Pitfalls in BA/BE-Studies

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Overview

- Plan studies keeping global acceptance in mind
- Avoid common design errors, both analytical and statistical
- Deal with inadequate profiles, missing data, and outlying subjects
- Work up the courage to adopt unusual proce-dures (*e.g.*, add on designs, nonparametric statistics, population PK…)

...to be remembered

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!*

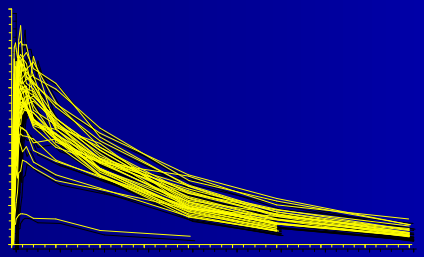
Leslie Z. Benet

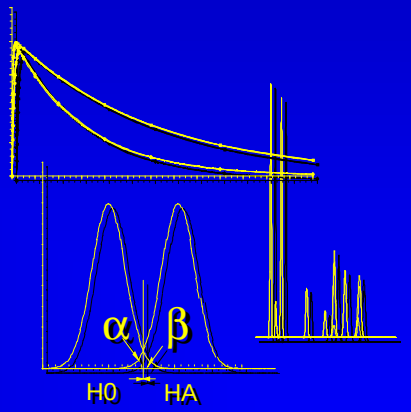
Assumptions

- General
- Pharmacokinetics
- Analytics
- Statistics

Assumptions (General)

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

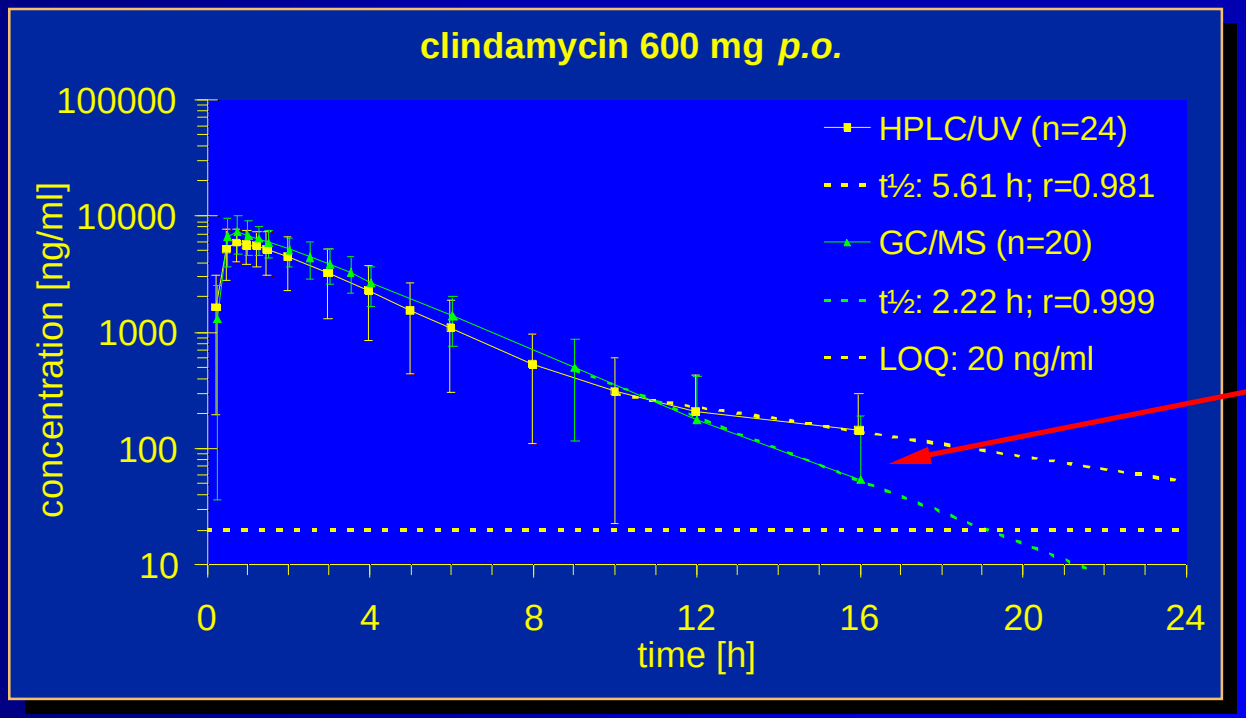
Assumption 2: $CL_1 = CL_2$

Assumptions (Analytics)

- Specifity
  - No coeluting compounds?
    - granted only for MS
    - highly probable for Fluorescence
    - UV?
  - Matrix effect? (LC/MS)
- Protein-Binding
  - Only total concentration (free+bound) generally measured

Case Study 1

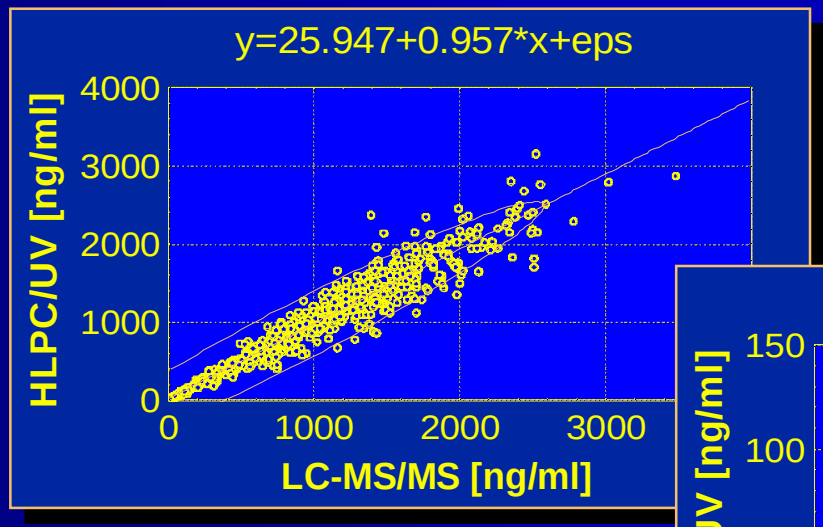
Cross-Validation

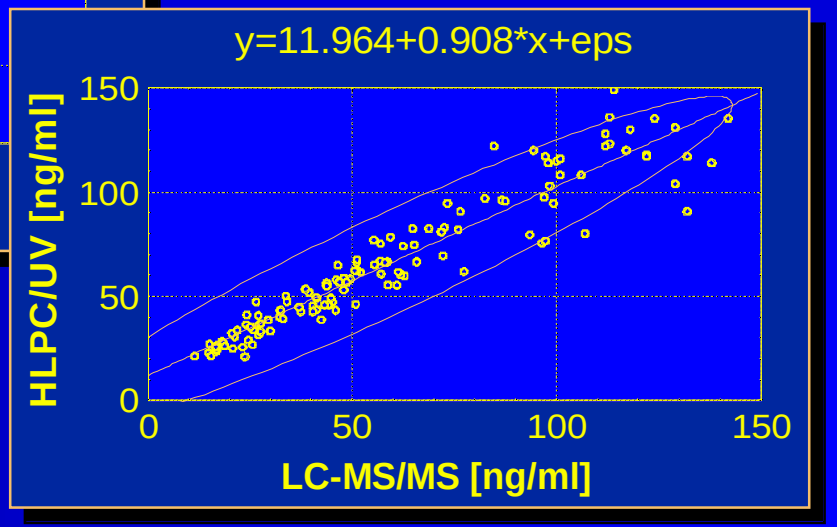


Identical LLOQ, but bias in lower concentration range?

Case Study 1

Cross-Validation



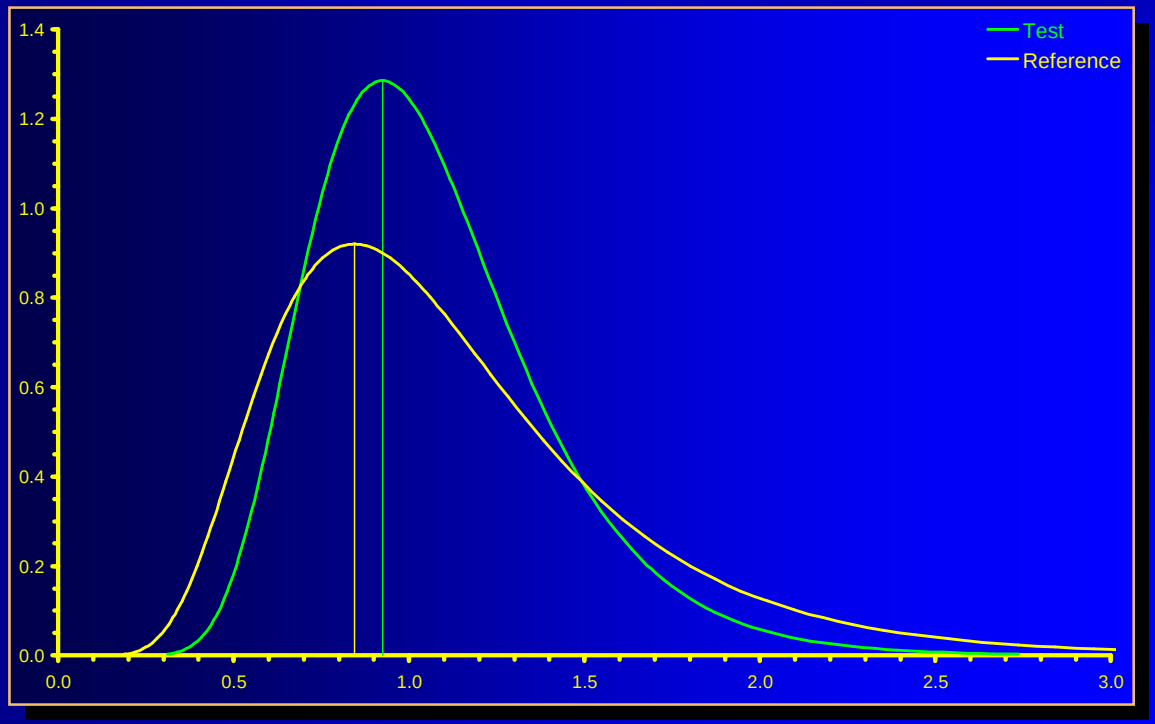


Bias in lower concentration range!

Assumptions (Statistics)

Distribution

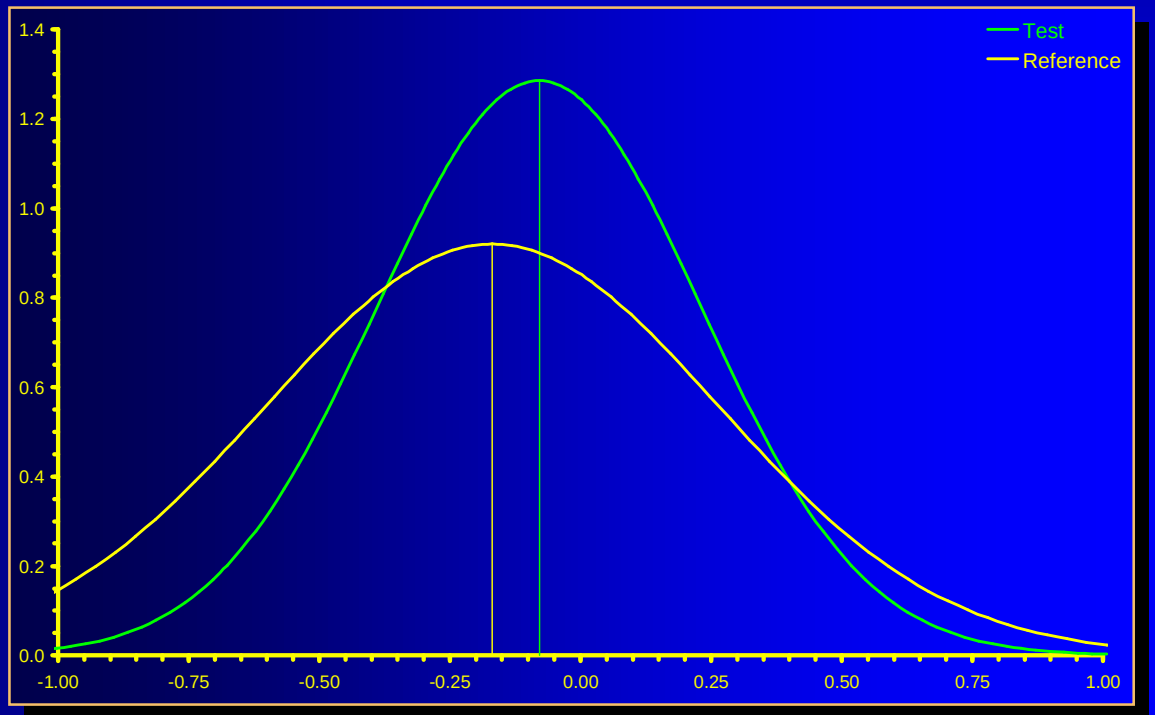
- IDD (Independent Identically Distribution)



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.
http://www.ich.org/MediaServer.jser?@_ID=485&@_MODE=GLB (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.

