Bioequivalence – Still an Applied Science or already a Cookbook?

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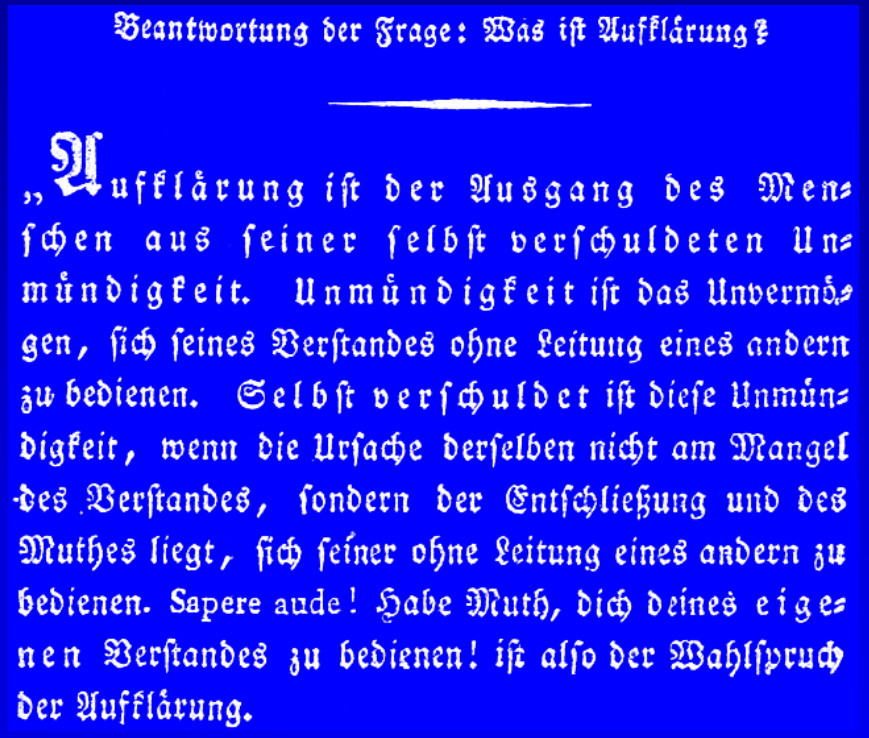
Answering the Question: What is Enlightenment?

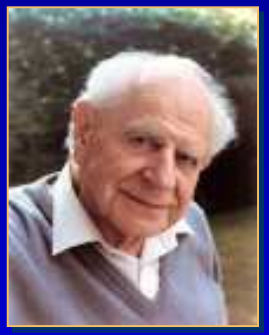

Beantwortung der Frage: Was ist Aufklärung?

„Aufklärung ist der Ausgang des Menschen aus seiner selbst verschuldeten Unmündigkeit. Unmündigkeit ist das Unvermögen, sich seines Verstandes ohne Leitung eines andern zu bedienen. Selbst verschuldet ist diese Unmündigkeit, wenn die Ursache derselben nicht am Mangel des Verstandes, sondern der Entschließung und des Muthes liegt, sich seiner ohne Leitung eines andern zu bedienen. Sapere aude! Habe Muth, dich deines eigenen Verstandes zu bedienen! ist also der Wahlspruch der Aufklärung.

Enlightenment is man's emergence from his self-imposed immaturity for which he himself was responsible. Immaturity and dependence are the inability to use one's own intellect without the direction of another. **One is responsible** for this immaturity and dependence, if its cause is not a lack of intelligence, but a lack of determination and courage to think without the direction of another. ***Sapere aude!*** Have courage to use **your own** understanding! is therefore the slogan of Enlightenment. *Immanuel Kant (1784)*

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

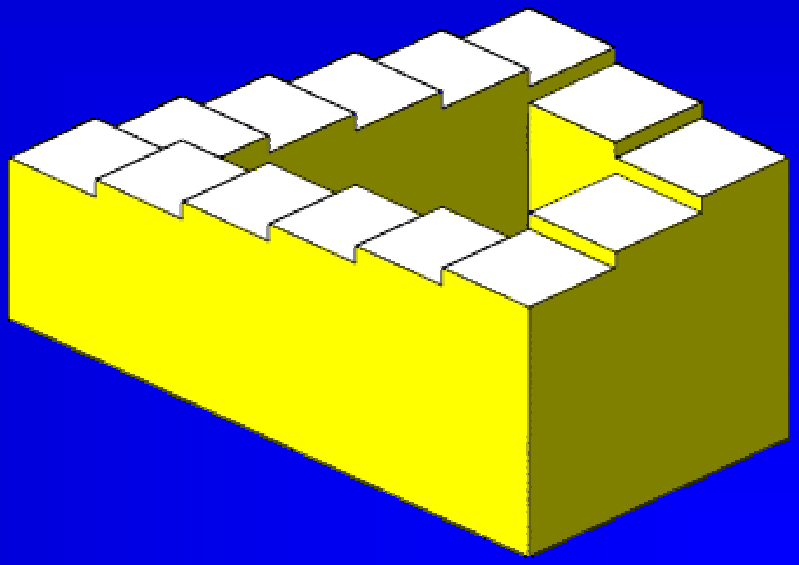
Even though it's *applied* science we're dealin' with, it still is – *science!*

Leslie Z. Benet

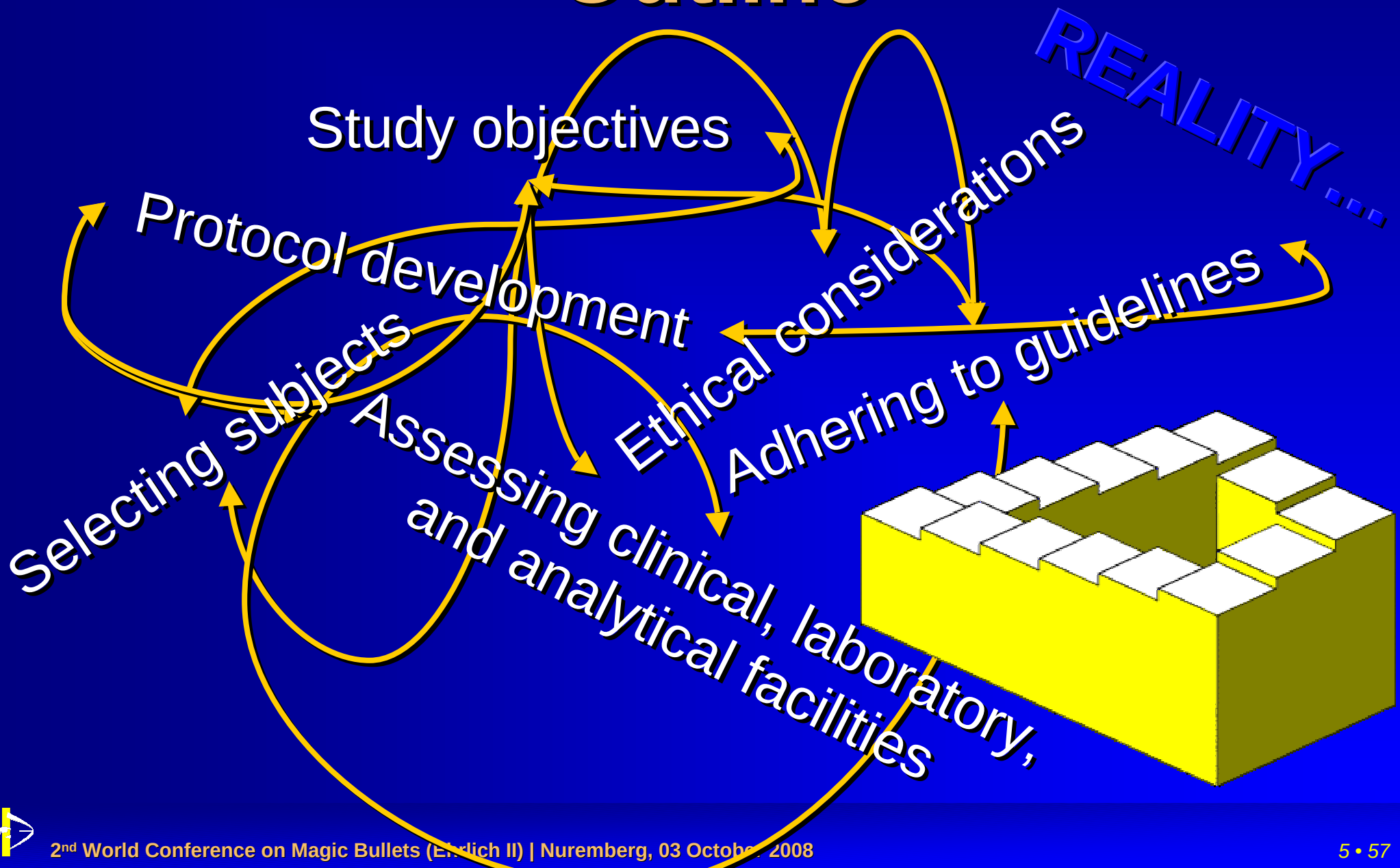
Key Aspects of BE Studies

DREAM...

