Bioavailability and Bioequivalence Studies

Part II: Biometrics

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Outline

- Typical BA and BE metrics
- Statement of objective
- Planned data treatment
- Design of experiment
- Number of subjects
- Reporting

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Principal Biometrics

Primary Test Parameters

- Single dose studies:
  - C_{max}, t_{max}, AUC_t, AUC_∞, (Ae_t, Ae_∞)
- Steady state studies
  - C_{max}, C_{min}, C_{av}, AUC_τ,
  Fluctuation: (C_{max}-C_{min}/C_{av})

Secondary Test Parameters

- MRT, $t_{½}$, others

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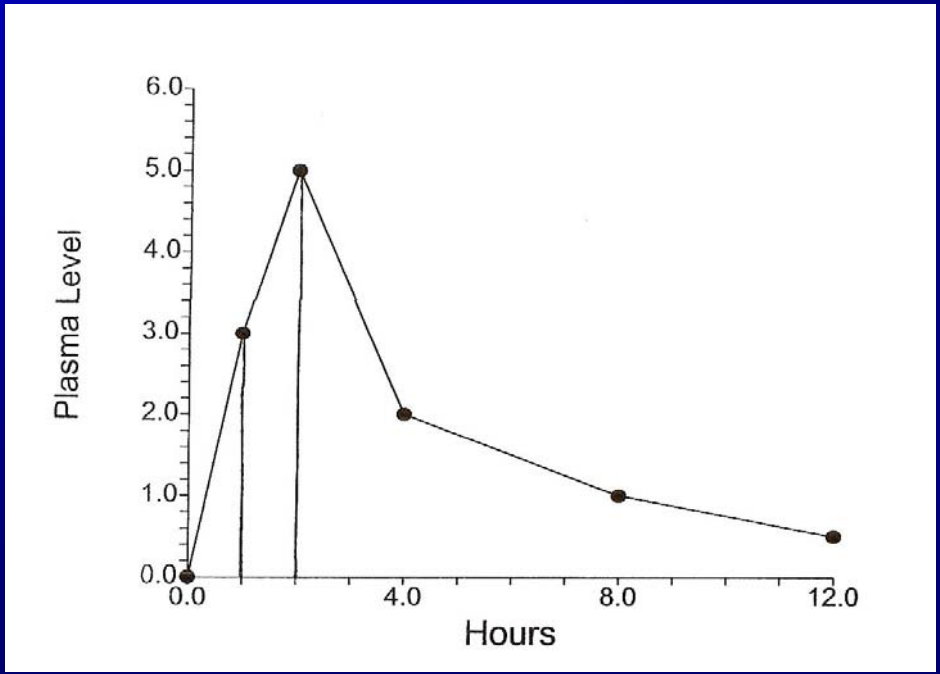
Primary BA/BE Biometrics

C_{max}: average of observed values (different T_{max} possible)

T_{max}: median or range

AUC: calculated using trapezoidal method



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Study Goals

- Comparison of primary bioavailability indicators
  - averages: arithmetic mean, geometric mean
  - median, range
  - logarithmic transformation of data
  - ANOVA is recommended

- Coupled with confidence interval calculation, where the range of 80-125% is considered clinically equivalent

- Bioequivalence: emphasis on AUCτ

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Analytes and Data Processing

- Parent compound vs. (active) metabolite(s)
- Validated analytical method, LOQ,
- Appropriate sampling times
- Method of calculation for biometrics to be described in study protocol
- Exclusive use of PK model estimates not recommended
- If PD effects are assessed, a sufficiently detailed time course of the effect should be provided

Clear Statement of Study Objective and Preparation for Robust Statistical Analysis

- Concentration on major difference (product) → *Study Design* and *Statistical Treatment of Data*
- Variation of biological data → *Number of Subjects* needed for the study
- Point estimates → averaged data

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Study Design for BA/BE Comparisons

- Average BE
  - focus on comparison of averages from T and R

  (to date analysis used most often)
- Population BE
  - assesses total variability of the test parameters
- Individual BE
  - assesses within-subject and subject-by-formulation interaction of T and R

Conceptual issues: Steinijans,V., Drug Information Journal, 35, 893-899 (2001)

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Study Design (Nonreplicated):

