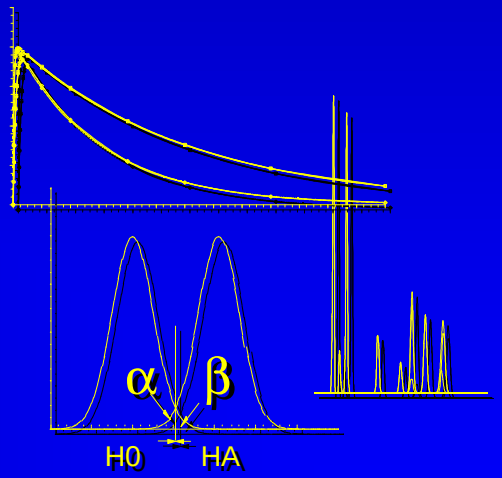
Even though it's *applied* science we're dealin' with, it still is – *science!*

Leslie Z. Benet

Assumptions

World *'Reality'*





Model *'Data'*

Theory *'Truth'*

Pilot Studies

- Rationale (FDA/CDER, BA/BE Studies – General Considerations, 2003)
  - Validation of analytical methodology
  - Assessment of variability
  - Optimization of sample collection time intervals
  - A pilot study that documents BE can be appropriate, provided its design and execution are suitable and a sufficient number of subjects (*e.g.*, 12) have completed the study.

Pilot Studies

- Sample size planning (EMEA NfG, 2002)
  - The number of subjects required is determined by
    - the error variance associated with the primary characteristic to be studied as estimated from
      - ***a pilot experiment***,
      - previous studies, or
      - published data,
    - the significance level desired,
    - the expected deviation (Δ) from the reference product compatible with BE and,
    - the required power.

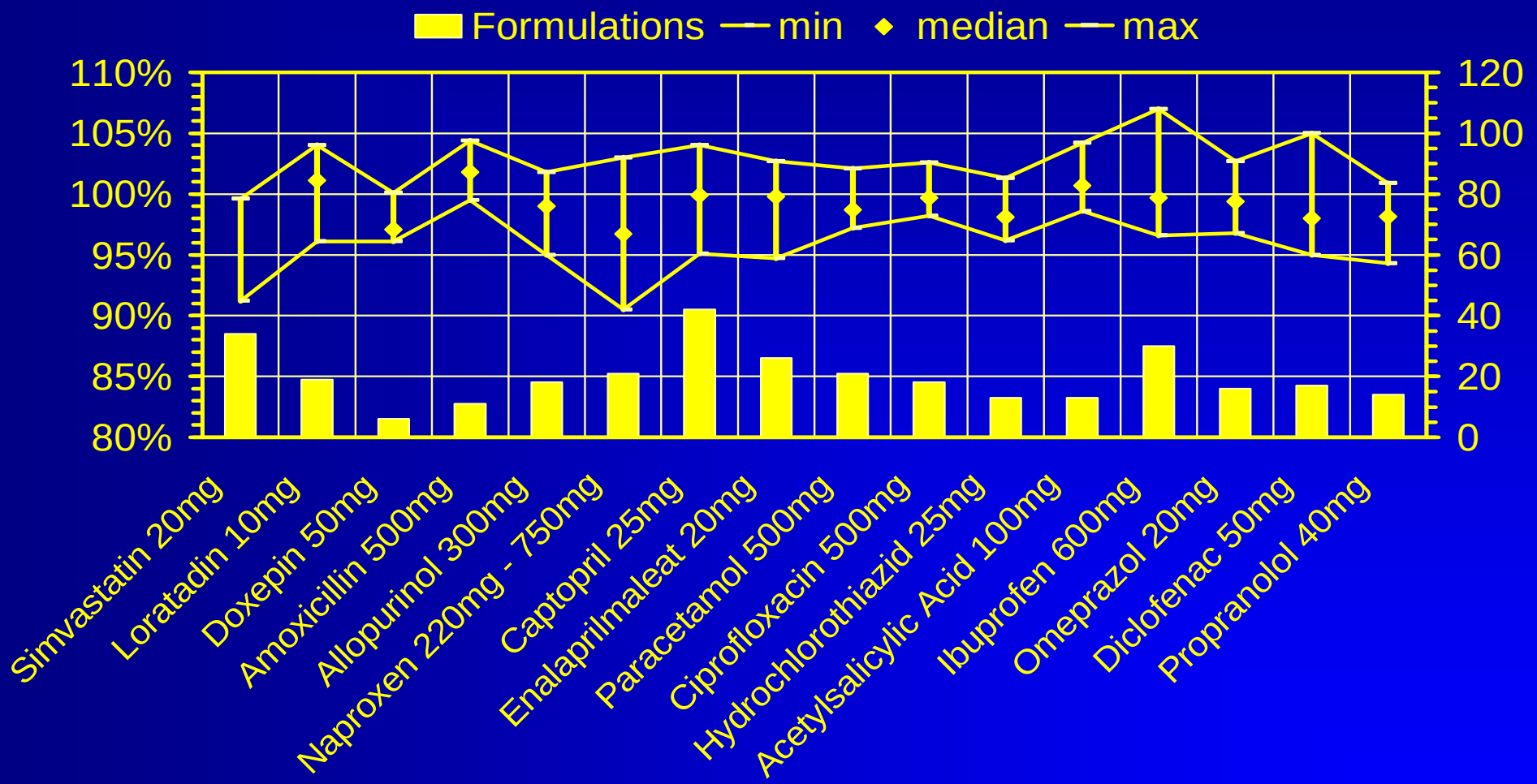
Pilot Studies

- Sample size planning (EMEA Draft BE Guideline, 2008)
  - The number of subjects to be included in the study should be based on an ***appropriate*** sample size calculation.