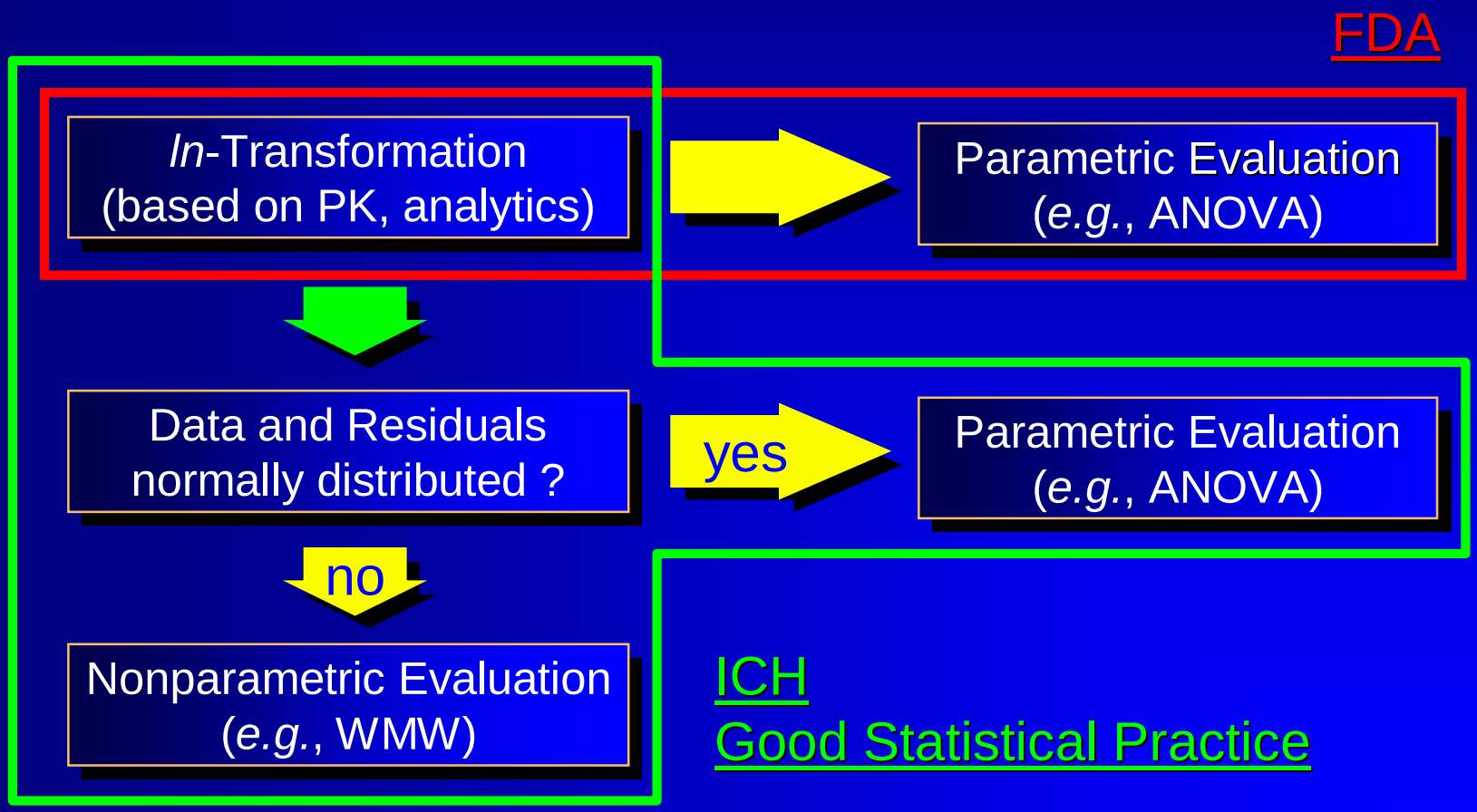
Jones, B. and M.G. Kenward; Design and Analysis of Cross-Over Trials.
2nd Edition, Chapman & Hall, Boca Raton, London, New York, Washington, D.C. (2003)

Global Harmonization?

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.
http://www.fda.gov/cder/guidance/3616fnl.pdf (January 2001)

Global Harmonization?



Global Acceptance?

- Canada
  Geometric Mean Ratio (PE) of C_{max} within 0.80–1.25 (*no* Confidence Interval)

  Maximum CV for BE within [0.80–1.25] for a sample size of 24

PE	84 %	85 %	87 %	90 %	95 %
CV_{max}	6.5 %	8.1 %	11.2 %	15.8 %	23.1 %

Anonymous (Health Canada, Therapeutic Products Directorate);
Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations Used for Systemic Effects (1992)
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/bio-a_e.pdf

Hauschke, D., Steinijans, V.W., Diletti, E. and M. Burke;
Sample Size Determination for Bioequivalence Assessment Using a Multiplicative Model.
J. Pharmacokin. Biopharm. 20/5, 557-561 (1992)

Global Acceptance?

- Extended Acceptance Range for C_{max} (*e.g.*, 0.75–1.33), if justified based on Safety and Efficacy Grounds, and specified in the Study Protocol
  - ✓ EU, WHO, Australia, NZ, Turkey, Malaysia, Taiwan, ASEAN States, Argentina
  - ✓ RSA: Standard for all drugs (no justification)
  - ✓ Japan, Switzerland (even for AUC)
  - – FDA, Brazil, India

Global Acceptance?

- Outliers
  - 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 justfied, *e.g.*,
      - Lacking compliance (subject did not take the medication),
      - Vomiting (up to $2 \times t_{max}$ for IR, at all times for MR),
      - Analytical problems (*e.g.*, interferences in chromato-graphy);
      - not acceptable if only based on statistical grounds.
    - Remedy: Application of a valid statistical method!
    - Drawback: Regulatory acceptance?

Global Acceptance?

- Outliers
  - Parametric methods are very sensitive to outliers
    - Optional: stay with the parametric method, but
      - evaluation of both the Full Data Set, and the Reduced Data Set (outliers exluded), and
      - discuss influence on the outcome of the study.

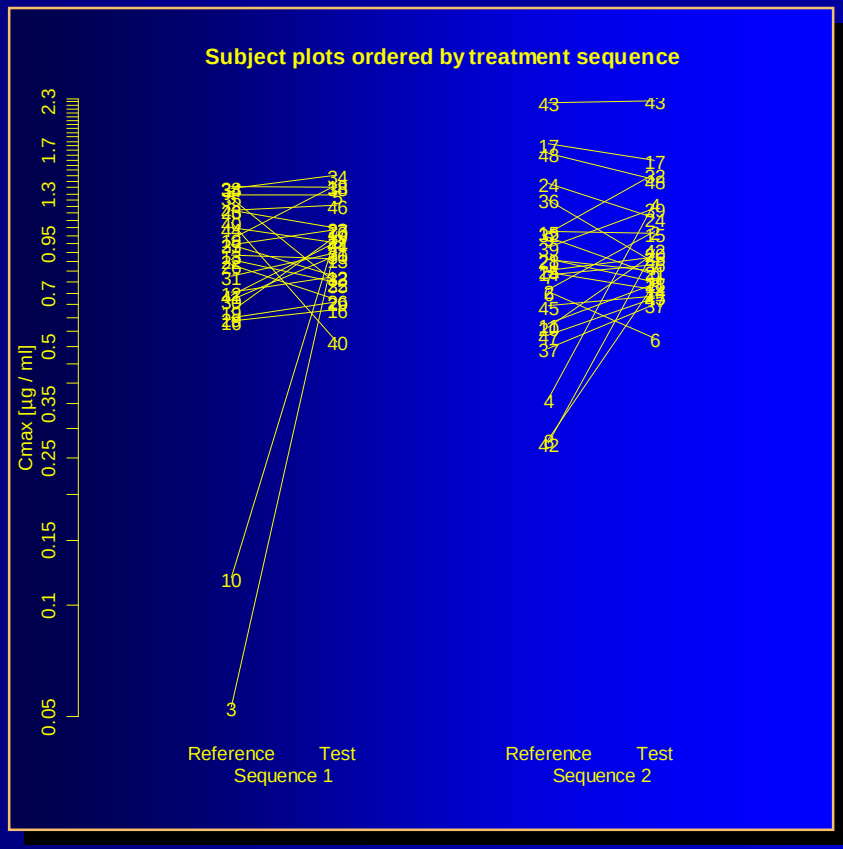
Case Study 2

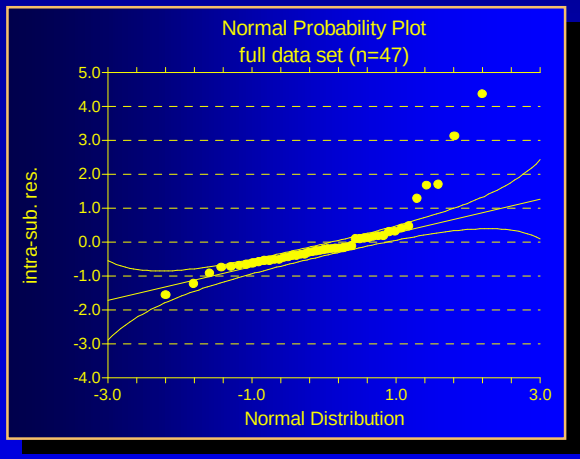
- Proton Pump Inhibitor (trt. of peptic ulcer)
  - BE study
  - Deviations from Normality expected
  - 47 m subjects, fasting
  - test/reference 30 mg DR capsule
- Analytics
  - validated HPLC method
  - LLOQ 50 ng/ml

Case Study 2

- Statistics
  - ANOVA, but
    - Graphical Checks of Residuals
      - Stem-Leaf, Box-Plot, Normality-Plot
    - Shapiro-Wilk test for Normality of
      - *intra*-subject Residuals
      - *inter*-subjects Residuals
      - if p_w<0.10 → Nonparametric Evaluation (Wilcoxon-Mann-Whitney)
- Acceptance Range for C_{max} 0.75–1.33

Case Study 2





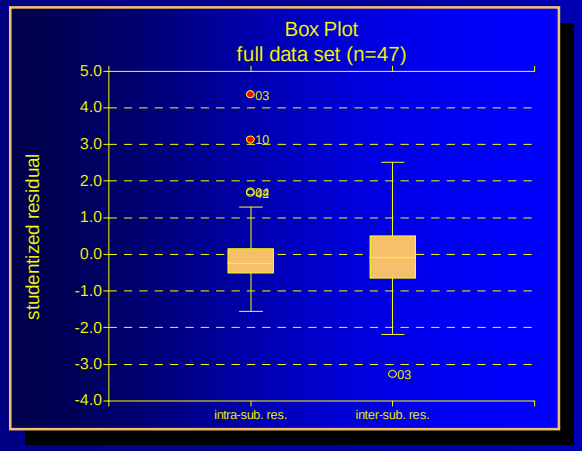
Independent Identically Normal Distribution?

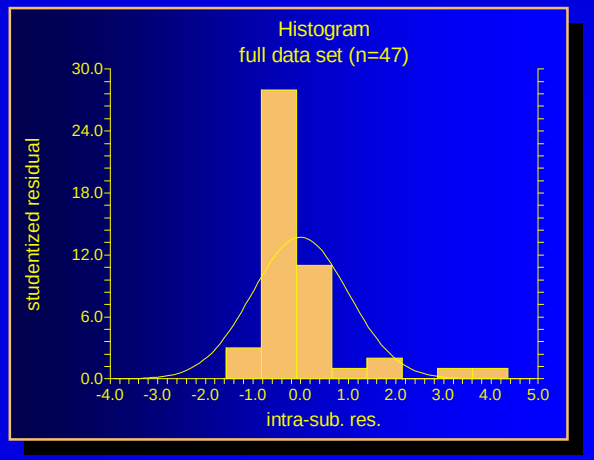
Requirement for ANOVA!