Randomized Block Design

Subject	Period 1	Period 2	Period 3	Period 4
1	B	C	A	D
2	D	C	A	B
3	B	C	D	A
4	A	C	B	D
5	C	D	A	B
6	D	C	B	A

Study Design (Nonreplicated):

Latin Square Design

Subject	Period 1	Period 2	Period 3	Period 4
1	A	B	C	D
2	D	C	A	B
3	C	D	B	A
4	B	A	D	C

Study Design (Nonreplicated):

Balanced Incomplete Block Design

[four formulations, 2n(2n-1) subjects, 2 per subject]

Subject	Period 1	Period 2
1	B	C
2	D	C
3	B	C
4	A	C
5	C	D
6	D	C

Study Design (Nonreplicated): BIBD

[five formulations, 2n(2n+1) subjects, 2 per subject]

Subject	Period	Period
1	A	B
2	B	C
3	C	D
4	D	E
5	E	A
6	A	C
7	C	E
8	E	B
9	B	D
10	D	A

Study Design (Replicated):

Example: two-sequence, four-period

	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R	R	T
Sequence 2	R	T	T	R
Sequence 3	T	T	R	R
Sequence 4	R	R	T	T

Number of Subjects

(for balanced cross-over designs)

- (based on 90% confidence interval for the difference of T – R)
- Minimum n = 12
- Allowance for drop-outs
- Statement in protocol, if drop-outs are replaced
- Statement in protocol, if trial is planned as a sequential design

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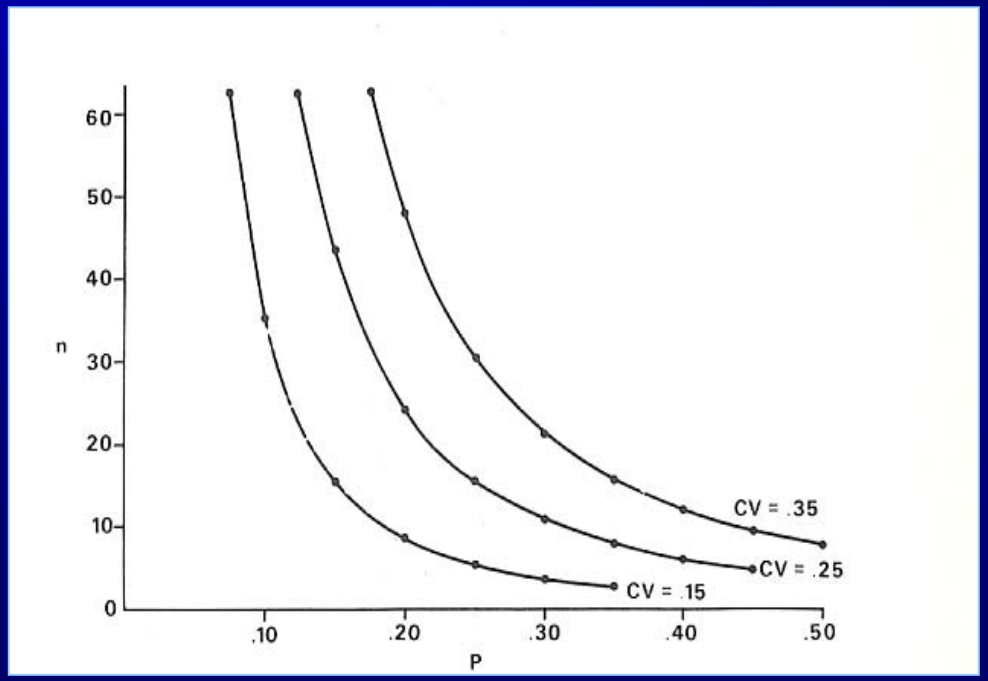
Number of Subjects

Influence of variation in biodata and difference to be detected (balanced cross-over):