Potency

- Sample size planning (EMEA Draft BE Guideline, 2008)
  - The assayed content of the batch used as test product should not differ more than 5% from that of the batch used as reference product determined with the test procedure proposed for routine quality testing of the test product. In order to demonstrate that a representative batch of the reference product […] has been selected, the applicant should pre-sent dissolution profiles and content analysis of at least 3 batches of the reference […].

Potency



Various Authors;
Formulations marketed in Germany; Content Analyses performed by the Zentrallaboratorium Deutscher Apotheker (Central Laboratory of German Pharmacists – ZL)
Pharm Ztg (2001-2006)

Potency

- ANDAs approved by FDA/OGD 1996–2005 (1636 studies, 12–127 subjects)
  - with few exceptions: single dose, fasting
  - data referring to studies demonstrating BE on AUC_∞, AUC_t, C_{max}; deviation test/reference:
    - AUC_∞ 3.12% (±2.66%)
    - AUC_t 3.19% (±2.72%)
    - C_{max} 4.50% (±3.57%)

Nwakama PE, Haidar SH, Yang YS, Davit BM, Conner DP, Yu LX
Generic Drug Products Demonstrate Small Differences in Bioavailability Relative to the Brand Name Counterparts: A Review of ANDAs Approved 1996 – 2005
12th Annual FDA Science Forum, April 2006: Board A-18
http://www.accessdata.fda.gov/scripts/oc/scienceforum/sf2006/Search/preview.cfm?keyword=A&abstract_id=897&type=category&backto=search