Case Study 2

Normality Tests of *intra*-subject residuals

Test	Value	Probability	Decision (5%)
Shapiro-Wilk W	0.7339928	<0.000001	Reject normality
Anderson-Darling	3.98384	<0.000001	Reject normality
Martinez-Iglewicz	4.224289		Reject normality
Kolmogorov-Smirnov	0.2312414		Reject normality
D'Agostino Skewness	5.1629	<0.000001	Reject normality
D'Agostino Kurtosis	4.1551	0.000033	Reject normality
D'Agostino Omnibus	43.9204	<0.000001	Reject normality





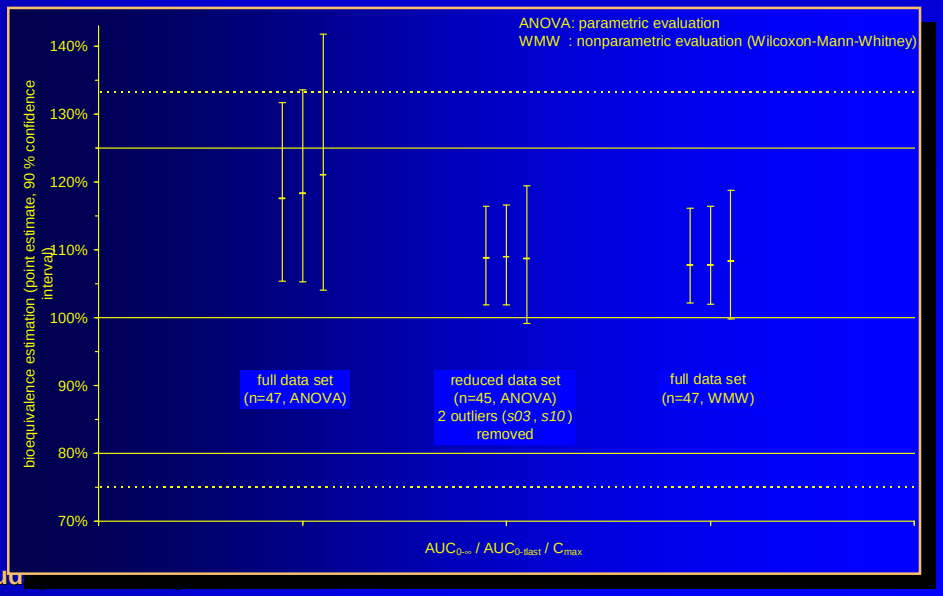
Case Study 2

- Results: Nonparametric (Per Protocol)
  - $AUC_{0-\infty}$ 107.7 % [102.2 % – 116.1 %]
  - AUC_{0-t} 107.7 % [102.0 % – 116.4 %]
  - C_{max} 108.3 % [99.8 % – 118.8 %]
- Deficiency Letter:
  - BE not assessed by ANOVA
  - CI for C_{max} calculated by ANOVA outside 0.80–1.25
  - Lacking Justification and valid Explanation of Nonnormality

Case Study 2

- ANOVA (reduced Data Set, n=45)
  - $AUC_{0-\infty}$ 108.8 % [101.8 % – 116.4 %]
  - AUC_{0-t} 108.9 % [101.8 % – 116.7 %]
  - C_{max} 108.6 % [99.1 % – 119.4 %]

…so what?

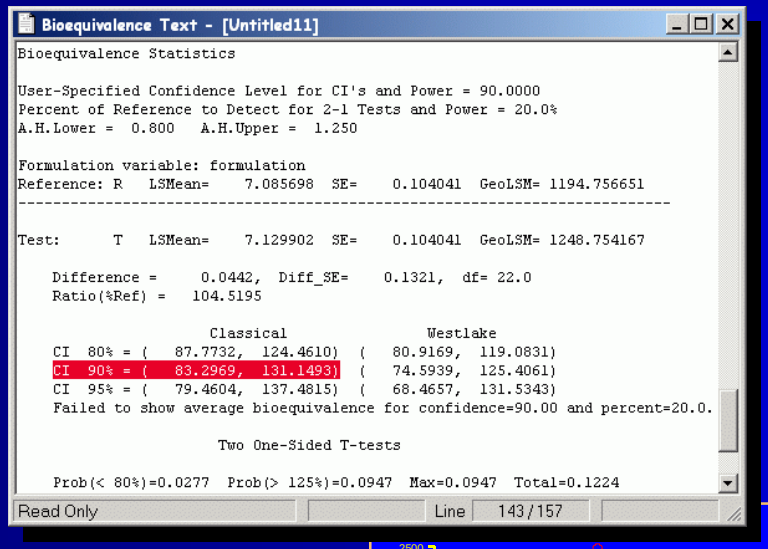


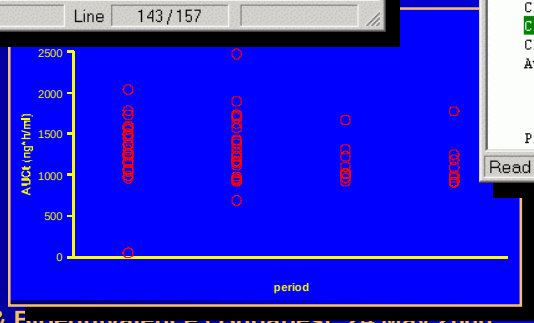
Example

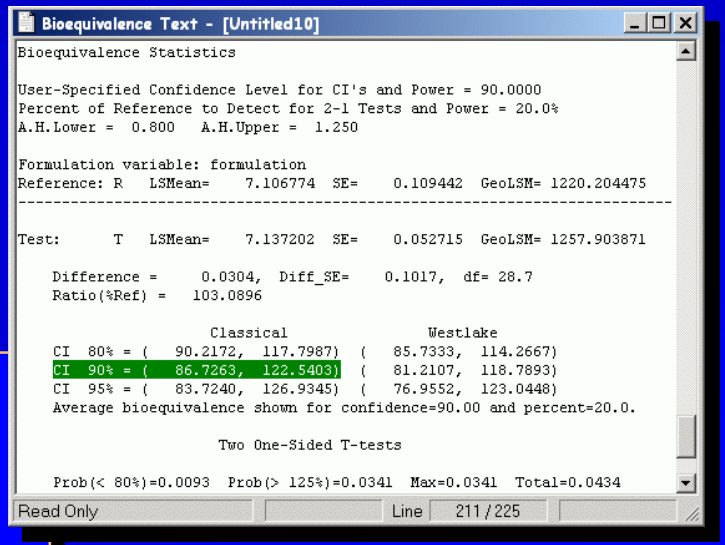
- Exclusion of Outliers / Re-testing of Subjects
  - Nonparametric methods are sensitive to Outliers
    - If you suspect a product failure of the reference formulation, you may consider Re-testing;
    - the outlying subject should be re-tested,
      - at least with the reference,
      - preferably with both the test and reference.
    - Include at least five subjects, who showed 'normal' responses in the main study (*i.e.,* size of re-tested group ≥6 or 20 % of subjects, whichever is bigger).
    - Expect questions from Regulators anyway (although sometimes accepted by the FDA, not covered in any guideline; the statistical evaluation is not trivial…)

Example

- Exclusion of Outliers / Re-testing of Subjects







Global Acceptance?

- Some National Guidelines are *very closely* followed by other countries:
  - USA
    - ➔ Brazil, Saudia Arabia
  - EU
    - ➔ South Africa, Turkey, Malaysia, ASEAN States, Australia: EU-guidelines adopted

Global Acceptance?

- One should not never rely on the first look, traps are already set in the back…
  - Analytical Method Validation must show lack of any interferring substance(s) in blank sample matrix (plasma) from six different sources.
    Rule applies on this planet, except in…
    - Brazil (ANVISA)
      …where four 'normal' plasma samples, one sample of haemolytic plasma, and one sample of lipaemic plasma must be included in the Validation.

Global Acceptance?

- Other National Guidelines represent an independent approach, *e.g.*,
- Japan
  - Guidelines follow an interwoven network of fasting/fed BE studies, and dissolution testing.
    - It is practically impossible to get an approval with BE studies which were not designed especially for Japan.
    - CROs in Saõ Paulo may be an option (Japanese population ~2Mio)…

Global Acceptance?

- Truncated Areas (*e.g.*, $AUC_{0\text{-}72h}$) for Drugs with long elimination half-lives
  - ✓ EU, WHO, Japan, Brazil, RSA, Taiwan, ASEAN States
  - ± USA, India: Acceptable, *but*: For drugs demonstrating high intrasubject variability in distribution and clearance, […] sponsors and/or applicants should consult the appropriate review staff.
  - New Zealand, India: The use of truncated AUCs, […] is undesirable but it may be unavoidable in certain circumstances such as in the presence of enterohepatic recycling where the terminal elimination rate constant cannot be calculated accurately.

Global Acceptance?

- Drugs with a narrow therapeutic range
  - USA, Japan: No difference to other drugs
  - WHO, EU, NZ, India: 90 % CI
    Acceptance range may be tightened
  - RSA: 90 % CI within 0.80–1.25 (C_{max})
  - Brazil: 95 % CI within 0.80–1.25
  - Canada: No different procedure given in guideline, but considering new procedure
    AUC: 90 % CI within 0.90–1.12
    Cmax: 90 % CI within 0.80–1.25

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-gpsa/pdf/prodpharma/crit_dose_e.pdf (5 Jul 2005)

Global Acceptance?

- Fed Studies
  - USA: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces (120 g) of hash brown potatoes and 8 ounces (240 ml) of whole milk. Substitutions in this test meal […] similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and *viscosity*.
  - Canada: = USA (but no substitutions)

    http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/fedstate_sujetsjeun_e.pdf

Global Acceptance?

- Add on Designs (*e.g.*, uncertain sample size estimate, ethical reasons)
  - ✓ Canada: If BE not shown, additional subjects are included; *F*-test (equality of variances), pooled analysis. No α-adjustment.
  - ✓ Japan: 2^{nd} part with sample size $\geq 1^{st}$ part / 2
  - ✓ RSA: max. sample size must be stated *a-priori*
  - ✓ NZ: Group Sequential Design (with α-adjustment)
  - – USA
  - ± EU: Evaluation of first part by an independent statistician (CV only!). Not covered in NfG.

Global Acceptance?

- Add on Designs
  - ± EU: Group Sequential Design
    - Group sequential designs are standard in clincial research.
    - Although discussed at BioInternationals ’89 to ’96, no concensus was reached.
    - Personal Experience:
      - A proposed method*) was not accepted in the planning phase (3 cases Germany).

*) L.A. Gould;
Group Sequential Extension of a Standard Bioequivalence Testing Procedure.
J. Pharmacokin. Biopharm. 32(1), 57-86 (1995)

Global Acceptance?

- Add on Designs
  - ± EU: Group Sequential Design
    - Personal Experience:
      - Evaluation of first part by an independent statistician (CV only!), performance of a second part, evaluation of pooled data without Bonferroni-correction – 90 % CI (2 cases Germany, 1 case France).
      - May be a reasonable approach, because Add on Designs are in practice in Canada (since 1991), and Japan (since at least 1997).

Global Acceptance?

- Highly Variable Drugs / Drug Products (intra-subject variability >30 %)
  - ✓ USA: Replicate Design recommended.
  - ± EU: […] under certain circumstances […] alternative well-established designs could be considered such as […] replicate designs for substances with highly variable disposition.
  - ± NZ: […] studies in which treatments are replicated within each subject, may improve discriminatory power for highly variable medicines.
  - ? Reference Scaled Average Bioequivalence (only stated in South African Guidelines).

Global Acceptance?

- Study Designs for more than two formulations
  - Advantages
    - Allows to choose between two ore more candidate test formulations.
    - Comparison of a test formulation with several references.
    - Standard design for establishment of Dose Proportionality.

Global Acceptance?

- Study Designs for more than two formulations
  - Disadvantages
    - Not mentioned in any Guideline (except Brazil's ANVISA).
    - Statistical analysis more complicated (especially in the case of drop outs).
    - May need measures against multiplicity (increasing the sample size).