- Study objectives
- Ethical considerations
- Adhering to guidelines
- Protocol development
- Assessing clinical, laboratory, and analytical facilities
- Selecting subjects
- *&c., &c., …*

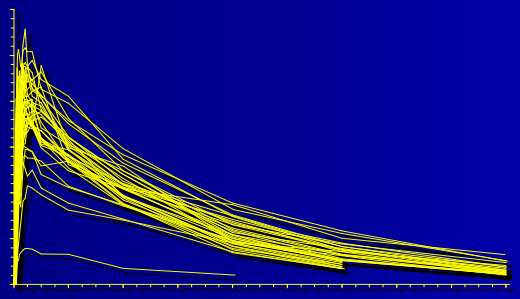


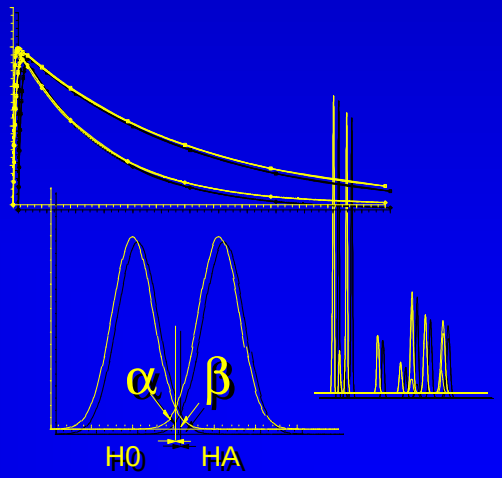
Outline


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

Assumptions

World *'Reality'*





Model *'Data'*

Theory *'Truth'*

Assumptions: Pharmacokinetics

$$\frac{f_1 \cdot AUC_1}{D_1 \cdot CL_1}, \frac{f_2 \cdot AUC_2}{D_2 \cdot CL_2}$$

$$f_{rel}(BA) = \frac{AUC_1}{AUC_2}$$

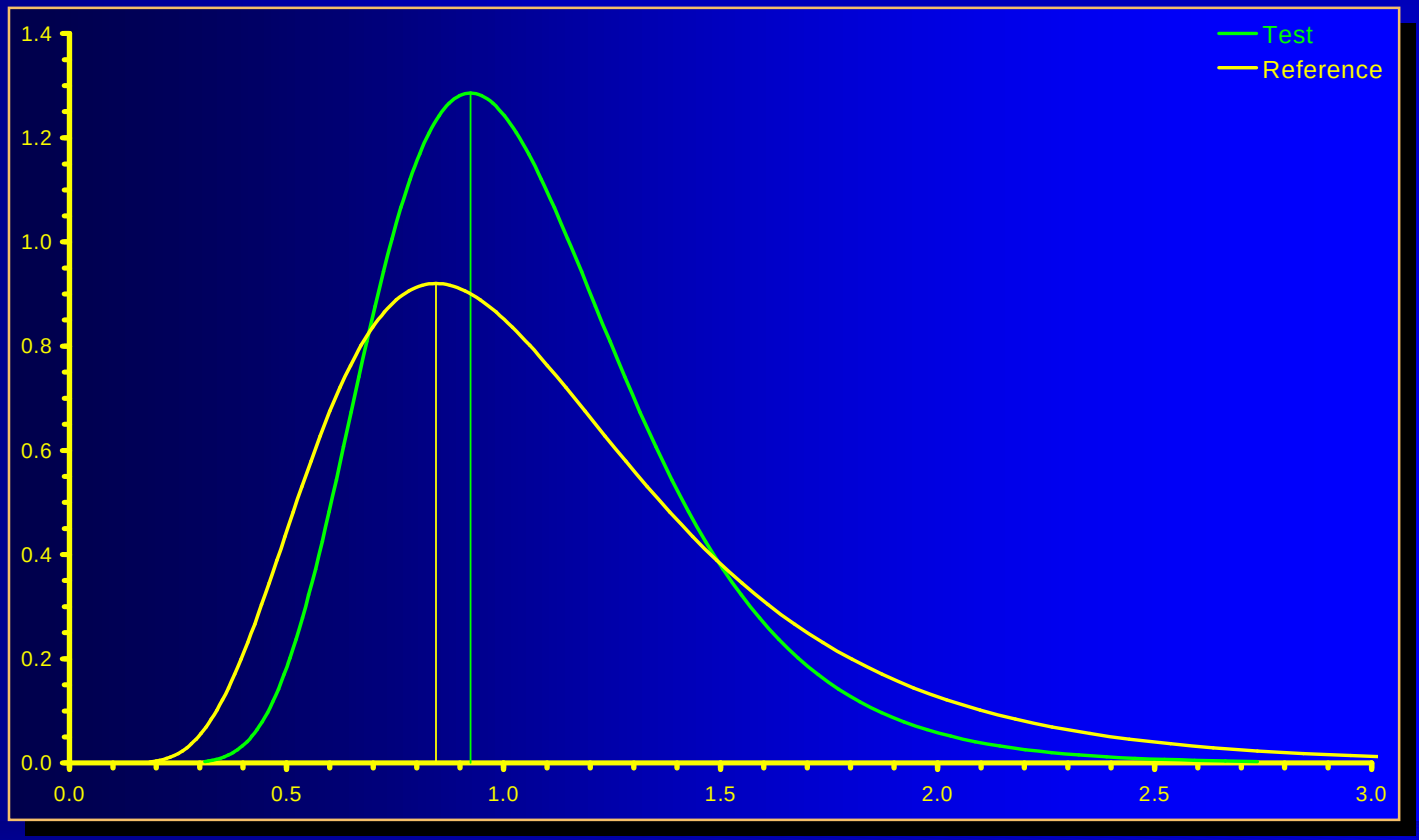
Assumption 1: $D_1 = D_2$ ($D_1/D_2 = 1^*$)

Assumption 2: $CL_1 = CL_2$

Assumptions: Statistics

Distribution

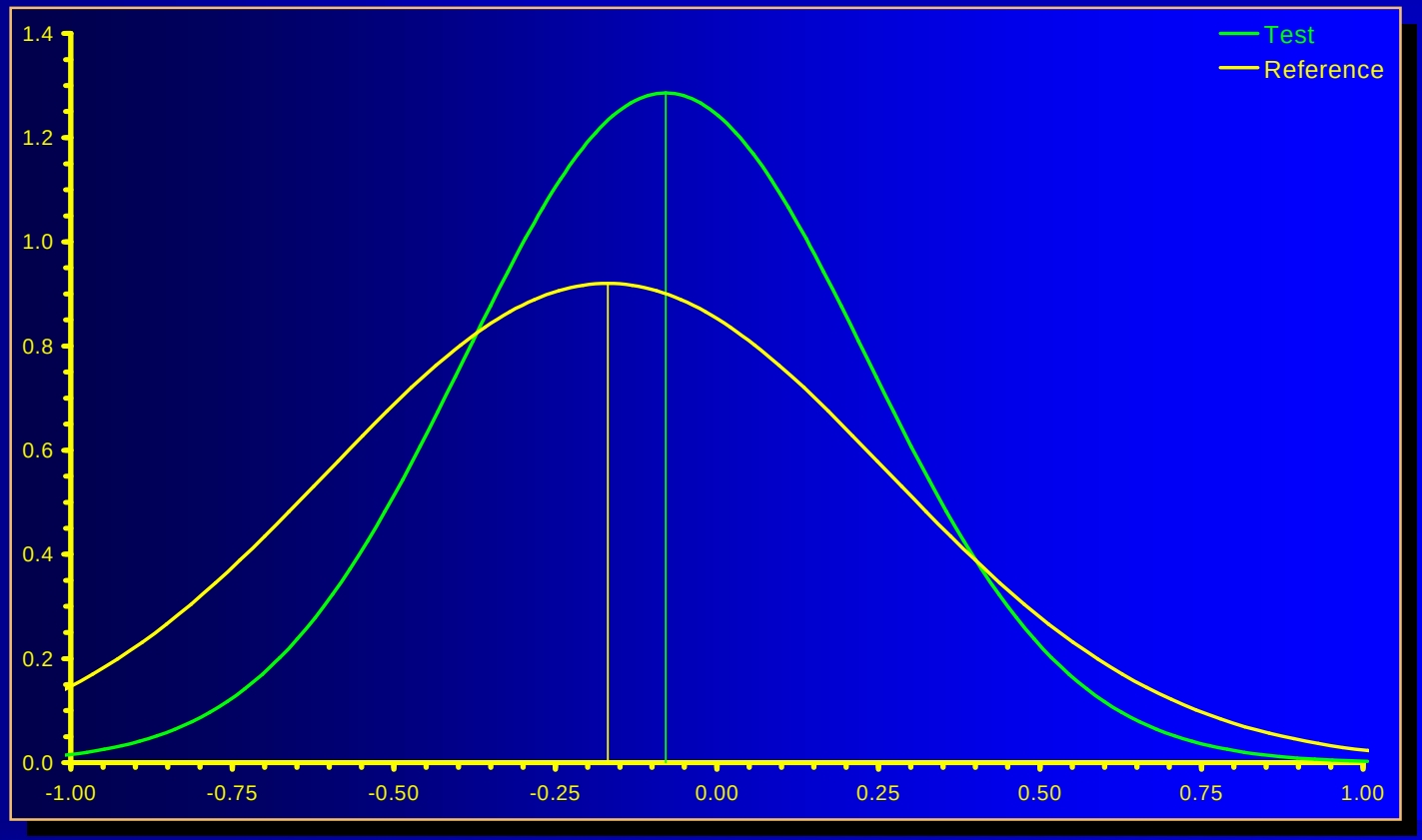
- IDD (Independent Identically Distribution)



Assumptions: Statistics

Multiplicative Model

- Log-Transformation (PK, Analytics)



Assumptions: Statistics

Multiplicative Model (without carryover)

$$X_{ijk} = \mu \cdot \pi_k \cdot \Phi_l \cdot s_{ik} \cdot e_{ijk}$$

X_{ijk}: *ln*-transformed response of j-th subject ($j=1,\ldots,n_i$) in i-th sequence ($i=1,2$) and k-th period ($k=1,2$), μ: global mean, μ_l: expected formulation means ($l=1,2$: $\mu_1=\mu_{test}$, $\mu_2=\mu_{ref.}$), π_k: fixed period effects, Φ_l: fixed formulation effects ($l=1,2$: $\Phi_1=\Phi_{test}$, $\Phi_2=\Phi_{ref.}$)

Assumptions: Statistics

Multiplicative Model (without carryover)

$$X_{ijk} = \mu \cdot \pi_k \cdot \Phi_l \cdot s_{ik} \cdot e_{ijk}$$

s_{ik}: random subject effect, e_{ijk}: random error

Main Assumptions:

- All $ln\{s_{ik}\}$ and $ln\{e_{ijk}\}$ are independently and normally distributed about unity with variances σ^2_s and σ^2_e.
- All observations made on different subjects are independent.