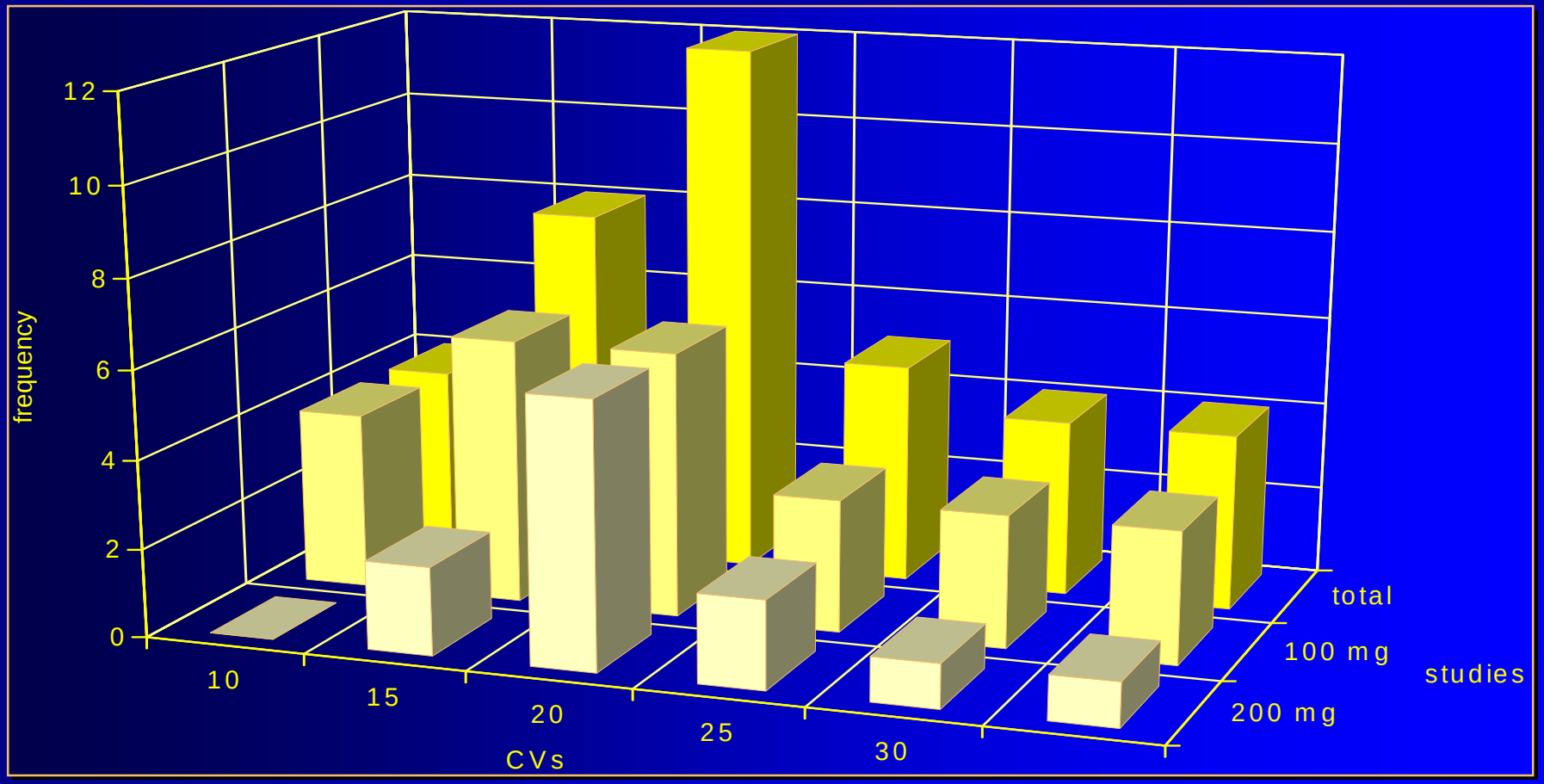
Potency

- Evaluation (EMEA Draft BE Guideline, 2008, Section 4.1.8)
  - The pharmacokinetic parameters should not be adjusted for differences in analysed content of the test and reference batch, i.e. content correction is not accepted, in the evaluation of bioequivalence studies included in applications for generic products.

Acceptable for Innovators (Scale-Up)?

Pilot Studies

- Sample size planning



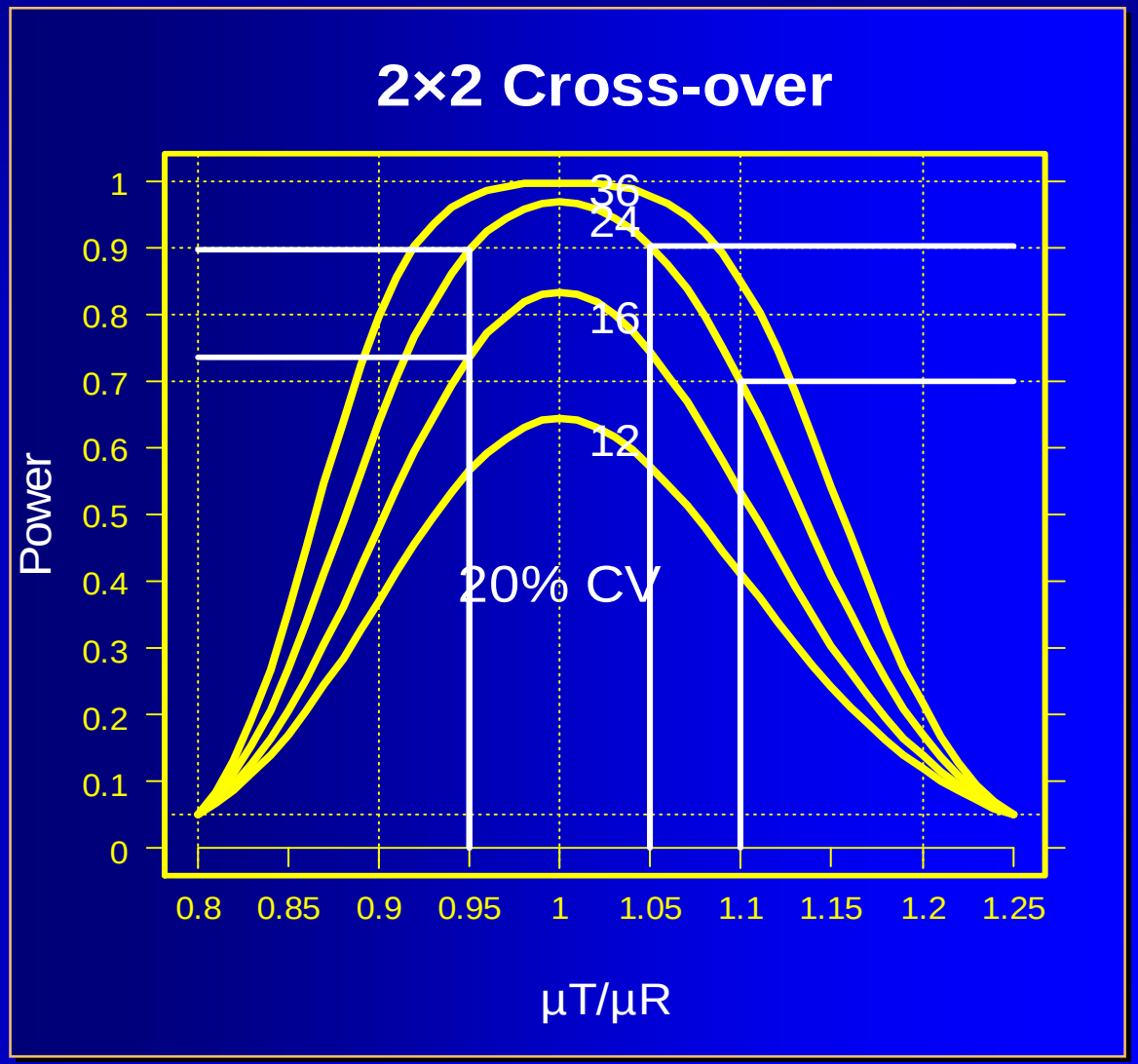
Doxicycline *(37 studies ref. by Blume/Mutschler, 1996)*