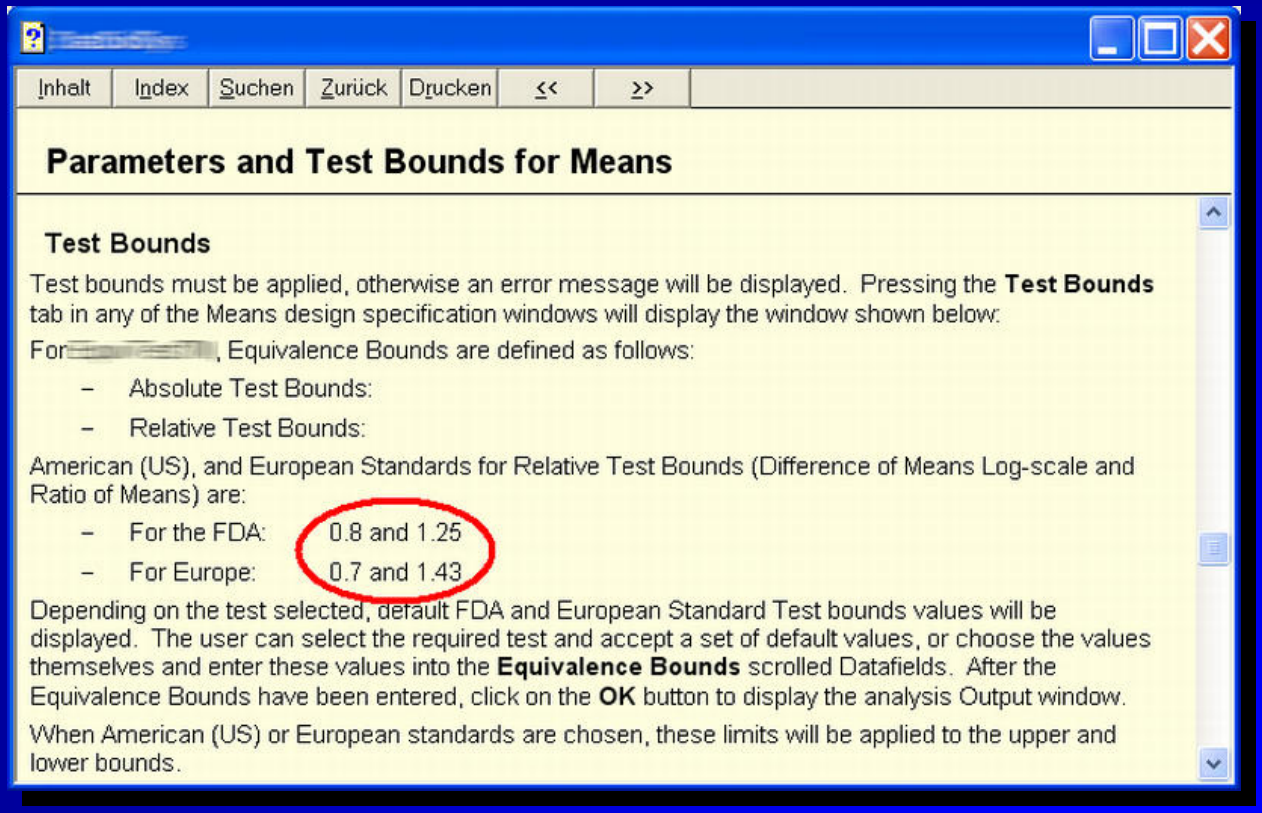
Global Acceptance?

- Study Designs for more than two formulations
  - Bonferroni-correction needed if more than one formulation will be marketed (for 3 simultane-ous comparisons without correction patient's risk is increased from 5 % to 14 %).

k	$P_{\alpha=0.05}$	$P_{\alpha=0.10}$	α_{adj}	$P_{\alpha adj}$	α_{adj}	$P_{\alpha adj}$
1	5.00%	10.00%	0.0500	5.00%	0.100	10.00%
2	9.75%	19.00%	0.0250	4.94%	0.050	9.75%
3	14.26%	27.10%	0.0167	4.92%	0.033	9.67%
4	18.55%	34.39%	0.0125	4.91%	0.025	9.63%
5	22.62%	40.95%	0.0100	4.90%	0.020	9.61%
6	26.49%	46.86%	0.0083	4.90%	0.017	9.59%

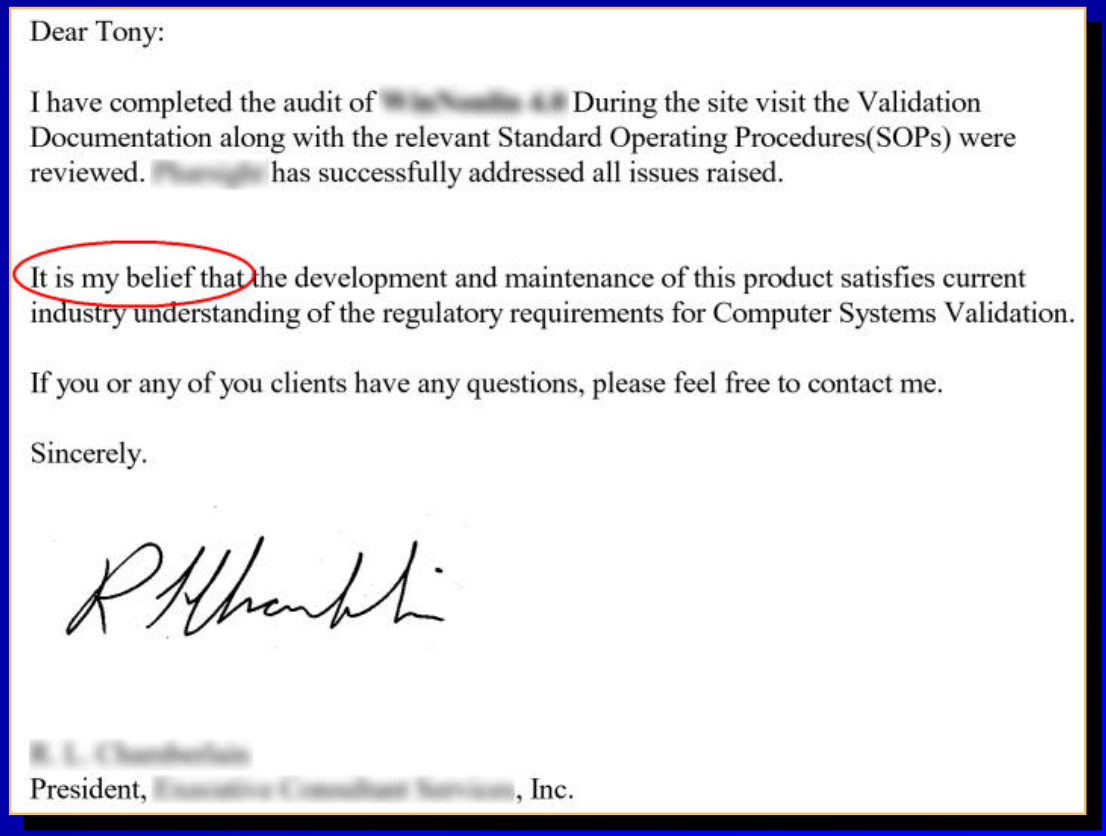
Software

validated,
sure,
but…



Software

strong beliefs…



Dear Tony:

I have completed the audit of [redacted] During the site visit the Validation Documentation along with the relevant Standard Operating Procedures(SOPs) were reviewed. [redacted] has successfully addressed all issues raised.

It is my belief that the development and maintenance of this product satisfies current industry understanding of the regulatory requirements for Computer Systems Validation.

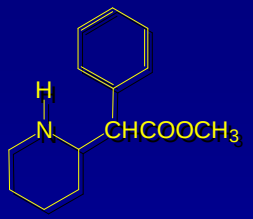
If you or any of you clients have any questions, please feel free to contact me.

Sincerely.

[redacted]
President, [redacted], Inc.

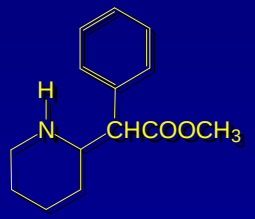
Inadequate Profiles

- If possible, plan a blinded Plausibility Review of analytical data by a Pharmacokineticist as early as possible
  - Consistency within subjects!
  - Pre-dose concentrations?
  - Rising values in the terminal phase?
  - Fluctuating values at C_{max}?
  - Re-analysis; values confirmed/rejected?



Case Study 3

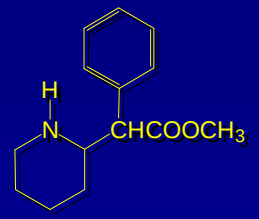
- Central stimulant (trt. of ADHD)
  - Development of a formulation combining IR and DR characteristics
  - 24 m+f subjects, fasting
  - test 10 mg IR + 10 mg DR
  - reference 20 mg oral solution
- Analytics
  - validated LC/MS-MS method
  - LLOQ 200 pg/ml



Case Study 3

- Plausibility Review
  - LLOQ *really* 200 pg/ml ?
  - in some subjects presumed to be >1.5 ng/ml
- LC/MS-MS stopped after 12 subjects
- Development of a GC/MS-method
  - stable isotope internal standardization
  - LLOQ 143 ng/ml

Case Study 3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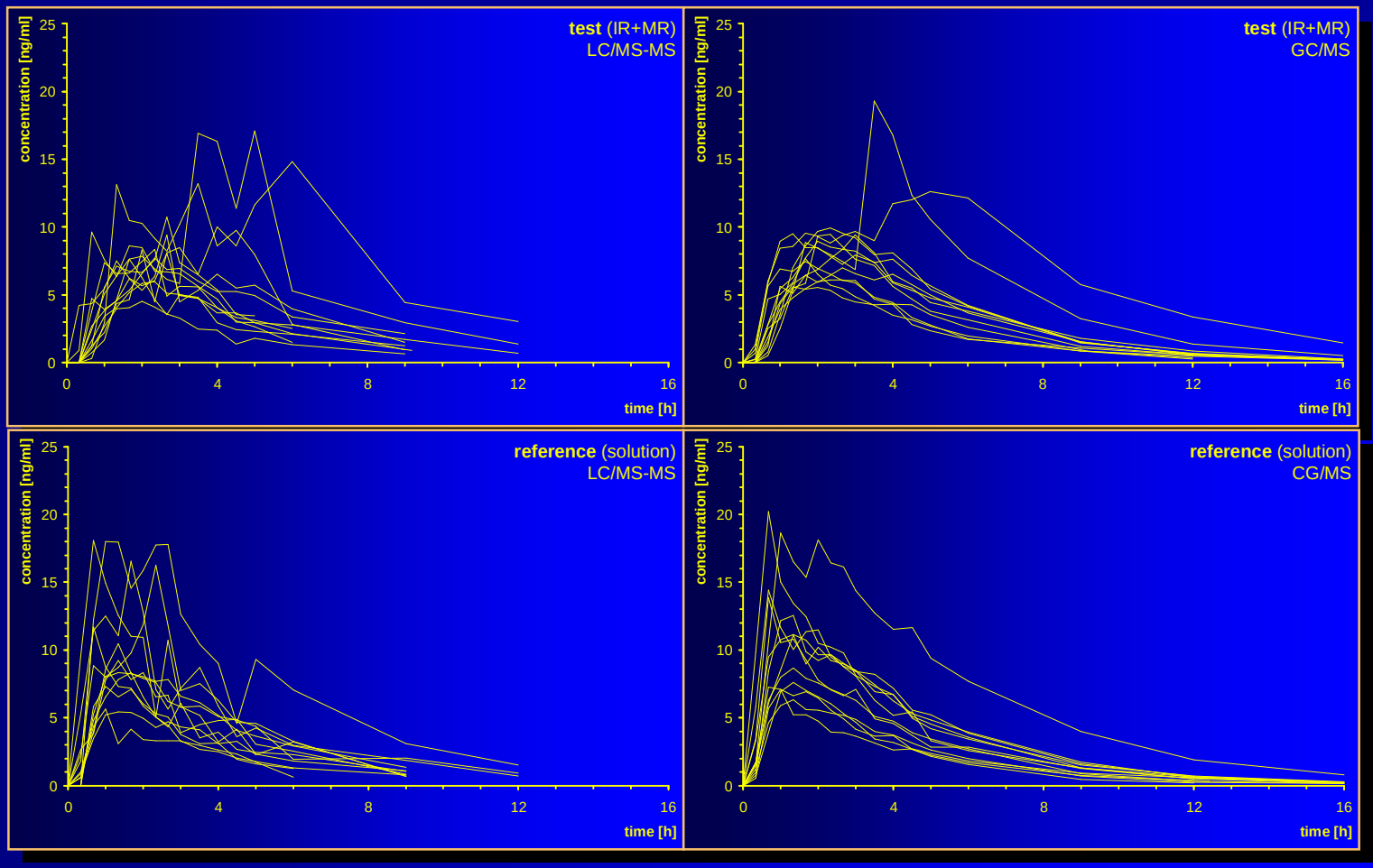
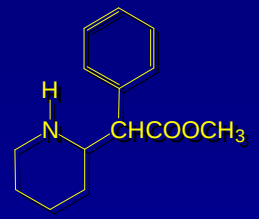
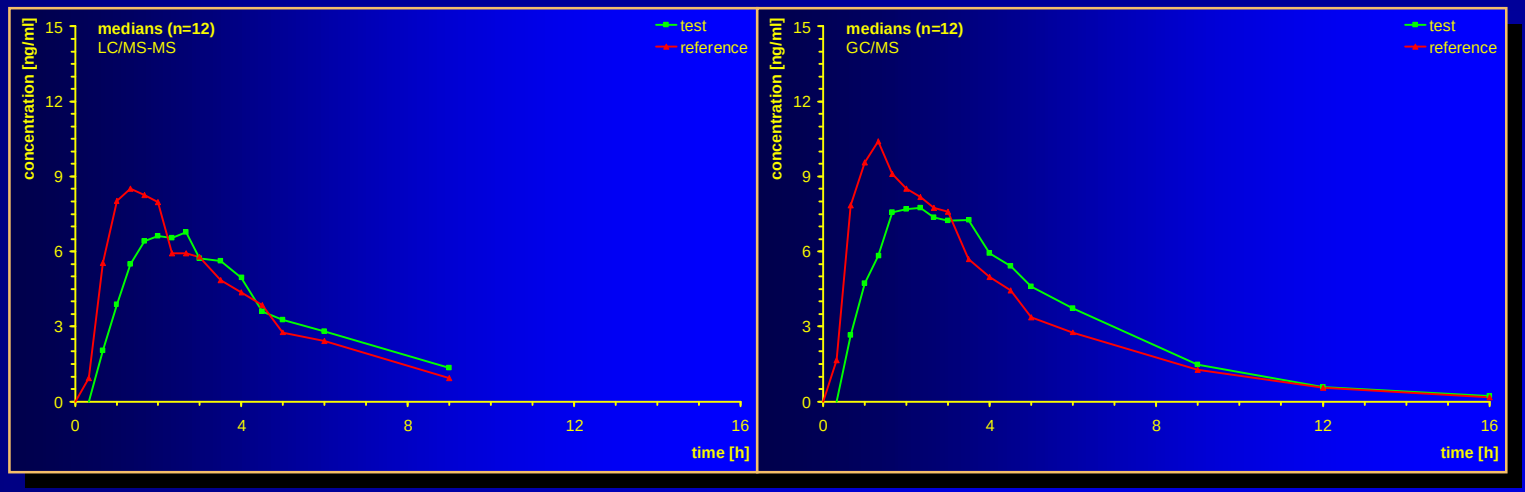
N
CHCOOCH3