Global Harmonization?

Transformations (e.g. […], logarithm) should be specified in the protocol and a rationale provided […]. The general principles guiding the use of transformations to ensure that the assumptions underlying the statistical methods are met are to be found in standard texts […].
In the choice of statistical methods due attention should be paid to the statistical distribution […]. When making this choice (for example between parametric and non-parametric methods) it is important to bear in mind the need to provide statistical estimates of the size of treatment effects together with confidence intervals […].

Anonymous [International Conference on Harmonisation]
Topic E 9: Statistical Principles for Clinical Trials, 5 February 1998

Global Harmonization?

No analysis is complete until the assumptions that have been made in the modeling have been checked. Among the assumptions are that the repeated measurements on each subject are independent, normally distributed random variables with equal variances. Perhaps the most important advantage of formally fitting a linear model is that diagnostic information on the validity of the assumed model can be obtained. These assumptions can be most easily checked by analyzing the residuals.

Jones B and MG Kenward
Design and Analysis of Cross-Over Trials
2nd Edition, Chapman & Hall, Boca Raton, London, New York, Washington, D.C. (2003)

Nonparametrics?

The limited sample size in a typical BE study precludes a reliable determination of the distribution of the data set. Sponsors and/or applicants are not encouraged to test for normality of error distribution after log-transformation […].

Anonymous [FDA, Center for Drug Evaluation and Research (CDER)]
Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001

Acceptable in:
Turkey (MOH, November 2005)
Saudia Arabia (SFDA, May 2005)

Global Harmonization?

FDA 2001, EMEA (Q&A on BA/BE 2006, BE Draft 2008)

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.*, WMW)

ICH Good Statistical Practice

Global Harmonization?

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

There can be only one!

Pilot Studies

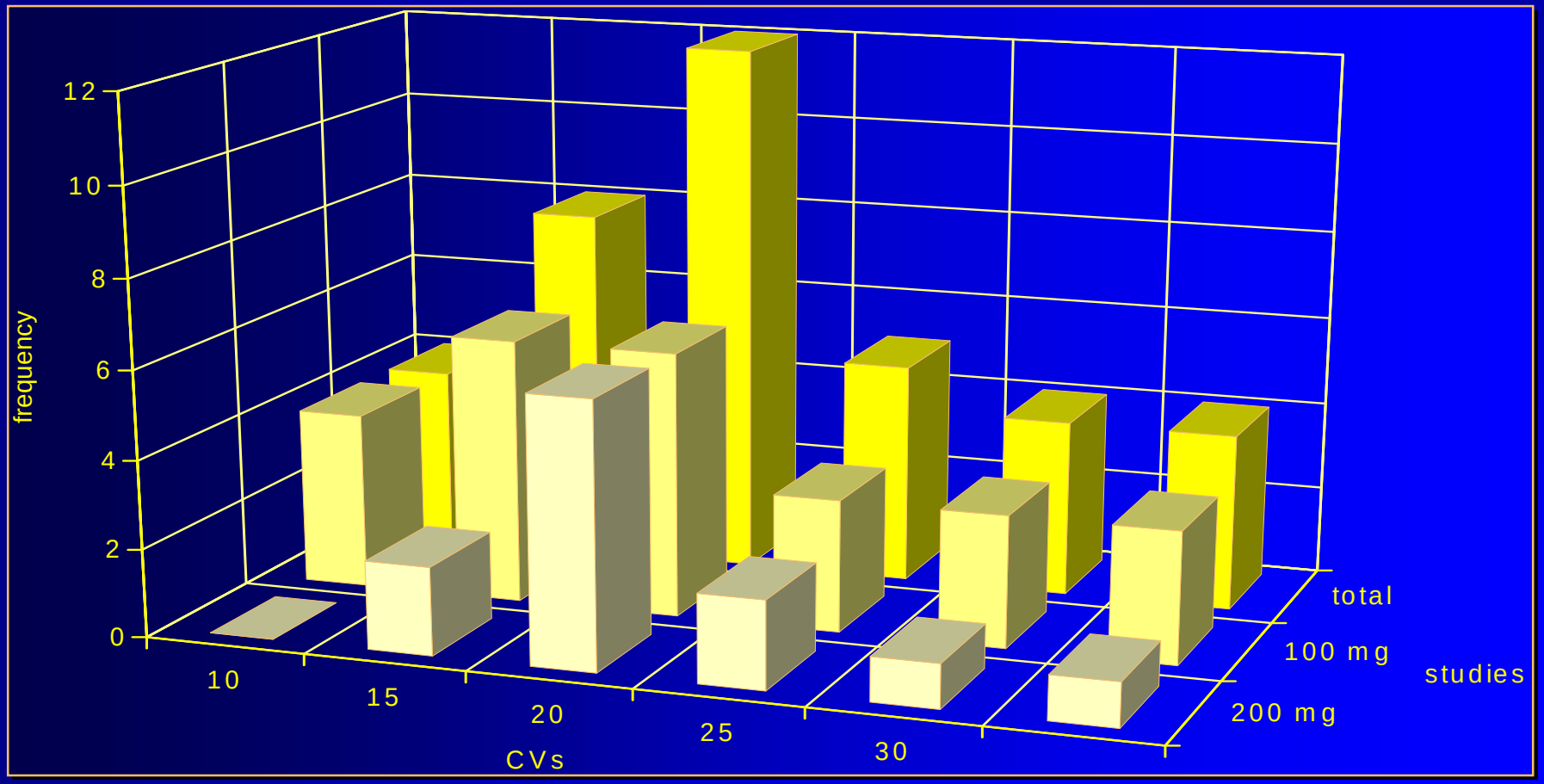
- Rationale (FDA/CDER, BA/BE Studies – General Considerations, 2003)
  - Validation of analytical methodology
  - Assessment of variability
  - Optimization of sample collection time intervals
  - A pilot study that documents BE can be appropriate, provided its design and execution are suitable and a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

Pilot Studies

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

Pilot Studies

Sample size planning…



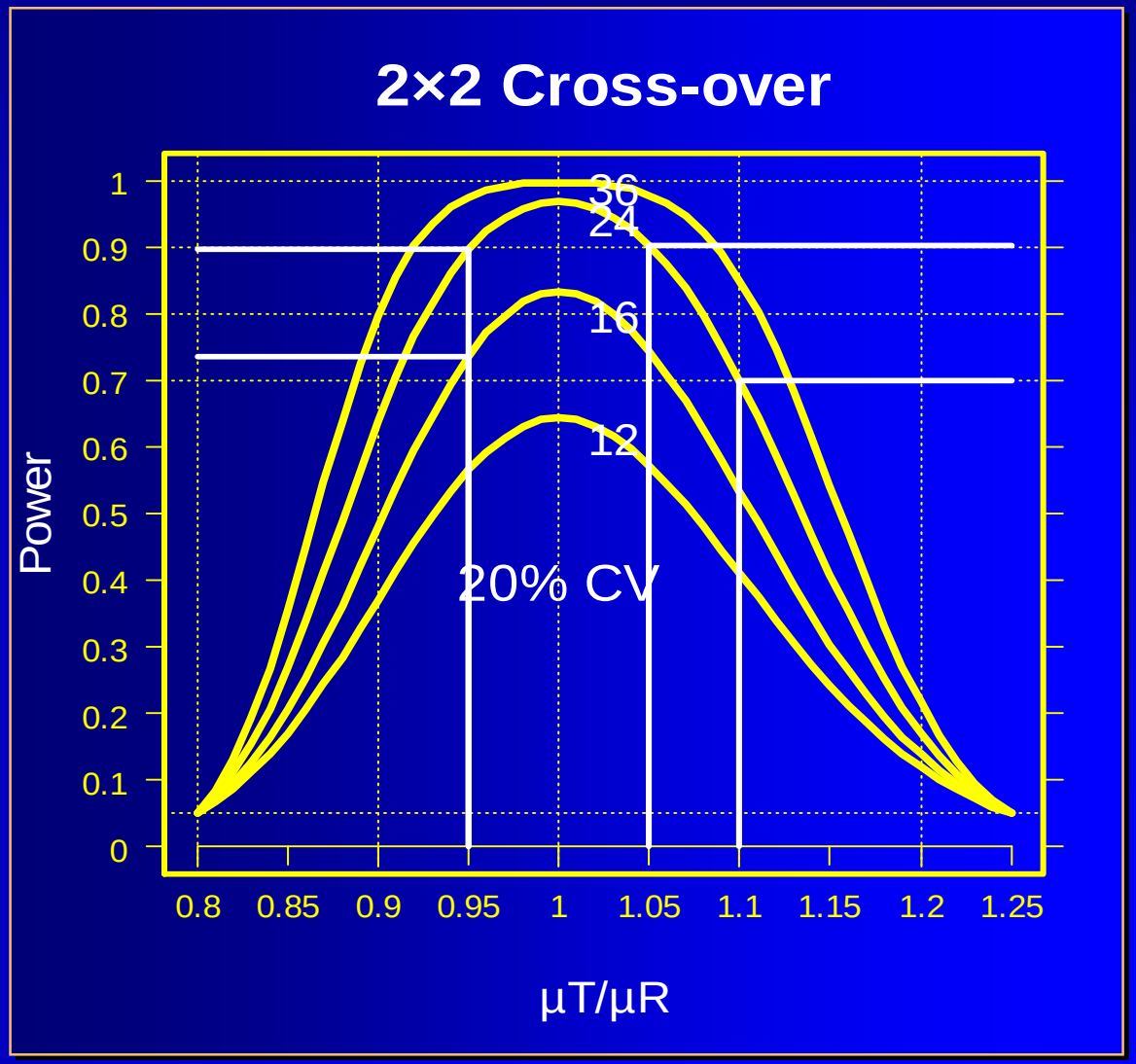
Doxicycline *(37 studies ref. by Blume/Mutschler, 1996)*