Pilot Studies

Power to show BE with 12 – 36 subjects for CV_{intra} = 20%

n 24 → 16:
power 0.896 → 0.735

μT/μR 1.05 → 1.10:
power 0.903 → 0.700



BE shown in Pilot Study

- EMEA NfG, 2002 (Section 3)
  - A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products.
- EMEA Draft BE Guideline, 2008 (Section 4.1.1)
  - The study should be designed in such a way that the formulation effect can be distinguished from other effects.

Two-Stage Design

- EMEA Draft BE Guideline, 2008
  - Section 4.1.8
    - Initial group of subjects treated and data analysed.
    - If BE not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis.
    - Appropriate steps to preserve the overall type I error (patient's risk).
    - First stage data should be treated as an interim analysis.

Two-Stage Design

- EMEA Draft BE Guideline, 2008
  - Section 4.1.8 (cont'd)
    - Both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%).
    - Plan to use a two-stage approach must be prespecified in the protocol along with the adjusted significance levels to be used for each of the analyses.

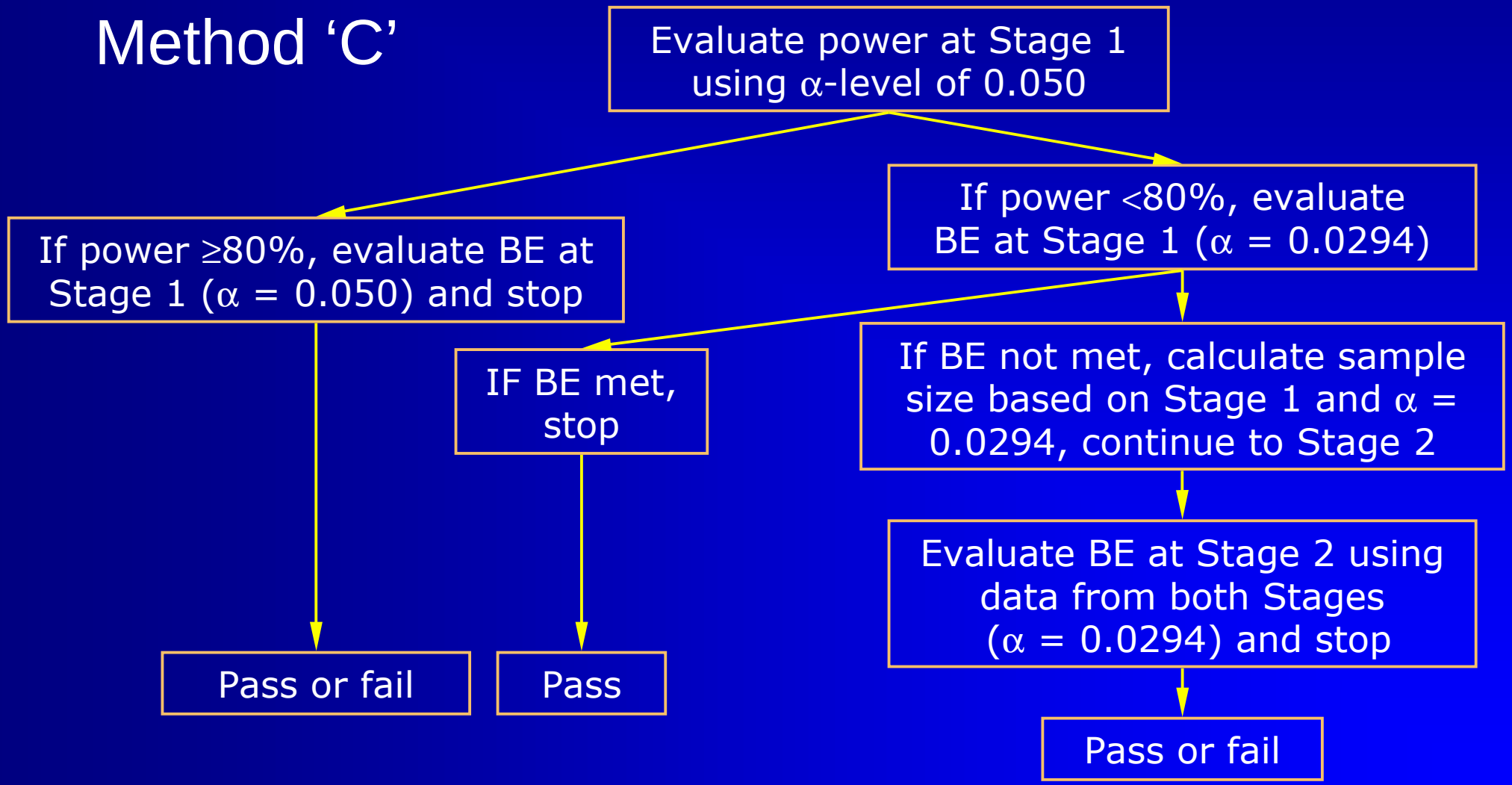
Two-Stage Design

- Critical Remarks
  - ‘BE not been demonstrated’ in initial group:
    If test at $\alpha \leq 0.05$, patient’s risk already spent!
  - ‘Adjusted significance levels’:
    Bonferroni not validated in BE setting; patient’s risk may be inflated (>0.05)!