test (IR+MR)
LC/MS-MS
concentration [ng/ml]
time [h]
test (IR+MR)
GC/MS
concentration [ng/ml]
time [h]
reference (solution)
LC/MS-MS
concentration [ng/ml]
time [h]
reference (solution)
CG/MS
concentration [ng/ml]
time [h]

Case Study 3

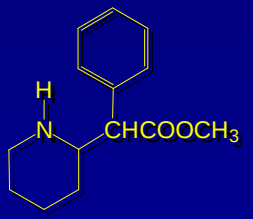


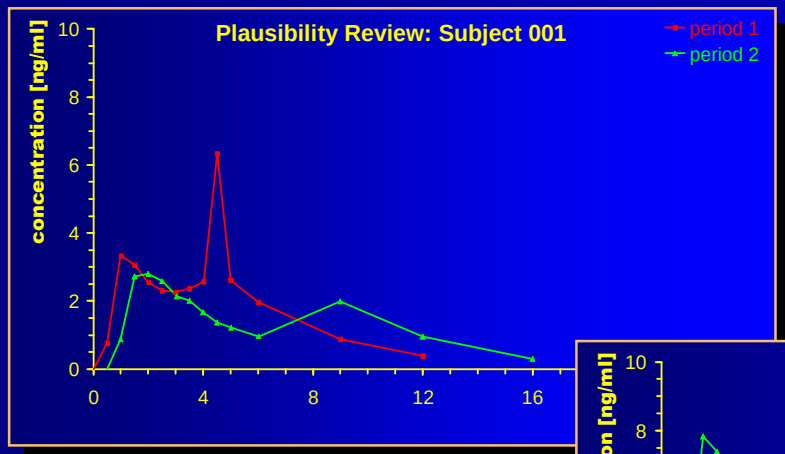


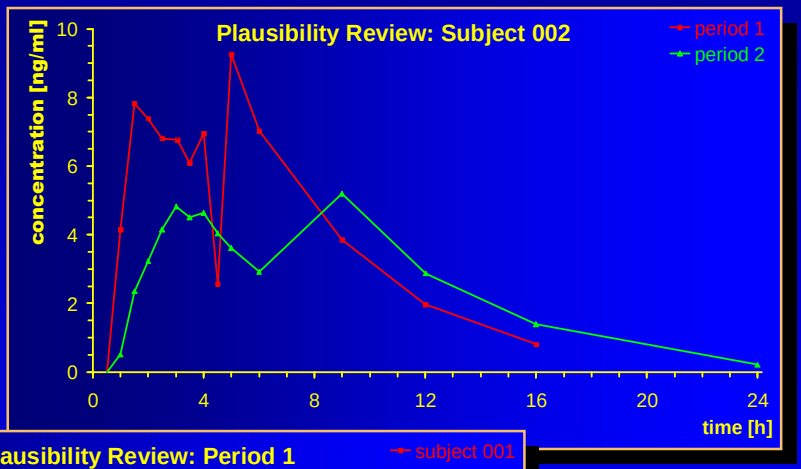
LC/MS-MS						
	statistic	CL-lo	CL-hi	PE	CV	CI
AUC	ANOVA	92.6%	114.4%	102.7%	14.1%	21.8%
	WMW	91.2%	116.2%	103.0%	–	24.9%
C_{max}	ANOVA	78.6%	99.8%	88.4%	16.5%	21.2%
	WMW	76.8%	97.4%	86.9%	–	20.6%
t_{max}	WMW	+0.58	+2.50	+1.33	–	1.92

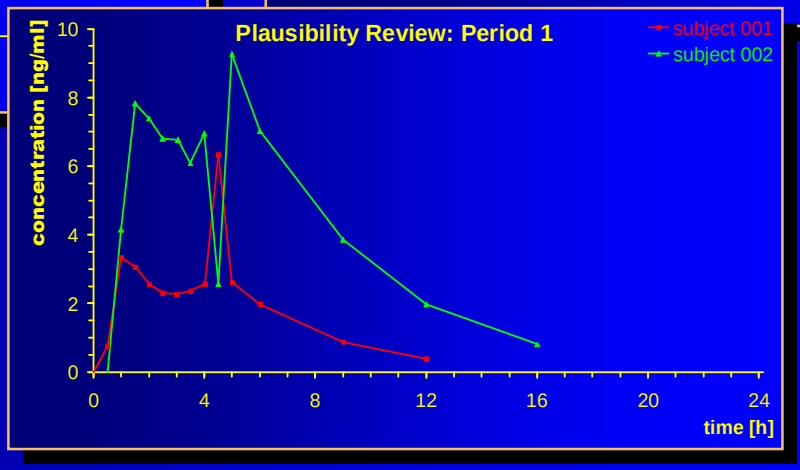
GC/MS						
	statistic	CL-lo	CL-hi	PE	CV	CI
AUC	ANOVA	93.8%	110.3%	101.6%	10.8%	16.5%
	WMW	93.2%	112.3%	102.6%	–	19.1%
C_{max}	ANOVA	71.1%	96.4%	82.5%	20.8%	25.3%
	WMW	72.6%	97.8%	81.4%	–	25.2%
t_{max}	WMW	+0.50	+2.17	+1.00	–	1.67

Case Study 3







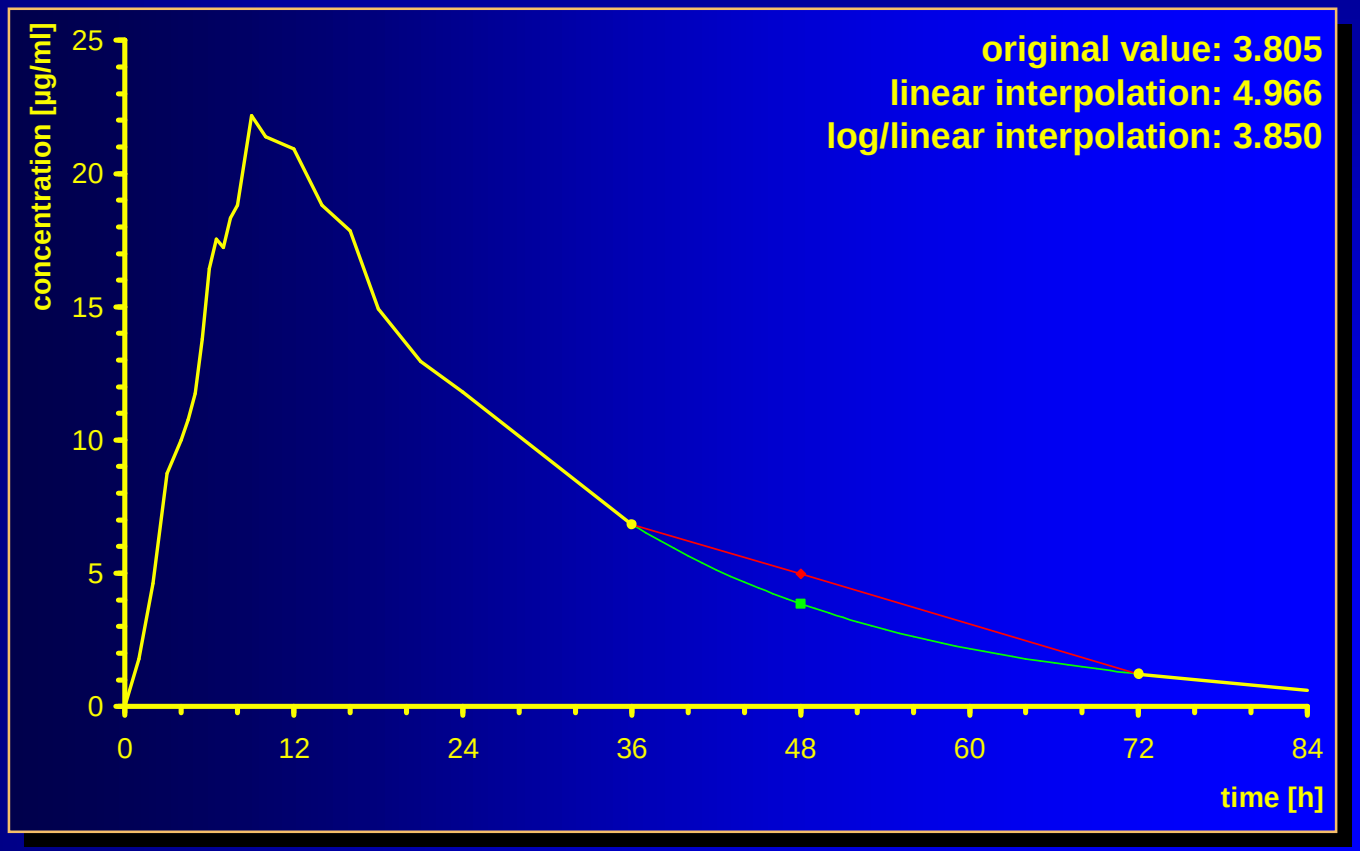


Suspected sample mix-up after centrifugation between two subjects; although not documented, verified by clinical laboratory values (γ-GT, albumine)…
→ Exchange of values justified.