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.

'Internal Pilot Study Design'

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 pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses.

Two-Stage Design

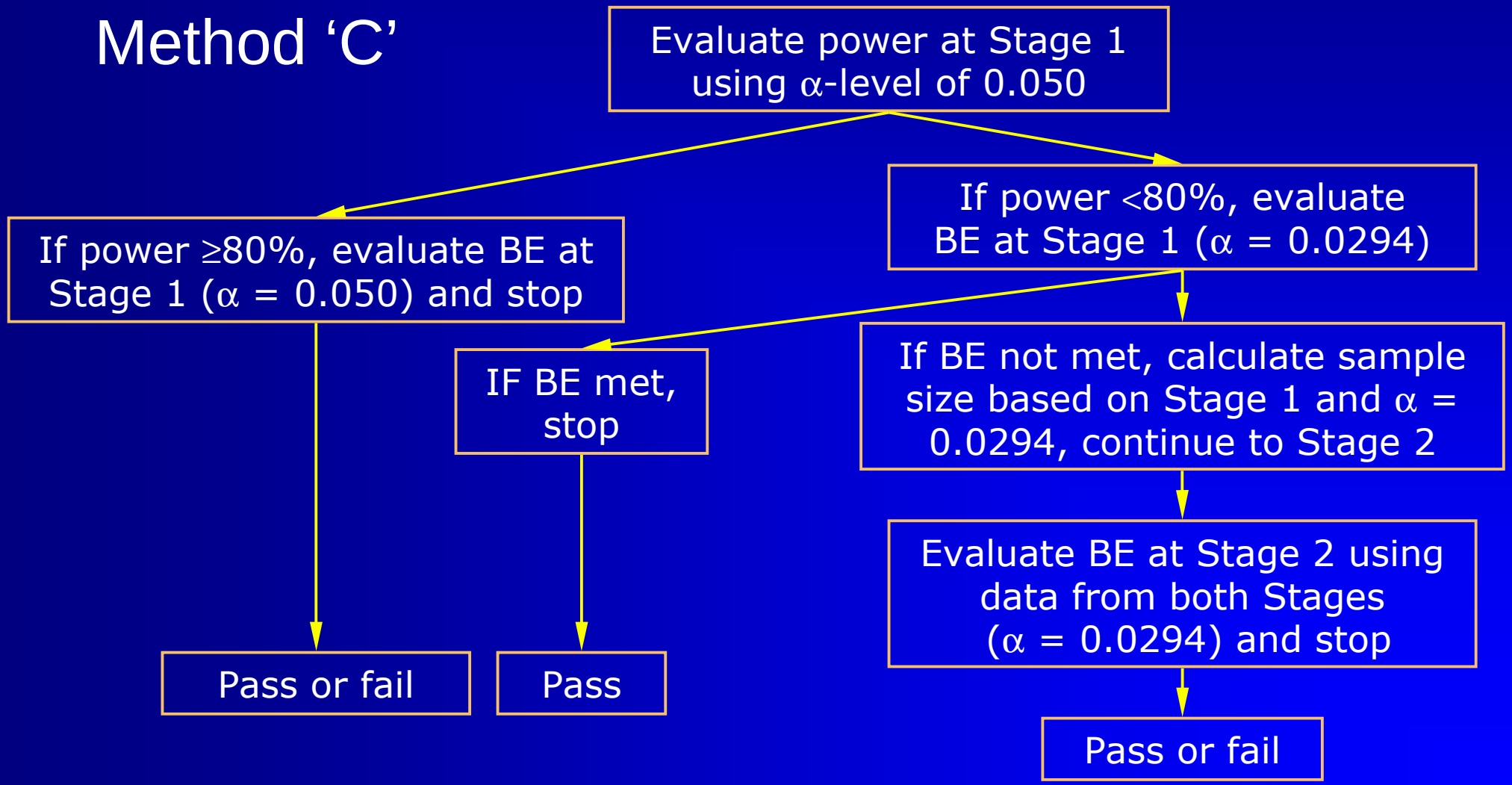
- Critical Remarks
  - ‘BE not been demonstrated’ in initial group:
    If test at $\alpha \leq 0.05$, patient’s risk already ‘spent’!
  - ‘Adjusted significance levels’:
    Bonferroni not validated in BE setting; patient’s risk may be inflated (>0.05)!

likely to be implemented by the FDA

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’



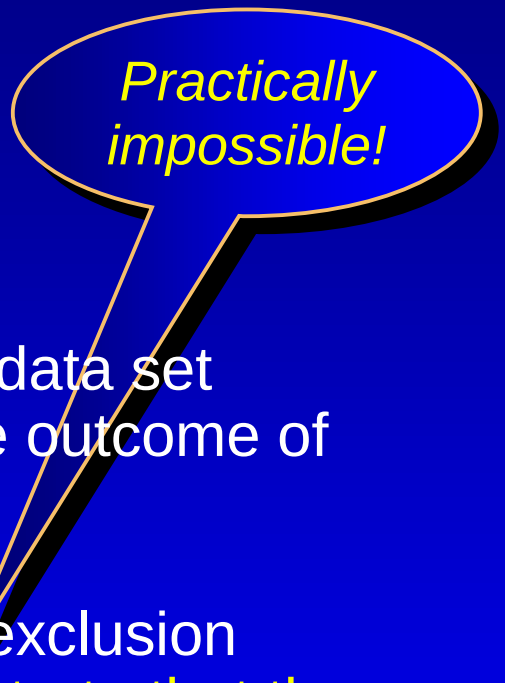
Outliers

- Problems
  - Parametric methods (ANOVA, GLM) are very sensitive to outliers
    - A single outlier may underpower a properly sized study.
    - Exclusion of outliers only possible if procedure stated in the protocol, and reason is justified, *e.g.*,
      - Lacking compliance (subject did not take the medication),
      - Vomiting (up to 2 × t_{max} for IR, at all times for MR),
      - Analytical problems (*e.g.*, interferences in chromato-graphy);
      - Not acceptable if only based on statistical grounds.

Outliers

- Solution I
  - Since assumptions are violated, you may apply a statistical method which does not rely on those!
  - Drawback: Regulatory acceptance?

Outliers



- Solution II
  - Stay with the parametric method, but
    - evaluate both the full data set and the reduced data set (outliers excluded) and discuss influence on the outcome of the study.
  - In accordance with EMEA's Q&A #3:
    - Exceptional reasons may justify post-hoc data exclusion […]. In such a case, the applicant must demonstrate that the condition stated to cause the deviation is present in the outlier(s) only and absence of this condition has been investigated using the same criteria for all other subjects.
    - Results of statistical analyses with and without the group of excluded subjects should be provided.

Re-testing of subjects

- If you suspect a product failure of the reference formulation, one may consider re-testing;
  - the outlying subject should be re-tested
    - with both the test and reference.
  - Include ≥5 subjects, who showed a 'normal' response in the main study (*i.e.,* size of re-tested group ≥6 or 20 % of subjects, whichever is larger).
  - Expect questions anyway (although *sometimes* suggested by the FDA, not covered in any guideline; statistical evaluation not trivial…)