Potvin D, Diliberti CE, Hauck WW, Parr AF, Schuirmann DJ, and RA Smith
Sequential design approaches for bioequivalence studies with crossover designs
Pharmaceut Statist (2007), DOI: 10.1002/pst.294
http://www3.interscience.wiley.com/cgi-bin/abstract/115805765/ABSTRACT

Sequential Design

Method ‘C’



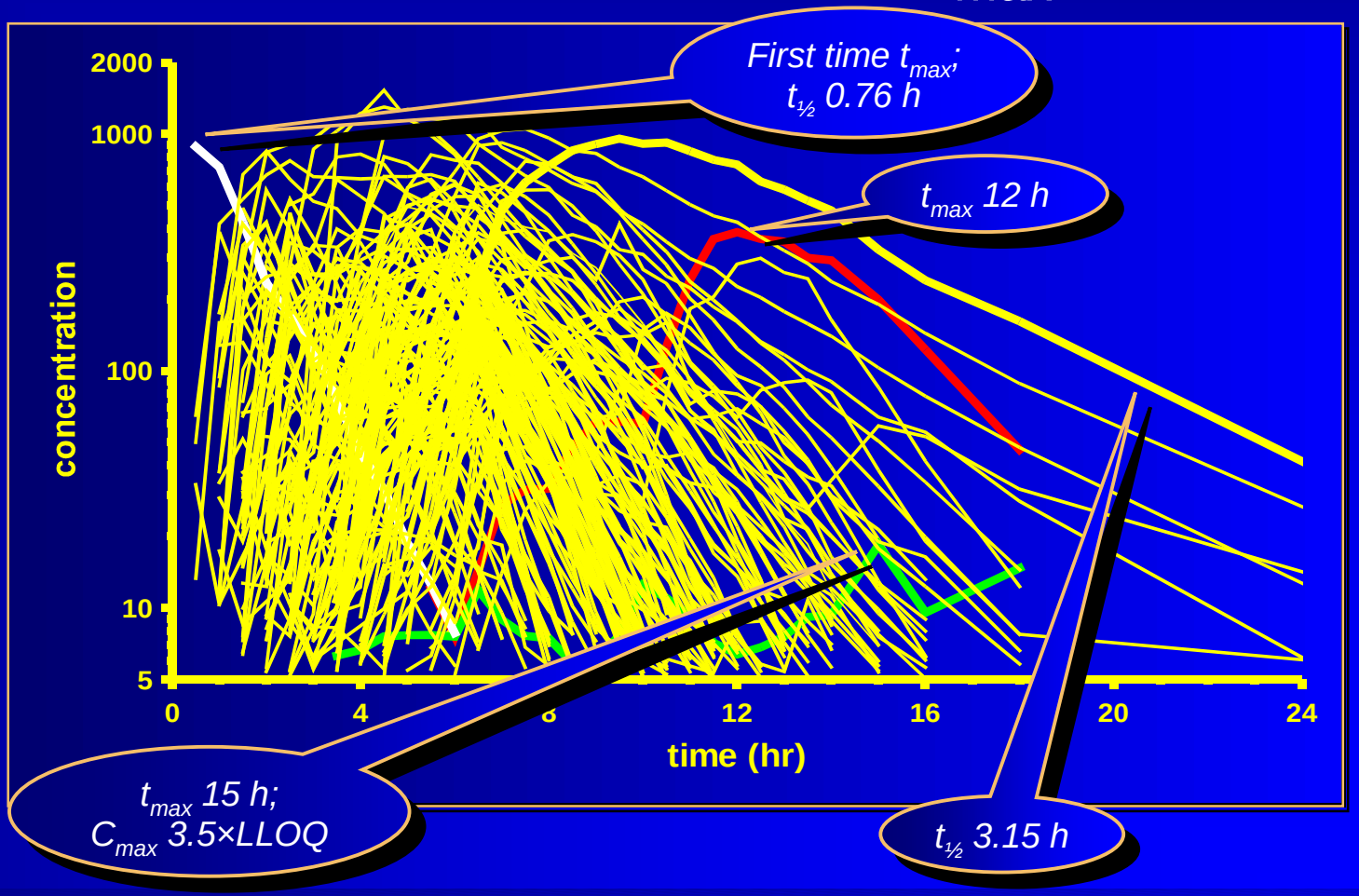
HVDs/HVDPs

- Using the PK profile help demonstrate bioequivalence when a conventional BE study is unsuitable, including practical examples.
  - Omeprazole: Highly Variable Drug Product (HVDP), higher variability in fed state as compared to fasted state commonly observed, sensitive to low pH, breakdown of gastric resistant coating (especially of the reference product) not unusual, high variability in C_{max}/t_{max} due to gastric emptying, …