Missing Data

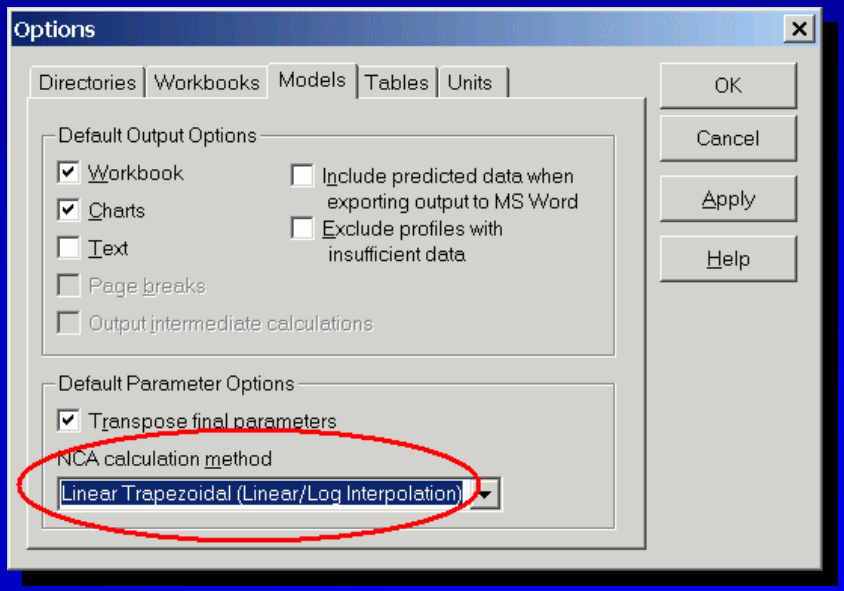
- Procedure for Imputation must be stated in the Protocol:
  - in the Absorption Phase ($t<t_{max}$) by *linear* Interpolation of two adjacent values
  - in the Elimination Phase ($t \geq t_{max}$) by *log/linear* Interpolation of two adjacent values
    - estimated value must not be used in the calculation of the terminal half live!

Missing Data



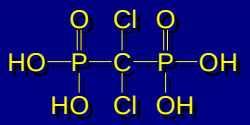
Missing Data

Recommended Procedure may not be the ‘default’ in your software (has to be actively set, *e.g.*, in WinNonlin 4.x)



Unusual Procedures

- Sometimes it is infeasible to show BE from a 'conventionally' designed study
  - Highly Variable Drugs / Drug Products: Replicate Designs, Multiple Dose
  - Drugs with long half lives: Truncated Areas, Parallel Groups
  - Antineoplastics for Children: Population PK



Case Study 4

- Clodronate (treatment of Paget's disease)

  Castrén-Kortekangas *et al.*; Pooling of Clodronate Urinary Excretion Data: A New Pharmacokinetic Method to Study Drugs with Highly Variable Gastrointestinal Absorption. J. of Bone and Mineral Res. 13, 1, 66-71 (1997)

  - BE study
  - very low and highly variable absorption (highly soluble, highly ionized)
  - 24 f+m subjects, multiple dose (7 days)
  - test 800 mg tablet / ref. 2×400 mg capsule
  - target parameter: $Ae_{0\text{-}t}$ (day 7)

Case Study 4

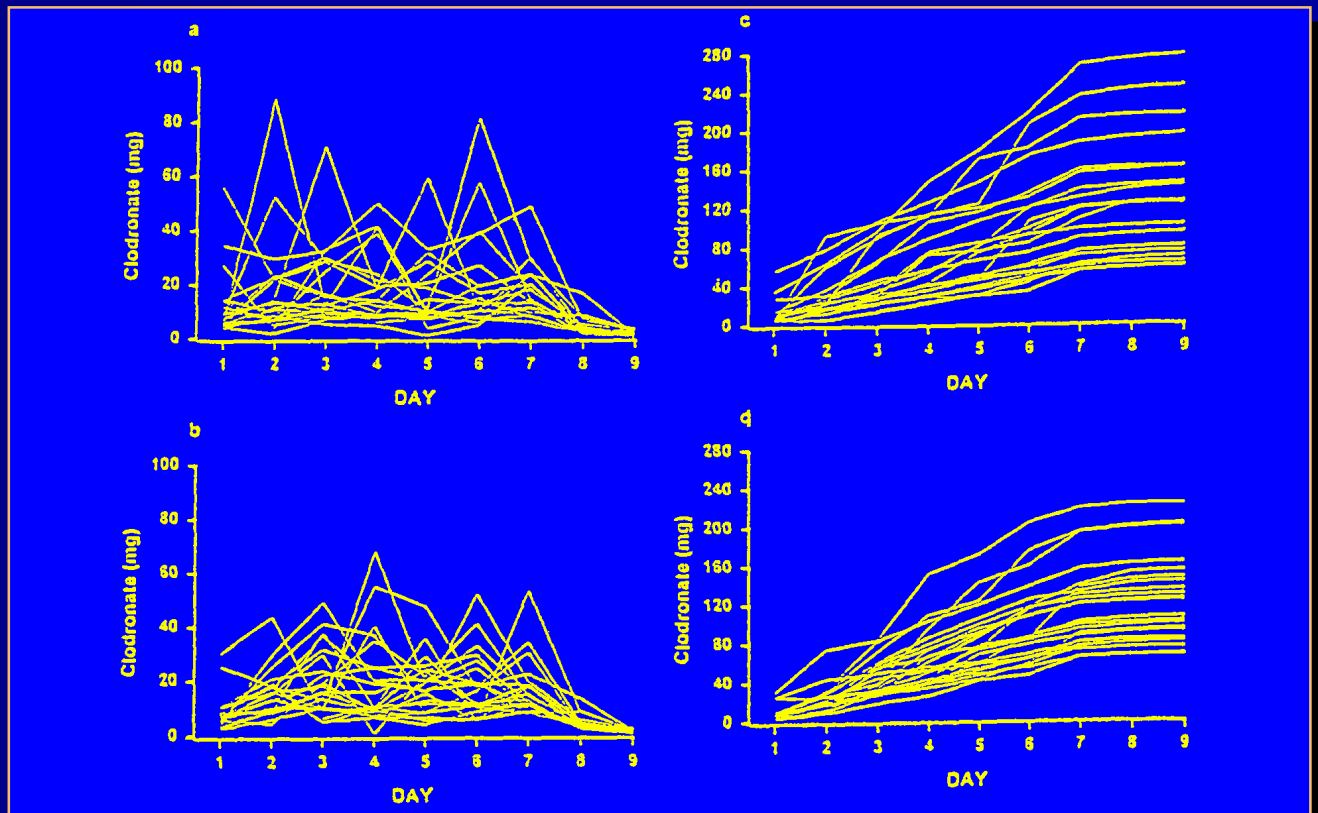


FIG. 4. Individual day-to-day urinary excretion of clodronate (a, b) and individual cumulative (day 1, days 1–2, days 1–3, etc.) urinary excretion of clodronate (c, d). Two upper panels (a, c) present 800 mg tablet data, the lower panels (b, d) demonstrate 2 × 400 mg capsule data.

Case Study 4

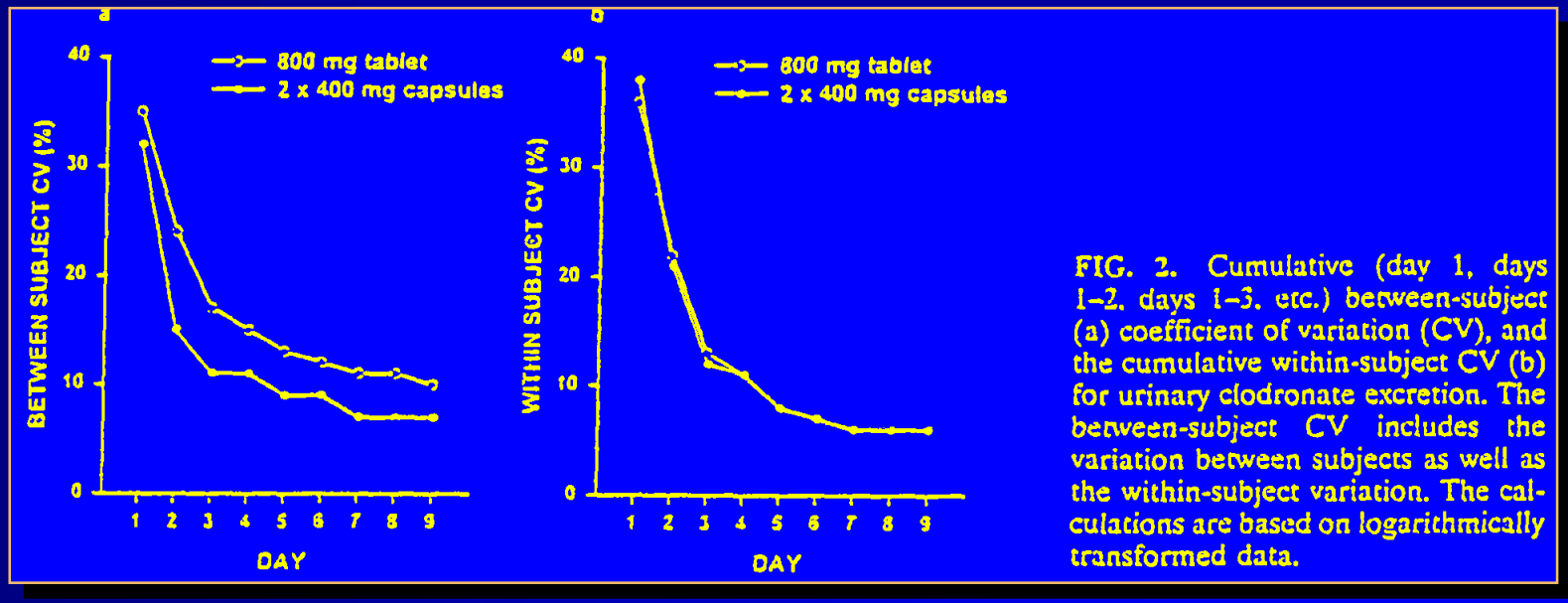
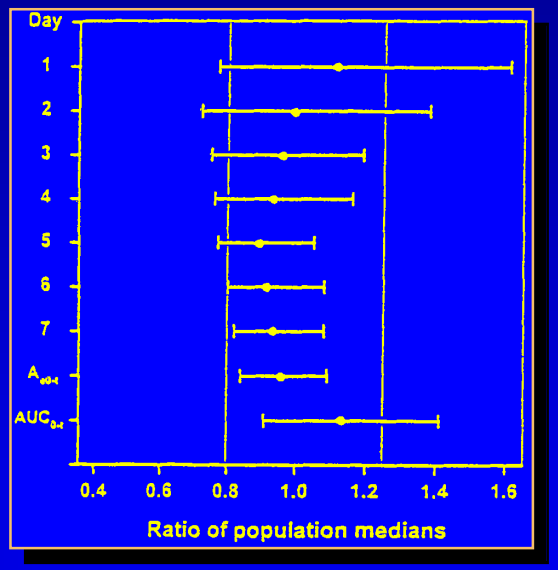
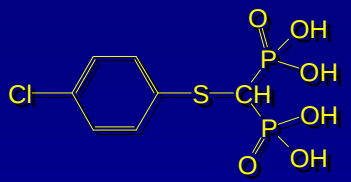


FIG. 2. Cumulative (day 1, days 1–2, days 1–3, etc.) between-subject (a) coefficient of variation (CV), and the cumulative within-subject CV (b) for urinary clodronate excretion. The between-subject CV includes the variation between subjects as well as the within-subject variation. The calculations are based on logarithmically transformed data.

Case Study 4

- $Ae_{0\text{-}t}$ 83 % – 109 %, CV 28.0 %
- $AUC_{0\text{-}t}$ 91 % – 141 %, CV 46.4 %
- C_{max} 72 % – 142 %, CV 77.3 %





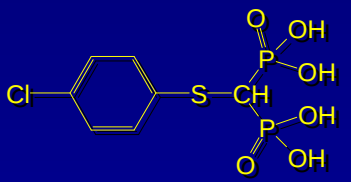
Case Study 5

- Tiludronate (trt. of Paget's disease)

  Maier *et al.*; Characterization of the highly variable bioavailability of tiludronate in normal volunteers using population pharmacokinetic methodologies.
  Eur. J. Drug Metab. Pharmacokin. 24, 2, 249-254 (1999)

  - Population PK-BE study (NONMEM, Constant Coefficient of Variation Model)
  - 153 m healthy subjects from 12 clinical trials (fasting, sd, md, >3500 samples)
  - 24 m subjects crossover (validation)
  - test/ref. 400 mg tablet

Case Study 5



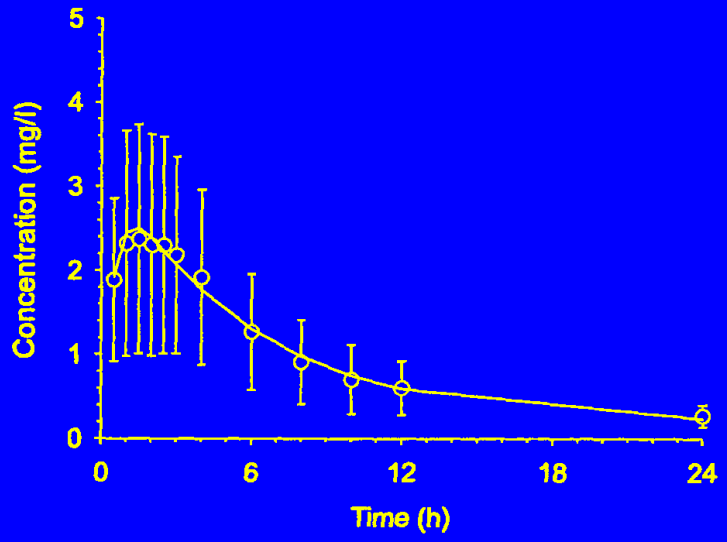


Fig. 1: Mean (SD) tiludronate concentration–time profile of the reference formulation (3C1). Model fit (solid line) compared to observed concentrations (open circles).