From Westlake in Dosage Form Design and BA, Lea & Febiger, 1973



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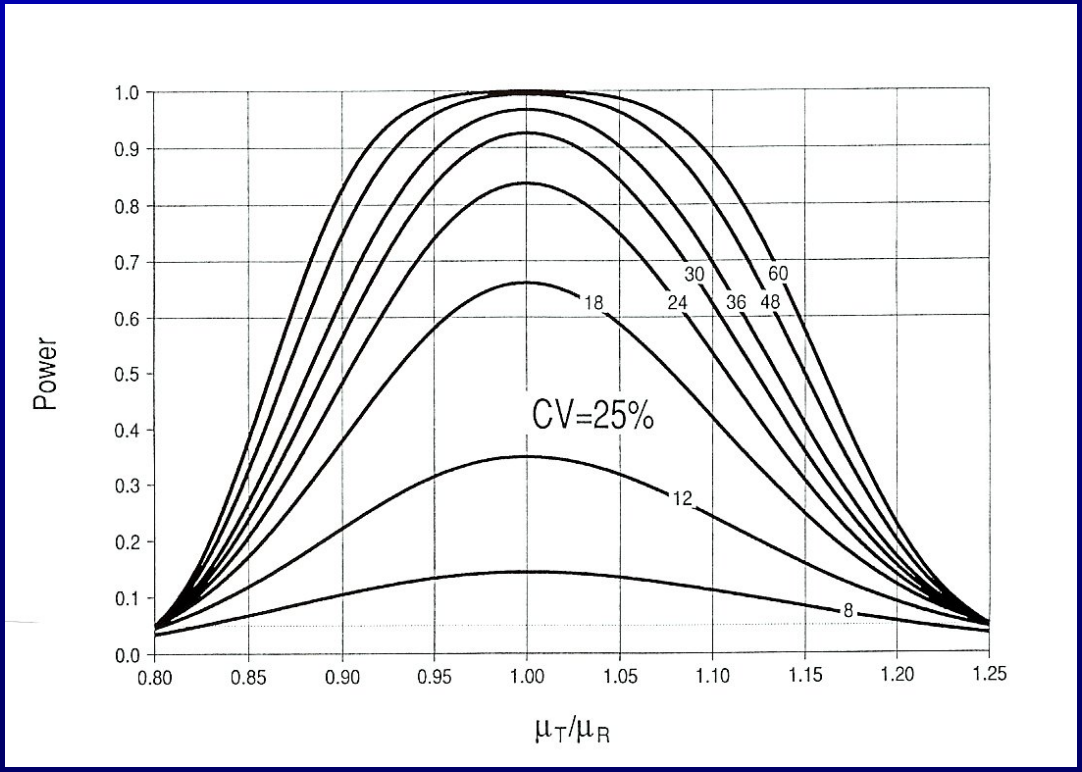
Number of Subjects

Influence of statistical power on required n (balanced cross-over):

From Diletti et al, Int J Clin Pharmacol, 29, 1-9, 1991



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Statistical Analysis (cont'd)

- Analysis of bioavailability, other univariate parameters, and patterns of blood levels
- Here: for BIB and Latin Square (special case of BIBD)
- Aim to single out: difference, subject effect, period effect, formulation effect, error
  → Analysis of Variance (ANOVA)

✓ ANOVA for AUC, Cmax
✓ ANOVA for PK constants
✓ ANOVA for each sampling point (aggregate for pattern)

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Statistical Analysis (cont'd)

- Hypothesis testing (Westlake)

  "The most minute difference will show up as significant if only the trial is made big enough"

- More realistic for the clinical situation: the use of confidence intervals for univariate parameters:

✓ 90% confidence interval on the basis of residual error from ANOVA (logarithmic data transformation)

✓ Two-sided t-test at 5% significance level

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Reporting the BA/BE Study

(for regulatory filing)

- Title, Responsible Persons, Quality Assurance Unit Statement, Signatures
- Study Synopsis
- Table of Contents
- Glossary of Abbreviations, Definition of Terms
- Independent Ethics Committee, Institutional Review Board, Ethical Conduct of Study, Informed Consent, Investigators, etc.
- Study Objectives
- Study Design
- Selection of Study Population, Inclusion and Exclusion Criteria, Treatments

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Reporting the BA/BE Study (cont'd)

- Identity of Products administered, blinding
- Clinical Observations: adverse effects
- Reporting of Data: individual, averages, statistical analysis (software used), numerical and graphical presentation, detailed such that analysis can be repeated elsewhere
- Deviation(s) from Protocol
- Discussion of Results and Conclusion
- Appendices: Protocol, Validation of Analytical Method, etc.