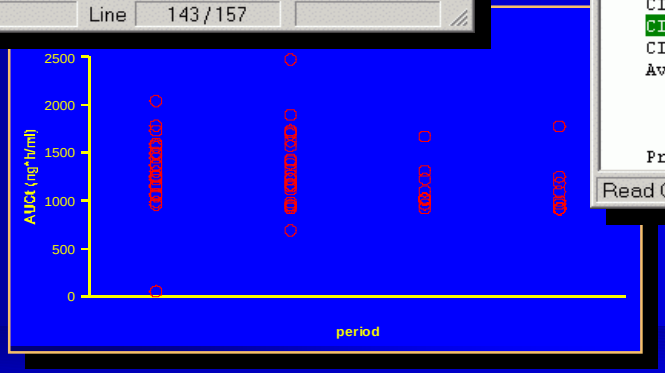
Re-testing of subjects

n=24: 83.3%–131.1% ⇒ +n=6: 86.7%–122.5%

Bioequivalence Text - [Untitled11]

```
Bioequivalence Statistics

User-Specified Confidence Level for CI's and Power = 90.0000
Percent of Reference to Detect for 2-1 Tests and Power = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250

Formulation variable: formulation
Reference: R   LSMean=    7.085698  SE=    0.104041  GeoLSM= 1194.756651
--------------------------------------------------------------------------

Test:      T   LSMean=    7.129902  SE=    0.104041  GeoLSM= 1248.754167

    Difference =     0.0442,  Diff_SE=    0.1321,  df= 22.0
    Ratio(%Ref) =   104.5195

                        Classical                Westlake
    CI  80% = (   87.7732,  124.4610)  (   80.9169,  119.0831)
    CI  90% = (   83.2969,  131.1493)  (   74.5939,  125.4061)
    CI  95% = (   79.4604,  137.4815)  (   68.4657,  131.5343)
    Failed to show average bioequivalence for confidence=90.00 and percent=20.0.

                       Two One-Sided T-tests

    Prob(< 80%)=0.0277  Prob(> 125%)=0.0947  Max=0.0947  Total=0.1224
```

Read Only | Line 143 / 157



Bioequivalence Text - [Untitled10]

```
Bioequivalence Statistics

User-Specified Confidence Level for CI's and Power = 90.0000
Percent of Reference to Detect for 2-1 Tests and Power = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250

Formulation variable: formulation
Reference: R   LSMean=    7.106774  SE=    0.109442  GeoLSM= 1220.204475
--------------------------------------------------------------------------

Test:      T   LSMean=    7.137202  SE=    0.052715  GeoLSM= 1257.903871

    Difference =     0.0304,  Diff_SE=    0.1017,  df= 28.7
    Ratio(%Ref) =   103.0896

                        Classical                Westlake
    CI  80% = (   90.2172,  117.7987)  (   85.7333,  114.2667)
    CI  90% = (   86.7263,  122.5403)  (   81.2107,  118.7893)
    CI  95% = (   83.7240,  126.9345)  (   76.9552,  123.0448)
    Average bioequivalence shown for confidence=90.00 and percent=20.0.

                       Two One-Sided T-tests

    Prob(< 80%)=0.0093  Prob(> 125%)=0.0341  Max=0.0341  Total=0.0434
```

Read Only | Line 211 / 225

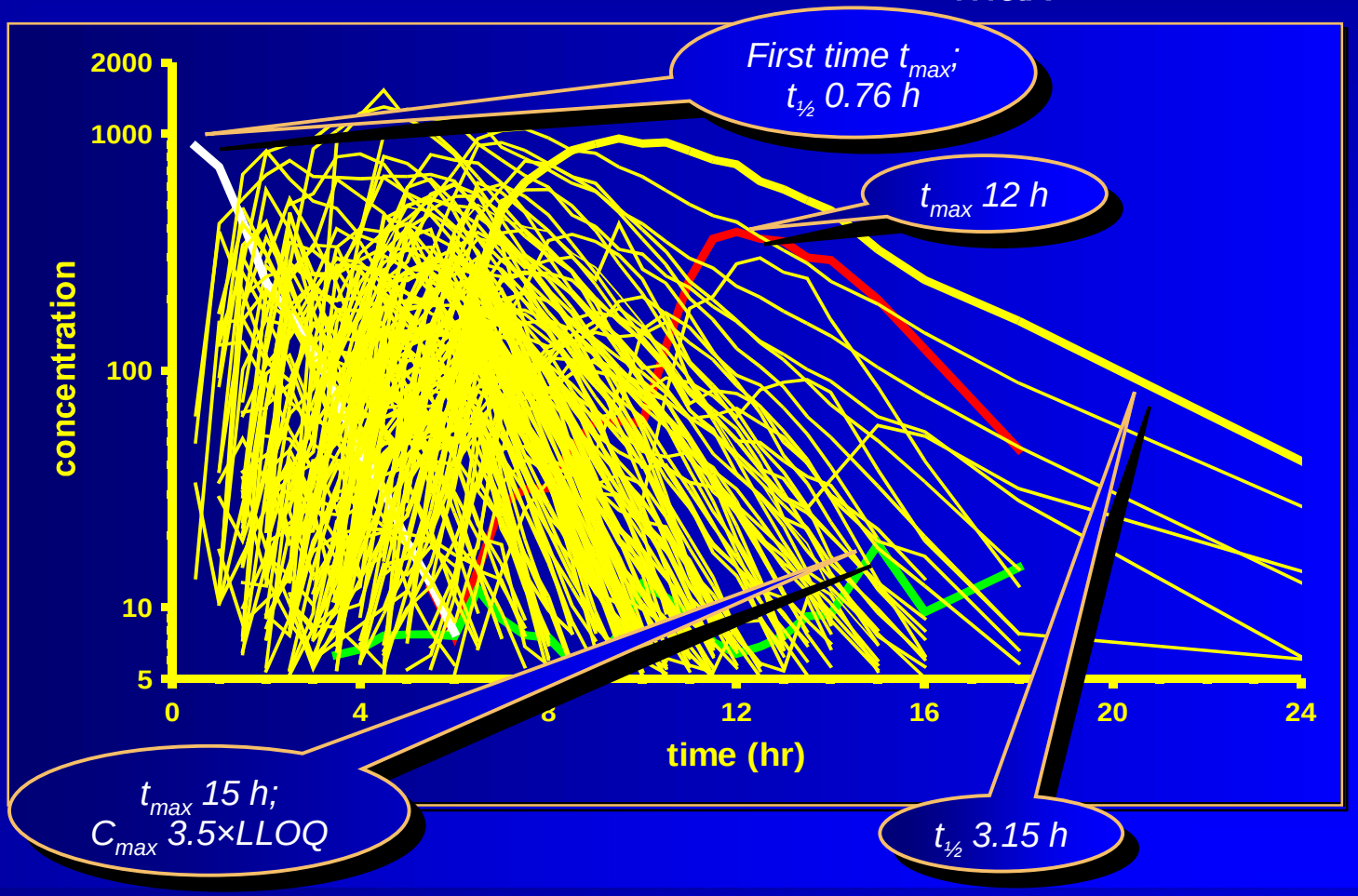
HVDs/HVDPs

- Does knowledge of the PK profile always help in demonstrating bioequivalence when a conventional BE study is unsuitable?
  - 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

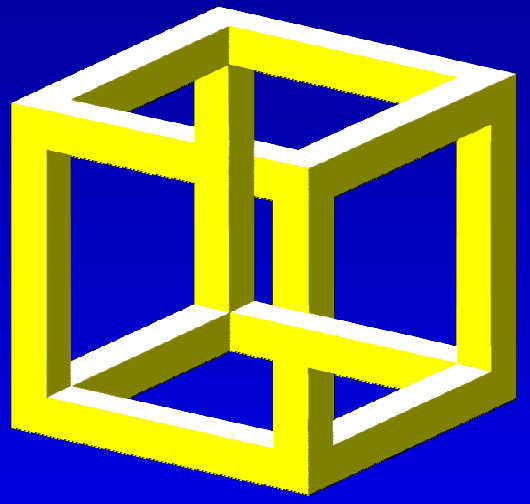
- Attempt to deal with high variability in C_{max}

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)



HVDPs

- 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

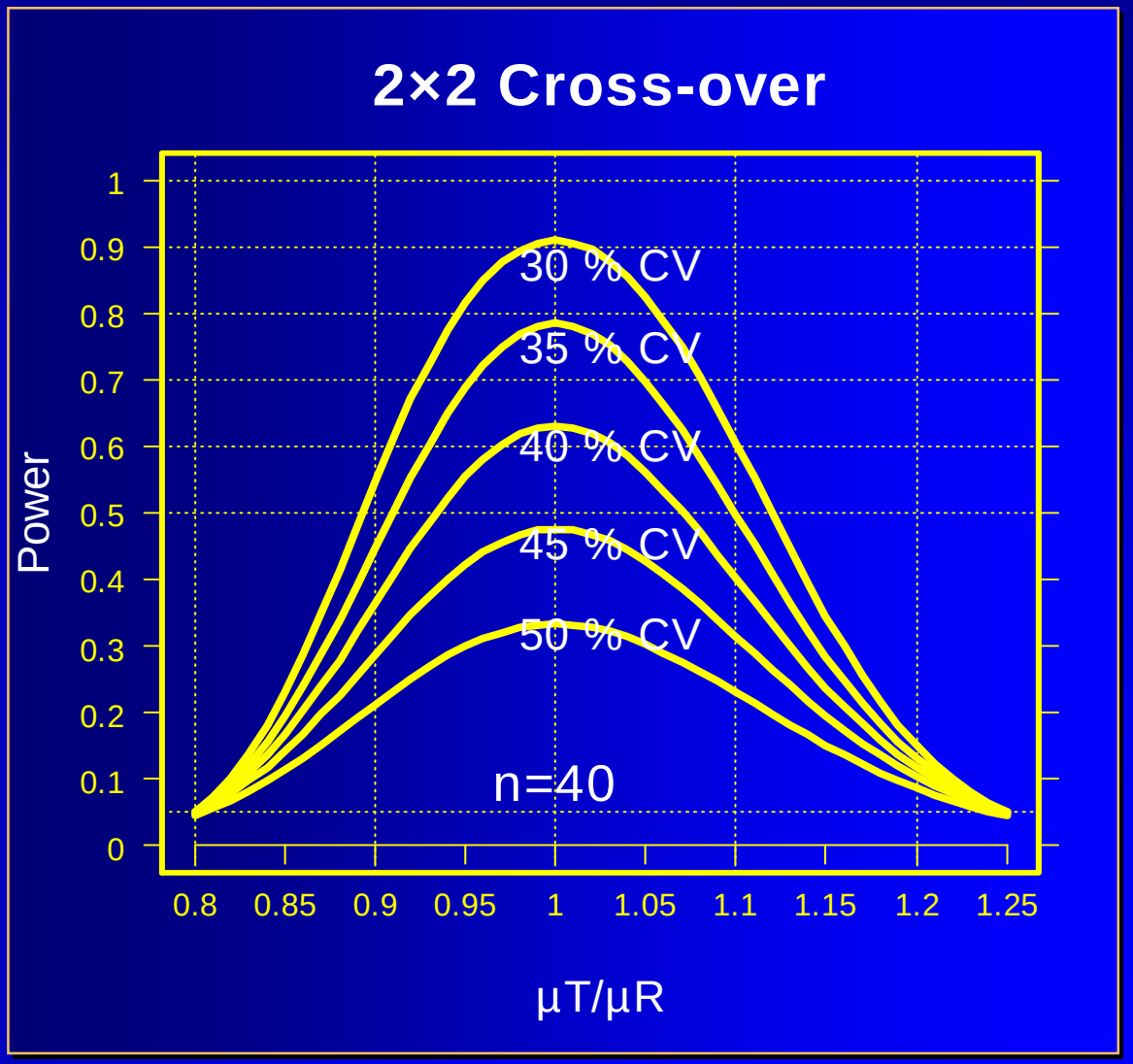
Davit BM, Conner DP, Fabian-Fritsch B, Haidar SH, Jiang X, Patel DT, Seo PR, Suh K, Thompson CL, and LX Yu
Highly variable drugs: observations from bioequivalence data submitted to the FDA for new generic drug applications
AAPS J 10(1): 148-56 (2008)