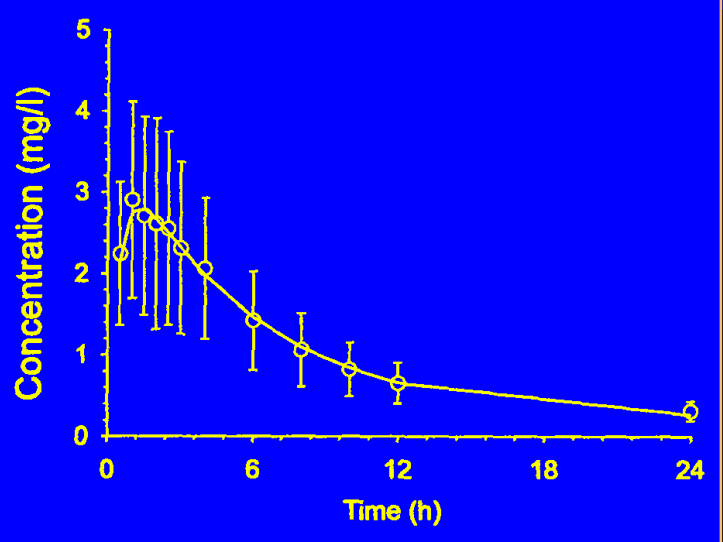
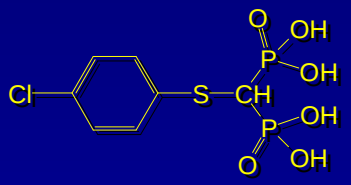


Fig. 2: Mean (SD) tiludronate concentration–time profile of the test formulation (9O1). Model fit (solid line) compared to observed concentrations (open circles).



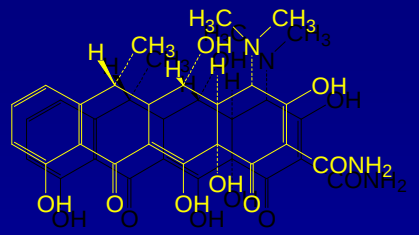
Case Study 5

- Population PK
  - AUC_{0-t} 117 % [98 % – 136 %] CV 38 %
- Conventional BE-Study
  - AUC_{0-t} 115 % [93 % – 142 %] CV 44 %

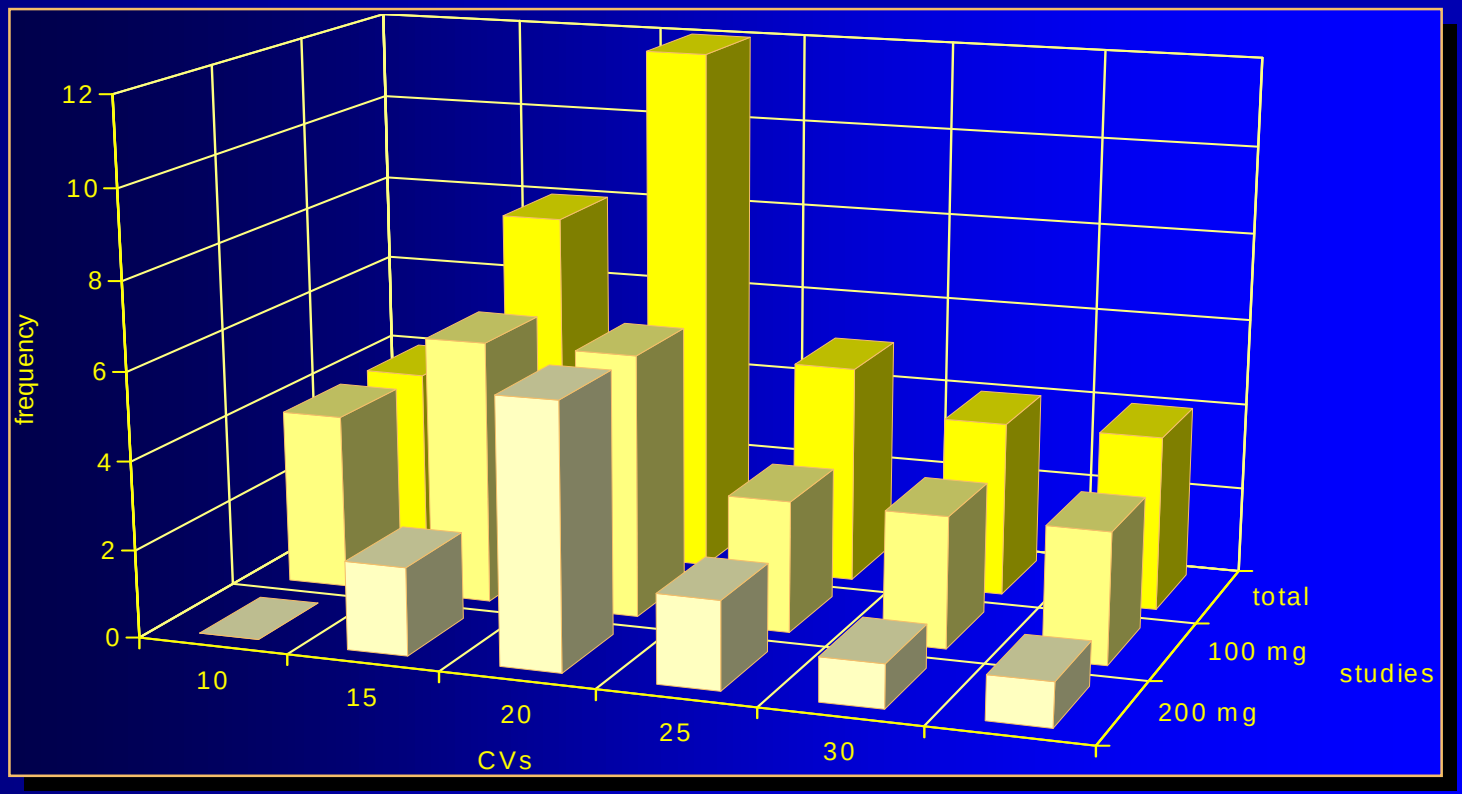
Sample Sizes

- Minimum Number of Subjects
  - 12: WHO, EU, CAN, NZ, AUS, Malaysia, Argentina, ASEAN States, South Africa (20 for MR)
  - 12 (?): USA: The total number of subjects in the study should provide adequate power for BE demonstration […]. For modified-release products, a pilot study can help determine the sampling schedule to assess lag time and dose dumping. A pilot study that documents BE may be appropriate, provided its design and execution are suitable and a sufficient number of subjects (*e.g.*, 12) have completed the study.
  - 24: Brazil

Sample Sizes

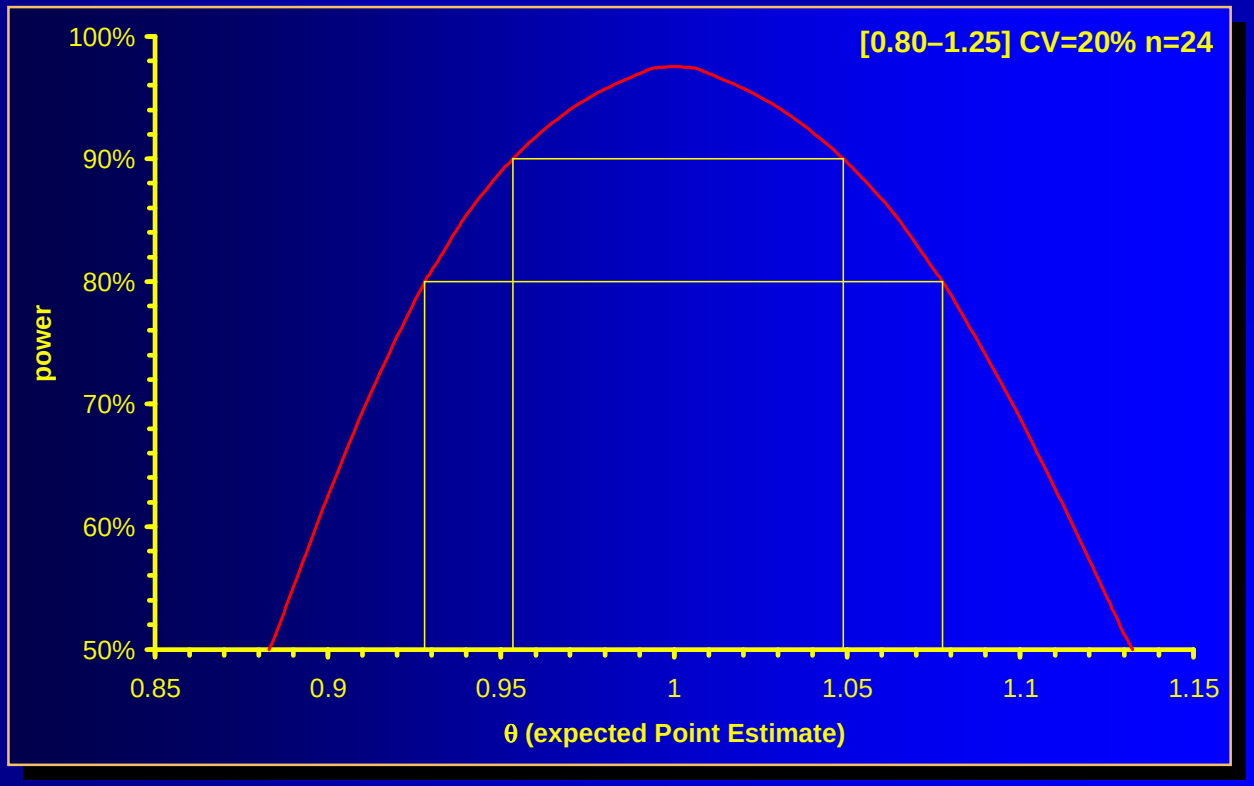


Doxicycline (37 studies ref. by Blume/Mutschler 1996)