HVDs/HVDPs

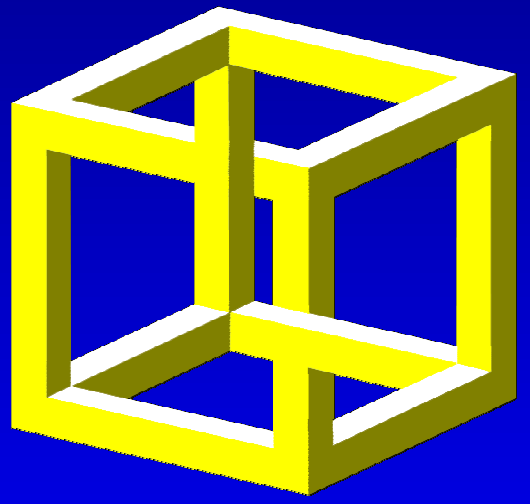
- Attempt to deal with high variability in C_{max}

Powered to 90% according to CV from previous studies; 140 (!) subjects and to 80% for expect-ed dropout rate. Sampling every 30 min up to 14 hours (7785 total).



HVDs/HVDPs

- Ways out?
  - Replicate designs could be considered e.g. for substances with highly variable pharmacokinetic characteristics.
    (BE Draft, Section 4.1.2)
  - Nonparametric methods
    A non-parametric analysis is **not acceptable**.
    (BE Draft, Section 4.1.8)
  - Compartmental (Population PK) methods
    The use of compartmental methods for the estimation of parameters is **not acceptable**.
    (BE Draft, Section 4.1.5)



HVDs

- All (!) ANDAs submitted to FDA/OGD 2003–2005 (1010 studies, 180 drugs)
  - 31% (57/180) highly variable (CV ≥30%)
  - of these HVDs/HVDPs,
    - 60% due to PK (*e.g.*, first pass metabol.)
    - 20% formulation performance
    - 20% unclear

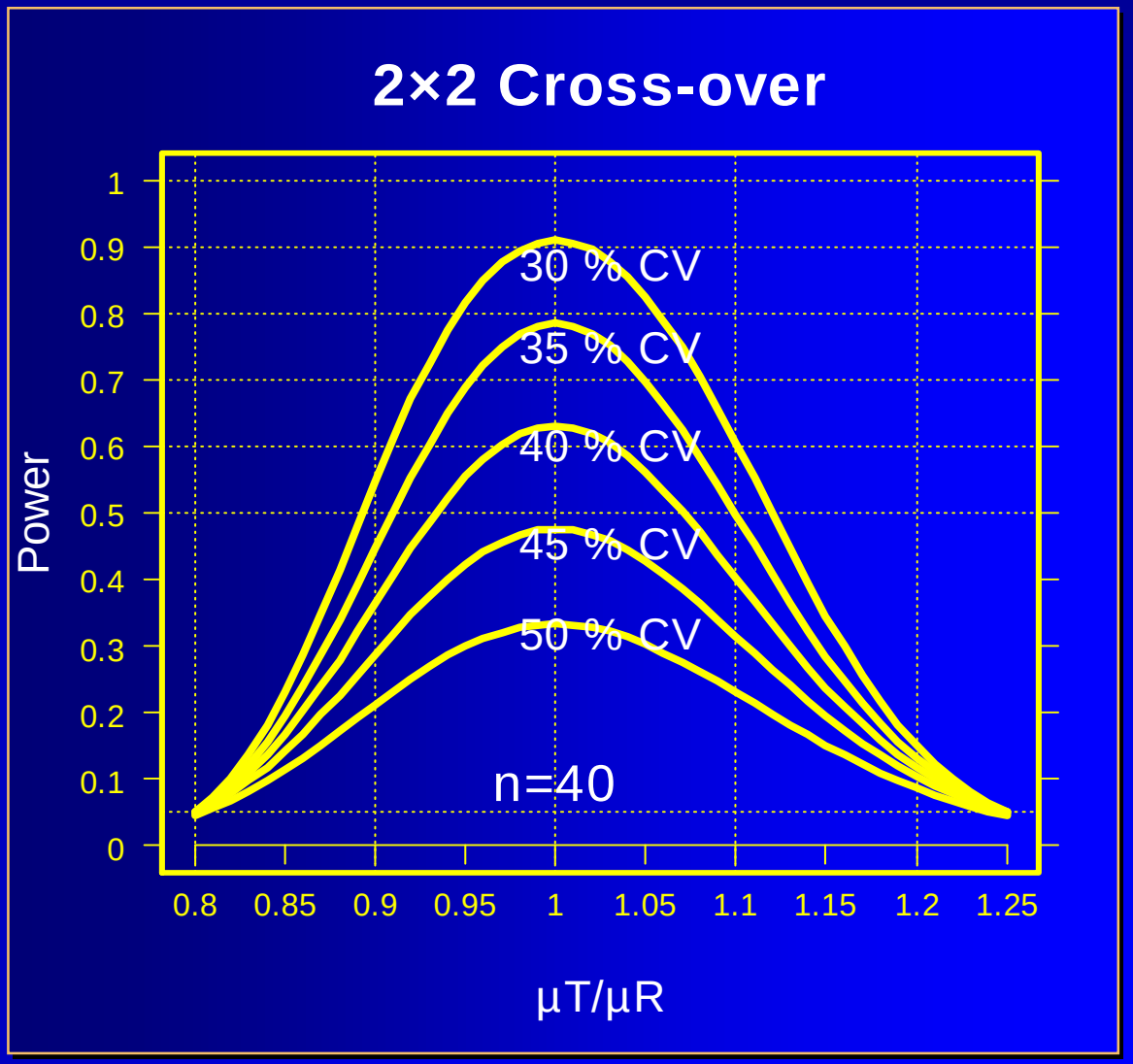
Davit BM, Conner DP, Fabian-Fritsch B, Haidar SH, Jiang X, Patel DT, Seo PR, Suh K, Thompson CL, and LX Yu
Highly variable drugs: observations from bioequivalence data submitted to the FDA for new generic drug applications
AAPS J 10(1): 148-56 (2008)