HVDPs

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)

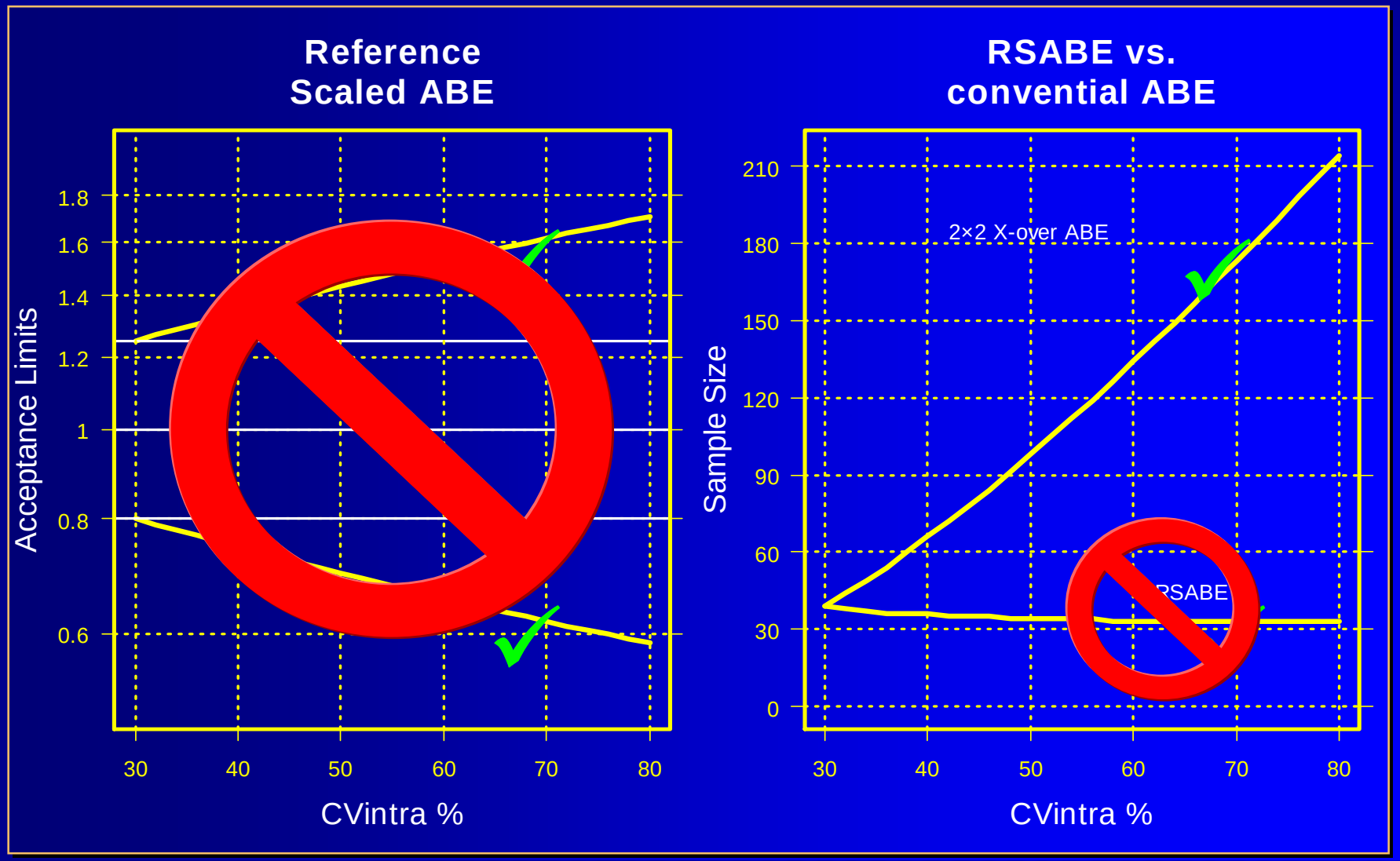


HVDPs (US/EU)

- 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

HVDPs (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 %

HVDs/HVDPs

- Is suggested EU-method of any good?
  - Replicate designs … (BE Draft, Section 4.1.2) **without scaling**
    - reduce the number of subjects (to 75% for a 3-period design and to 50% for a 4-period design as compared to a conventional 2×2),
    - but keep the *theoretical* number of treatments constant:
      - The potentional drop-out rate increases.
      - Practically *more* treatments must be administered in order to maintain the desired power!

HVDs/HVDPs

- Example
  - AR [0.80,1.25], CV_{intra} 49.5%, T/R 0.95%, power 80%, $n_{2\times2}$ 96
  - expected dropout rate of 10% per washout
    - 2×2 study: 96+10=106 subjects, 212 treatments
    - 4×2 study: 48+16=64 subjects, 256 treatments

Ethically?

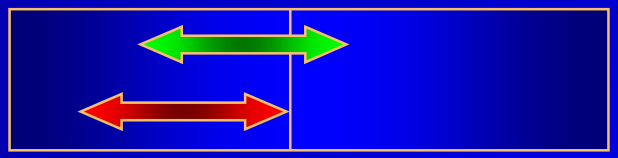
  - Proposed FDA Scaling-Method:
    AR [0.7006,1.4273], PE [0.80,1.25], n 34 (!)

HVDPs: $C_{ss,min}$

- EMEA Draft BE Guideline, 2008
  - Acceptance limits
    - [...] at steady state AUCτ, $C_{max,ss}$, and ***$C_{min,ss}$*** should be analysed using the same acceptance interval as stated above.
      - $C_{min,ss}$ was added probably after concerns for oxycodone, but this metric will be rather tough to meet for some drugs.
      - Since scaling is not allowed, sample sizes are expected to be *very* high (for HVDPs even in steady state the variability of $C_{ss,min}$ » $C_{ss,max}$).

Low Variability

- Drugs / Drug Products with CV_{intra} <10%
  - No specific statements in any guideline.
  - Problems may arise according to significant treatment effects in ANOVA (*i.e.*, although the 90% CI is within the acceptance range – 100% is not included) – even for the minimum sample size of 12.



  - Denmark
    - DKMA considers that the 90% CI for the ratio test versus reference should include 100% […].
    - Deviations may be accepted if they can be adequately justified not to have impact on either the overall therapeutic effect or safety profile of the product.

      Danish Medicines Agency (DKMA)
      Bioequivalence and labelling of medicinal products with regard to generic substitution (Jan 2006)
      http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6437

Nuisance: sequence effect

- In a ‘standard’ 2×2 cross-over design
  - the sequence effect is confounded with
    - the carryover effect, and
    - the formulation-by-period interaction.
  - Therefore, a statistically significant sequence effect could indicate that there is
    - a true sequence effect,
    - a true carryover effect,
    - a true formulation by period interaction, or
    - a failure of randomization.