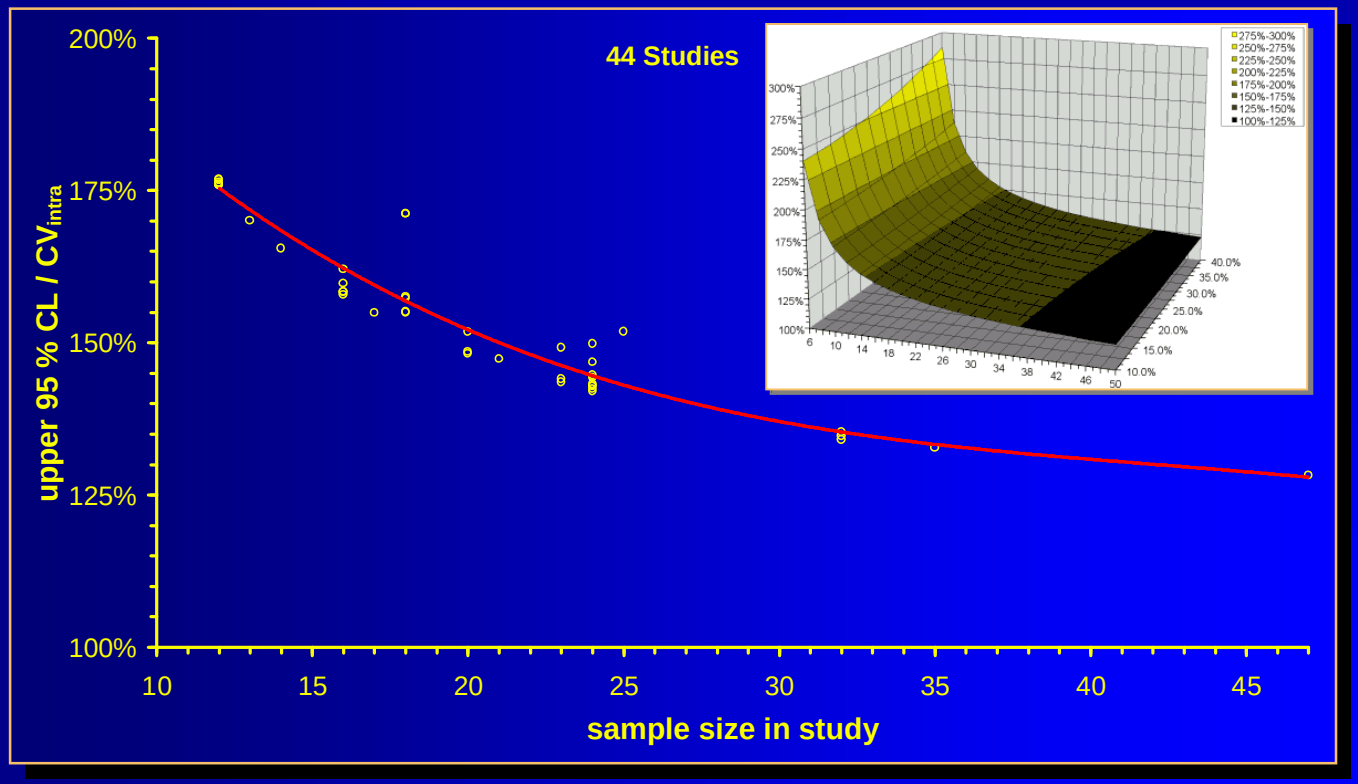
Sample Sizes

Power to demonstrate BE with 24 subjects



Sample Sizes

Estimated CV and upper 95 % CL



Sample Sizes

- Drugs / Drug Products with low variability (intra-subject variability <10 %)
  - No specific regulations in any Guideline.
  - Problems may arise according to significant treatment effects in ANOVA (*i.e.*, although Confidence interval within the acceptance range – 100 % is not included).

Example

- Drugs / Drug Products with low variability
  - Expected CV_{intra}: 10 %
  - Expected Deviation from reference product: -5 % / ratio 95 %
  - Power: 90 %
  - Estimated Sample size: 8, *but:*
    - 12 subjects minimum in most guidelines
    - 2 additional subjects to allow for drop-outs

Example

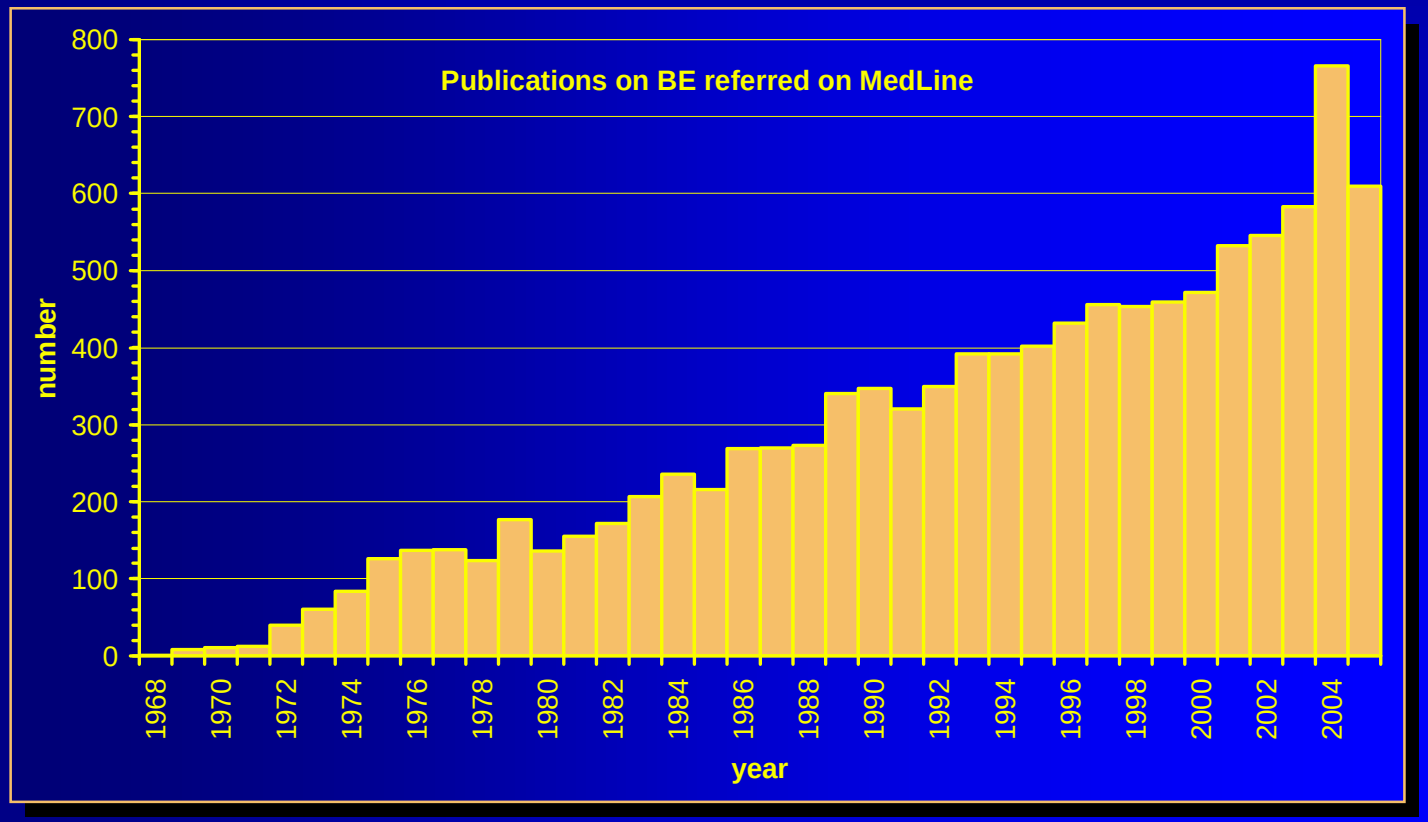
- Drugs / Drug Products with low variability
  - Observed CV_{intra}: 8.5 % (expected 10 %)
  - Observed Deviation: -6 % / ratio 94 % (expected -5 % / 95 %)
  - No drop-outs: sample size 14 (expected 12)
  - Power 99.6 % (expected 90 %)
  - Confidence interval 88.6 % – 99.4 %:
    - Within acceptance range of 80 % – 125 %
    - 100 % not included (treatment effect $P<0.05$)

Sample Sizes

- Maximum Number of Subjects
  - New Zealand:
    If the calculated number of subjects appears to be higher than is ethically justifiable, it may be necessary to accept a statistical power which is less than desirable. Normally it is not practical to use more than about 40 subjects in a bioavailability study.
  - all others: no Specifications (judged by IEC?)

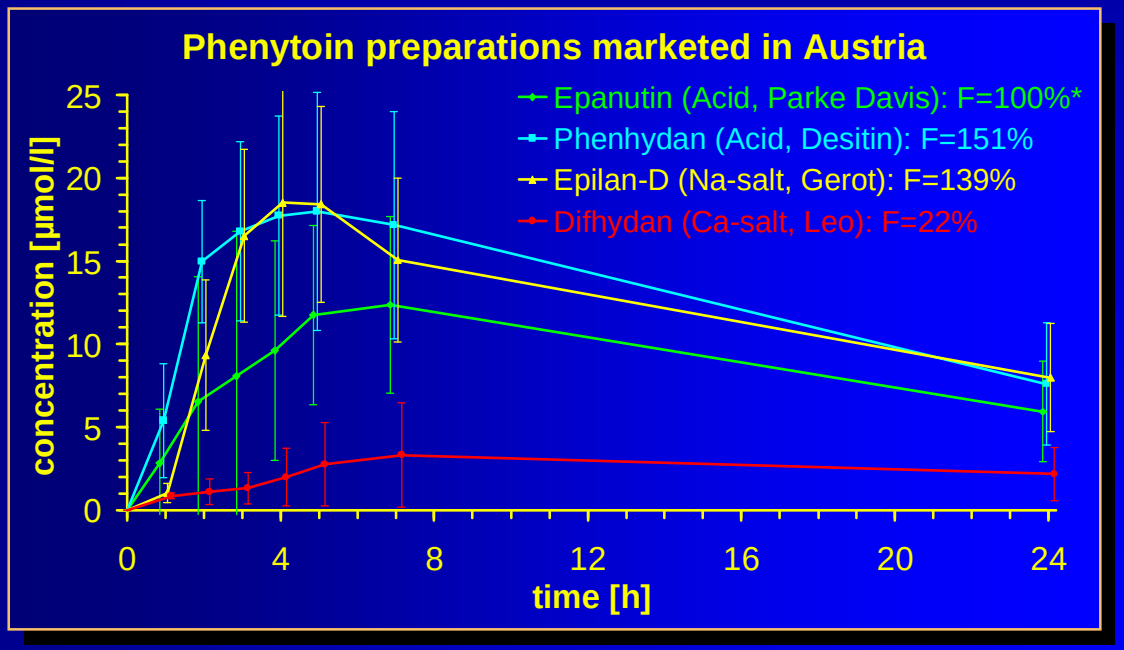
Free Flow of Information?

MedLine “bioequivalence” OR “comparative AND bioavailability”



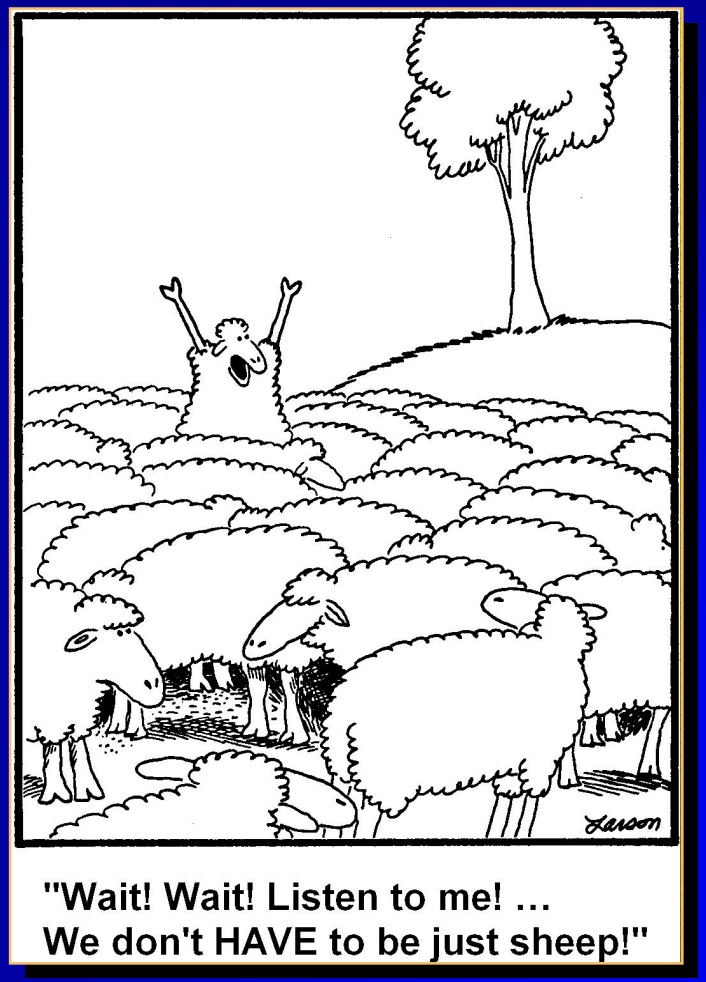
Heresy

Are our criteria for BE *really* based on *science?*



Nitsche, V., Mascher, H. and H. Schütz;
Comparative bioavailability of several phenytoin preparations marketed in Austria.
Int. J. Clin. Pharmacol. Ther. Toxicol. 22(2), 104-107 (1984)

Conclusion



Outlook

- Don’t stay sheep!
- David Bourne’s (Uni. Oklahoma) e-mail List
  - A rather active list (2800 members, about 50 postings/week) devoted to nearly everything about PK / PD / BA…
    - Subscription http://www.boomer.org/pkin/
    - Search page http://www.boomer.org/pkin/simple.html
- BA and BE Forum (BEBAC Vienna)
  - Specialized in dissolution / BA / BE / bioanalytics.
    - No registration necessary to read postings. http://forum.bebac.at/
    - Registration page http://forum.bebac.at/register.php

Pitfalls in BA/BE-Studies

Thank You!

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