HVDs

Power to show BE with 40 subjects for CV_{intra} = 30–50%

μT/μR 0.95, CV_{intra} 30%
→ power 0.816
μT/μR 1.00, CV_{intra} 45%
→ power 0.476 <
Roulette 0.486 (!)

μT/μR 0.95, CV_{intra} 45%
→ n=82 (power 0.807)

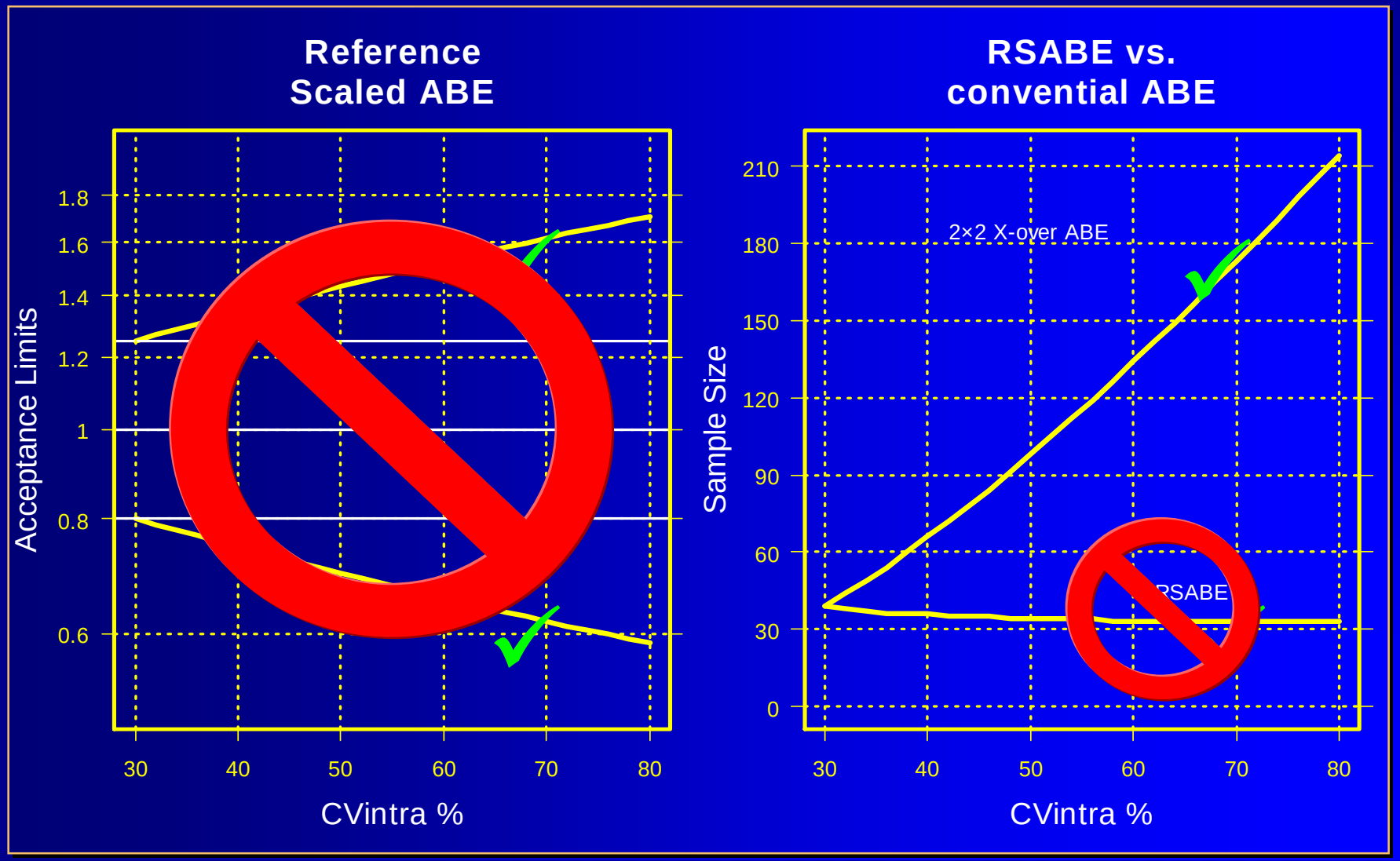


HVDs (US/EU)