Nuisance: sequence effect

- ‘Two-stage analysis’[1)] was – and still is – often applied.
  - Test for a significant sequence effect at α 0.10
  - If a significant sequence effect is found, evaluation of the first period as a parallel design
- This procedure was shown to be statistically flawed.[2)]

1) **JE Grizzle**
The two-period change over design and ist use in clinical trials
Biometrics 21, 467-480 (1965)

2) **P Freeman**
The performance of the two-stage analysis of two-treatment, two-period cross-over trials
Statistics in Medicine 8, 1421-1432 (1989)

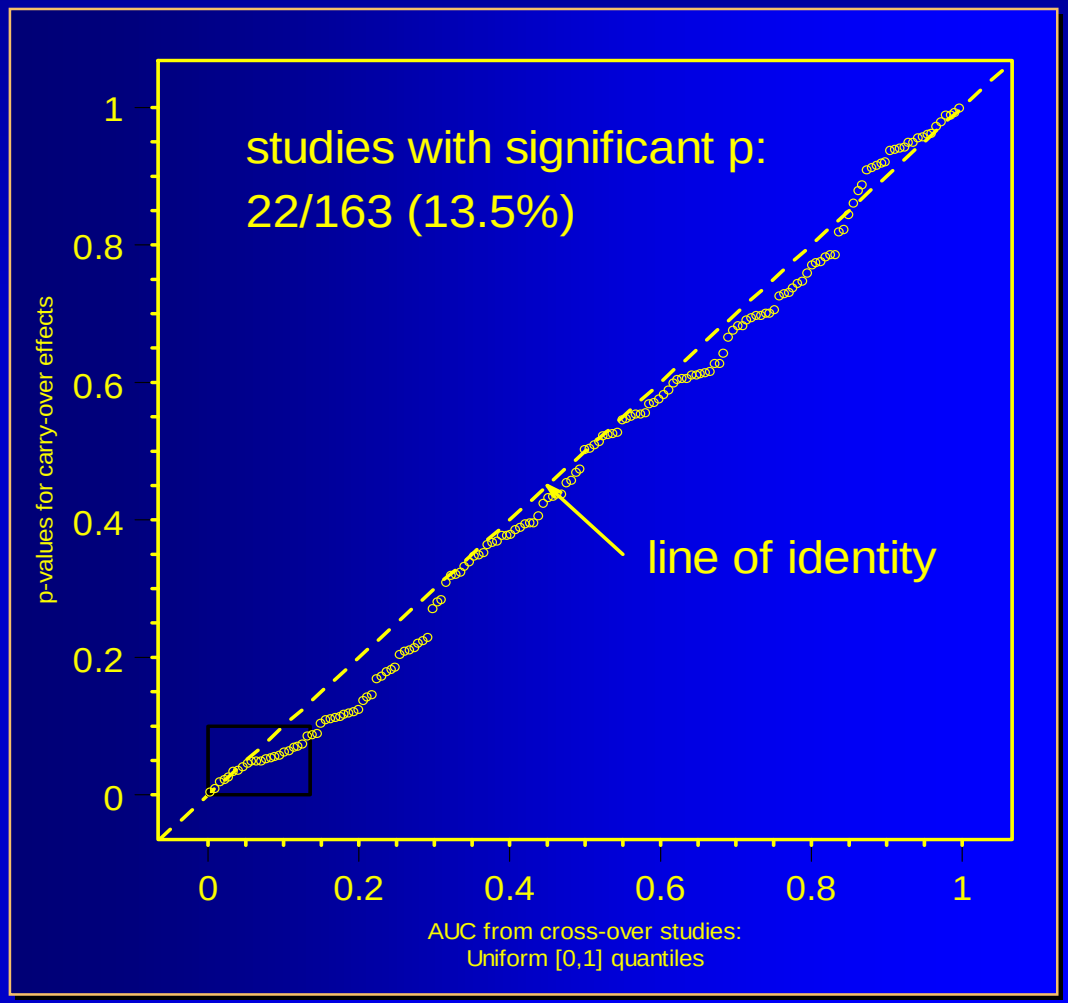
Nuisance: sequence effect

- In a large metastudy significant sequence effects were found at ≈ α, both for AUC and C_{max}.*)
  - 2×2 studies (n=324)
    - AUC: 34/324 (10.5%) C_{max}: 37/324 (11.4%)
  - 6×3 studies (n=96)
    - AUC: 4/96 (4.2%) C_{max}: 4/96 (4.2%)
  - For both metrics the distribution of *p* values followed closely Uniform [0,1]

*) **D'Angelo G, Potvin D, and J Turgeon**
Carry-over effects in bioequivalence studies
J Biopharm Stat 11, 35-43 (2001)

Nuisance: sequence effect

- These results could be con-firmed (20 published studies, 143 studies from BEBAC's database; AUC):
  - Significant sequence effects in 22/163 studies (13.5%)
- Significant sequence effects in properly planned studies should be considered a statis-tical artefact (significant results are obtained in α of studies)



Nuisance: sequence effect

- Conclusions
  - No valid procedure exists to correct for a true sequence/carry-over effect
  - A true sequence/carry-over is highly unlikely in a BE study if
    - the study is performed in healthy subjects,
    - the drug is not an endogenous entity, and
    - an adequate washout period (no predose concentrations) was maintained.
  - Testing for a sequence effect is futile…

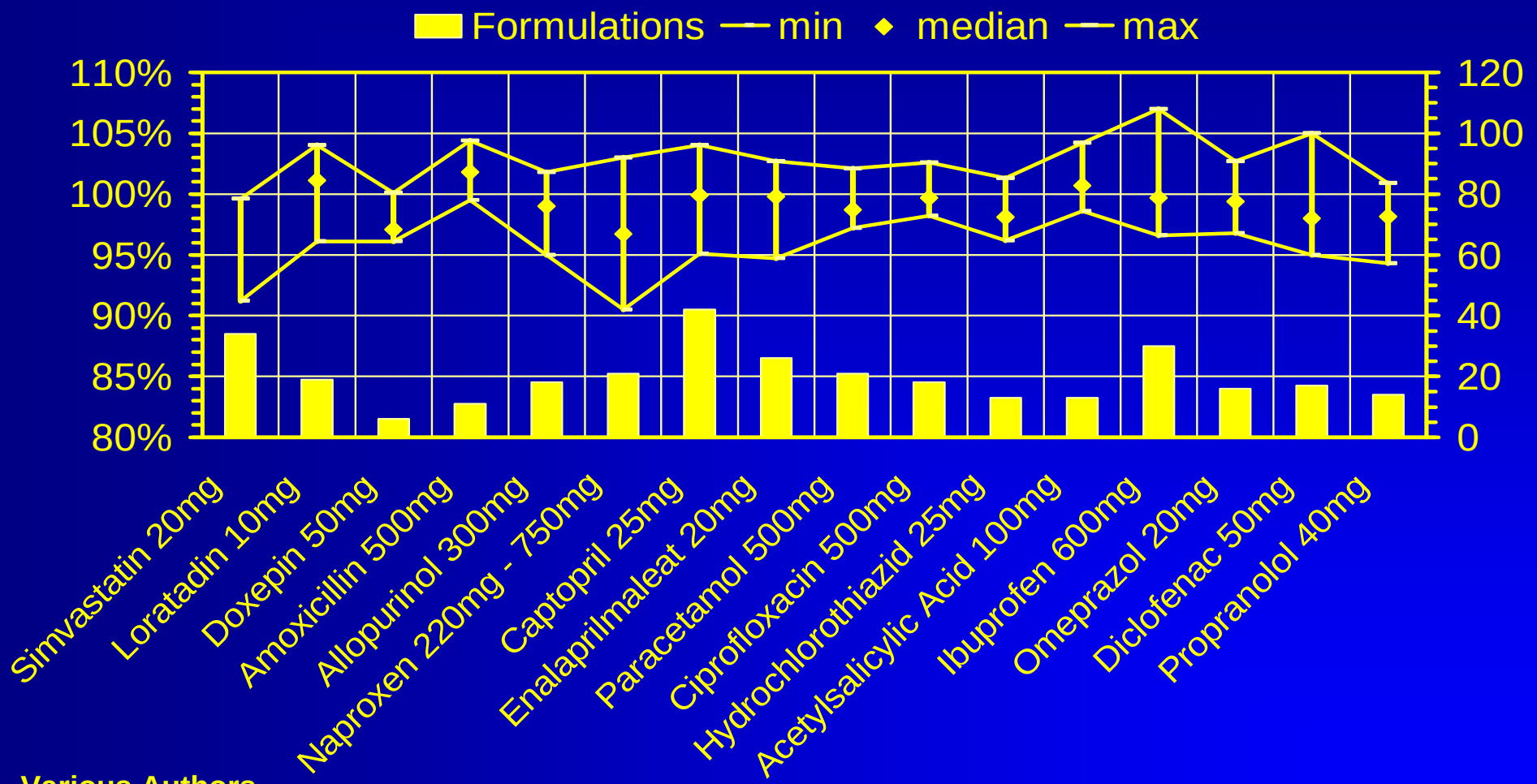
Nuisance: sequence effect

- Statistical analysis (EMEA Draft BE Guideline, 2008)
  - […] tests for difference and the respective confidence intervals for the treatment effect, the period effect, and the sequence effect should be reported for descriptive assessment. A test for carry-over should not be performed and no decisions regarding the analysis (e.g. analysis of the first period, only) should be made on the basis of such a test.
  - The potential for carry-over can be directly addressed by examination of the pre-treatment plasma concentrations in period 2 (and beyond if applicable). If there are any subjects for whom the pre-dose concentration is greater than 5 percent of the C_{max} value for the subject in that period, the statistical analysis should be repeated with those subjects excluded. Results from both analyses should be presented, but the analysis with the subjects excluded should be considered as primary.

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.

But acceptable for Innovators (Scale-Up)?