- Advisory Committee for Pharmaceutical Sciences (ACPS) to FDA (10/2006) on HVDs
- Follow-up paper in 2008 (likely to be implemented in next Guideline)
  - Replicate study design [TRR–RTR–RRT]
  - Reference Scaled Average Bioequivalence (RSABE)
  - Minimum sample size 24 subjects
  - Point estimate restricted to [0.80,1.25]

Haidar SH, Davit B, Chen M-L, Conner D, Lee LM, Li QH, Lionberger R, Makhlouf F, Patel D, Schuirmann DJ, and LX Yu
Bioequivalence Approaches for Highly Variable Drugs and Drug Products
Pharmaceutical Research 25/1, 237-241 (2008)
http://www.springerlink.com/content/u503p62056413677/fulltext.pdf

HVDs (US/EU)

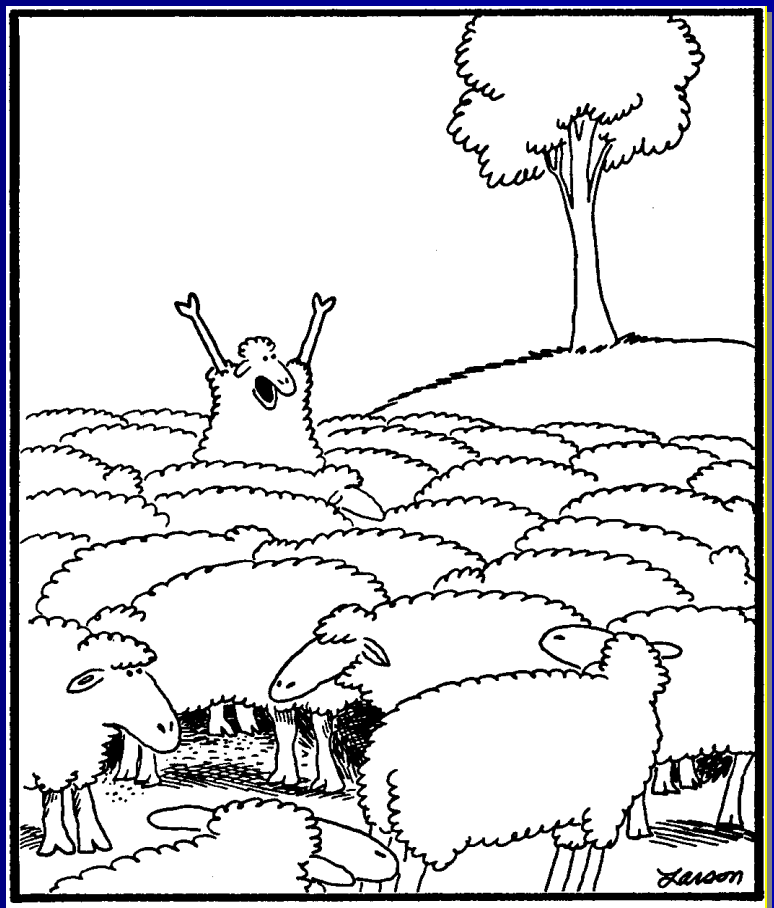

Reference
Scaled ABE
Acceptance Limits
1.8
1.6
1.4
1.2
1
0.8
0.6
30
40
50
60
70
80
CVintra %
RSABE vs.
convential ABE
Sample Size
210
180
150
120
90
60
30
0
2×2 X-over ABE
RSABE
30
40
50
60
70
80
CVintra %

Adhering to Cookbooks

- The ideal subject for any bioequivalence study probably is a Borg-Drone.
- Cookbooks in Science reflect the statistical principle of 'Regression to the Mean' – namely **'Regression to Mediocrity'**.

Resist in becoming a Borg!

Conclusions, Outlook



**“Wait! Wait! Listen to me! …
We don’t HAVE to be just sheep!”**

- David Bourne’s (Uni. Oklahoma) e-mail list
  - A rather active list (3200+ members, about 50 postings/week) covering almost any aspect of PK/PD/bio-analytics…
    - Subscription http://www.boomer.org/pkin/
    - Search page http://www.boomer.org/pkin/simple.html
- BA and BE Forum (BEBAC Vienna)
  - Specialized in BA/BE/bioanalytics.
    - No registration necessary to *read* posts. http://forum.bebac.at/
    - Registration (to post): http://forum.bebac.at/register.php

Thank You!

Cookbooks are for Housewives / men – not for Kitchen Chefs!

Open Questions?

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