Cookbooks

Guideline Collection

http://bebac.at/Guidelines.htm

- Brazil (ANVISA)
  Legislation en **Legislação** pt
  - Implementation of Relative BA and BE Studies: Apr 2006 (HTML pt, HTML pt, ~~May 2003~~ HTML pt)
  - Pharmaceutical Equivalence / Dissolution: Sep 2004 (HTML pt, ~~May~~ HTML pt, ~~May 2003~~ HTML pt, ~~Mar 2002~~ HTML pt)
  - BA / BE: May 2003 (HTML en, HTML pt)
  - Exemption and Substitution of BE Studies: May 2003 (HTML en, HTML ~~2002~~ HTML pt)
  - Bioanalytical Method Validation: May 2003 (56kB PDF en, HTML pt, HTML pt)
  - Statistics for BA/BE Studies: May 2003 (48kB PDF en, HTML pt, ~~Mar~~ HTML pt)
  - Protocol of BE Studies: May 2003 (HTML en, HTML pt, ~~Mar 2002~~ HT
  - Report of BE Studies: May 2003 (HTML en, HTML pt)
  - List of Reference Products: Current (154kB PDF pt)
  - Rules / Technical Regulations for CROs: May 2003 (HTML en, HTML
    - Annex I: Certification for BA/BE Centers: (Application Form 395 ~~148kB DOC~~; Renewal Form 370kB DOC, ~~365kB RTF~~)
    - Annex II: Guidelines for Inspection at Centers of BA/BE of Medicines (~~DOC~~ pt)
    - Annex III: Certificate of Good Practices of BA/BE of Medicines (1kB GIF pt)
    - Annex IV: Form for Outsourcing of Phase for Assays of BA/BE of

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Guidelines & Guidance Documents

ICH | WHO | EMEA | DKMA | MEB | FDA | HPFB | NIHS | MCC
TGA | Medsafe | CDSCO | PAHO | ANVISA | Secr. de Salud | ANMAT
SFDA | MoH | ACCSQ | BPFK | FDA | HSA | KFDA | CDE | Swissmedic
MoH | MoH | OECD

Introduction Main topic of this collection is Bioavailability / (*in-vivo*-) Bioequivalence, although GCP/GLP, dissolution/BCS, pharmacokinetics, bioanalytics and -statistics are also covered to some minor extent.

All linked guidances/guidelines are in English, unless stated otherwise. Language codes are given according to ISO 639-1 (*i.e.*, English en, French fr, German de, Spanish es, Danish da, Portuguese pt, Japanese ja, Chinese zh, Arabic ar,...)

Although links to documents are considered current with 08 June 2008, you should always consult websites of the respective regulatory body for any updated versions.

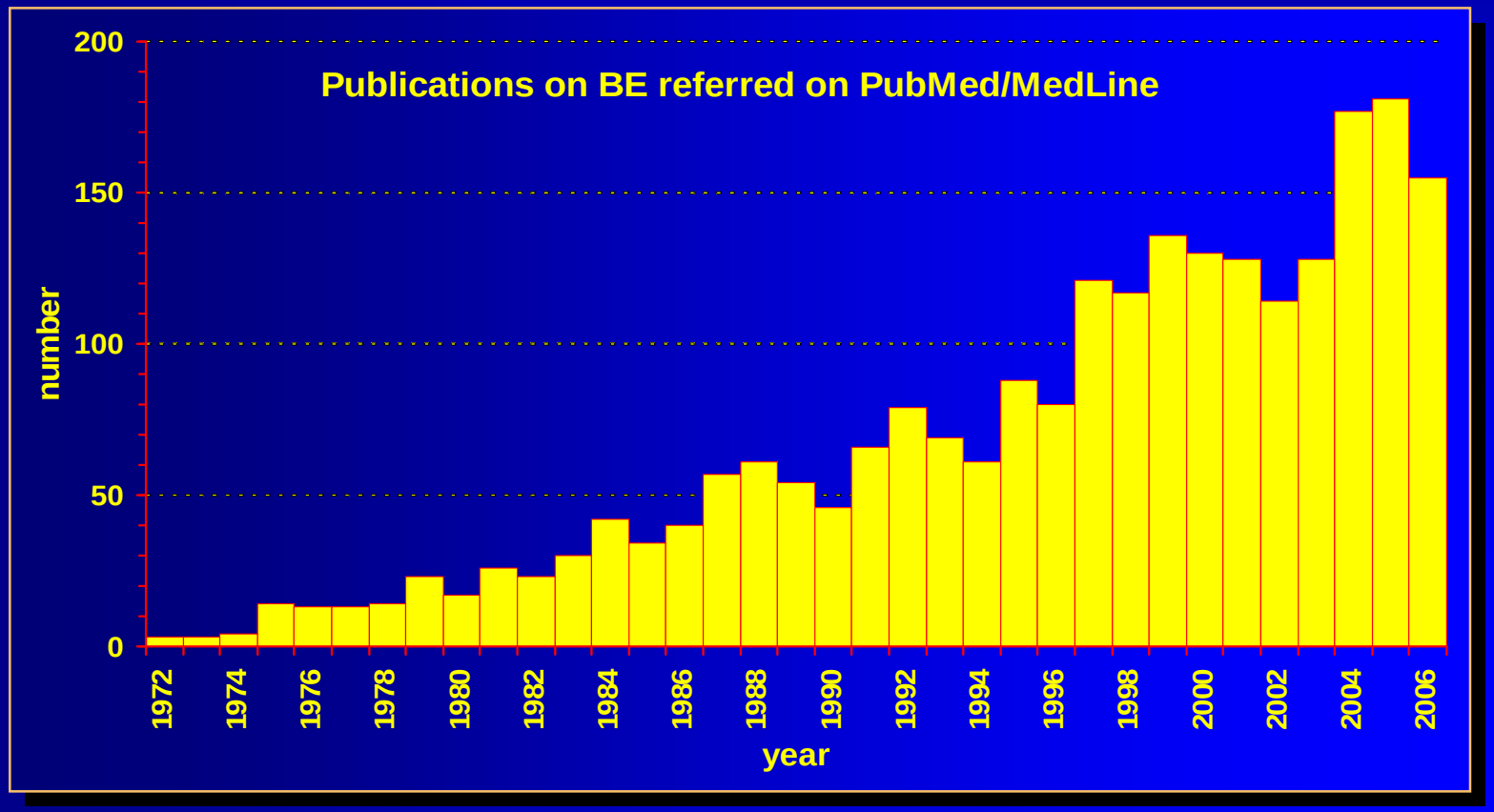
Documents superseded by newer versions are ~~striken through~~. While obsolete, previous versions are helpful in dealing with deficiency letters issued for older studies.

Documents published within the last two years are marked. Updates and additions in the last four months: →1, →2, →3, →4, →5.

If you encounter broken links or are acquainted with any missing / undated documents

Are we making Progress?

PubMed/MedLine: (bioequivalence) OR (comparative AND bioavailability),
Field: Title/Abstract, Limits: Humans, Publication Date



Are we making Progress?

- About 3 000 – 10 000 BE studies / year are conducted worldwide; only ~ 1 – 5% of them are published.
- Although a standard for publishing data of BE studies was already suggested in 1992,[1)]
  - a review in 2002 found only 17 complete data sets on AUC and 12 on C_{max}.[2)]
  - Since no 'real world' data are available, proposed methods (*e.g.*, reference-scaled ABE) rely entirely on simulations!
  - Studies seen by regulators are 'selection biased'.

1) **Sauter R, Steinijans VW, Diletti E, Böhm E and H-U Schulz**
Int J Clin Pharm Ther Toxicol 30/Suppl.1, S7-30 (1992)

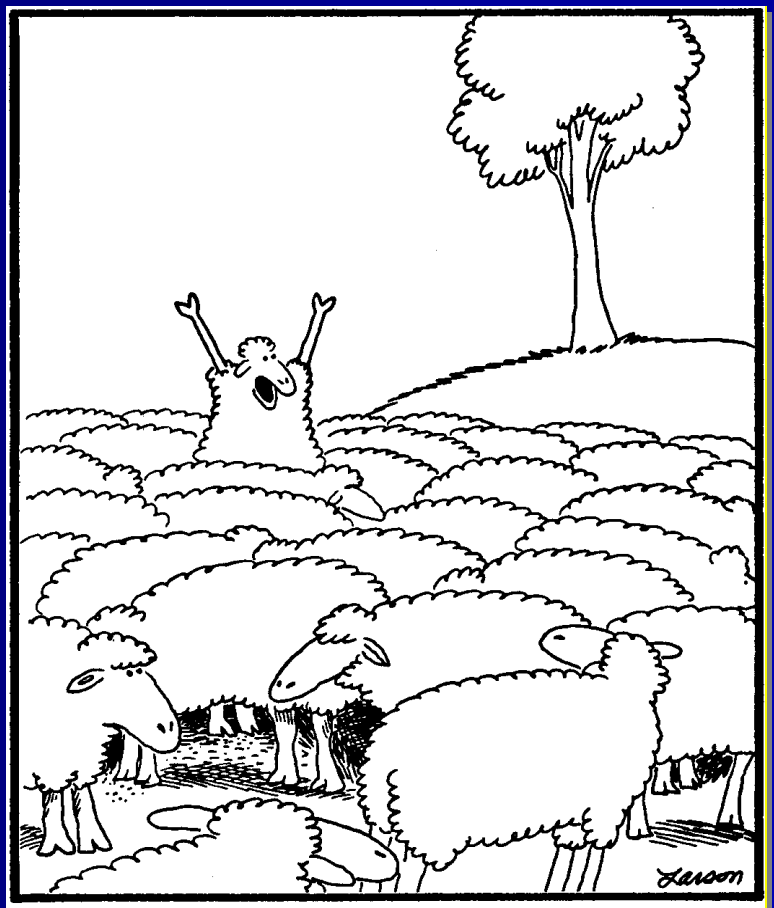
2) **Nakai K, Fujita M and M Tomita**
Int J Clin Pharmacol Ther 40, 431-438 (2002)

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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