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Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion

MAIN PAPER

Jürgen Hummel[1,*,†], Sue McKendrick[2], Charlie Brindley[3] and Raymond French[4]

[1] *PPD, Bellshill, Lanarkshire, Scotland, UK*
[2] *AAI Pharma Ltd, Edinburgh, Scotland, UK*
[3] *KinetAssist Ltd, Quothquan, Lanarkshire, Scotland, UK*
[4] *Charles River Laboratories Preclinical Europe, Tranent, Edinburgh, Scotland, UK*

This article reviews currently used approaches for establishing dose proportionality in Phase I dose escalation studies. A review of relevant literature between 2002 and 2006 found that the power model was the preferred choice for assessing dose proportionality in about one-third of the articles. This article promotes the use of the power model and a conceptually appealing extension, i.e. a criterion based on comparing the 90% confidence interval for the ratio of predicted mean values from the extremes of the dose range $(R_{\mathbf{dnm}})$ ***to pre-defined equivalence criterion*** $(\vartheta_L, \vartheta_U)$***. The choice of bioequivalence default values of*** $\vartheta_L = 0.8$ ***and*** $\vartheta_U = 1.25$ ***seems reasonable for dose levels only a doubling apart but are impractically strict when applied over the complete dose range. Power calculations are used to show that this prescribed criterion lacks power to conclude dose proportionality in typical Phase I dose-escalation studies. A more lenient criterion with values*** $\vartheta_L = 0.5$ ***and*** $\vartheta_U = 2$ ***is proposed for exploratory dose proportionality assessments across the complete dose range. Copyright © 2008 John Wiley & Sons, Ltd.***

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1. INTRODUCTION

The investigation of the pharmacokinetic (PK) properties of a compound typically includes an

*Correspondence to: Jürgen Hummel, PPD, Fleming House, Phoenix Crescent, Strathclyde Business Park, Bellshill, Lanarkshire ML4 3NJ, Scotland, UK.
† E-mail: Jurgen.Hummel@europe.ppdi.com

assessment of dose proportionality. In essence, this investigates whether an *r*-fold increase in dose leads to an *r*-fold increase in total or maximal systemic exposure, measured by the PK parameters AUC and C_{max}. Dose proportionality is a desirable property as it makes predicting the effects of dose adjustments easier, although in practice this is not a global property as it usually applies only to a certain dose range.

Dose proportionality is often assessed at two different stages of the drug development process. An exploratory assessment of approximate dose proportionality is often carried out using PK data from first time in human (FTIH) studies, whereas a definitive assessment of confirmatory dose proportionality is generally conducted during Phase II or III [1].

2. DESIGN OF FTIH STUDIES

While there is FDA guidance on the estimation of the starting dose in healthy volunteer studies [2], no such guidance exists on the design of FTIH studies, and as a result there is considerable variety in how such studies are conducted. A report with 21 recommendations on the design and analysis of FTIH studies [3, 4] was issued recently following the unfortunate outcome of the FTIH study conducted at Northwick Park Hospital in March 2006.

Generally, increasing doses are administered to 3–10 healthy volunteers per dose with a small number of concurrent subjects administered placebo (see [1, 5]). Single and repeat administrations are investigated separately. Patterson and Jones [1] state that, 'cross-over designs are generally employed for the purposes of informative dose-escalation in FTIH and Phase I studies'. This was not backed up by our experience gained in FTIH studies in different Contract Research Organizations (CROs) or by Buoen *et al.* [5], who conducted a survey of 105 Phase I dose-escalation trials in healthy volunteers between 1995 and 2004 and found ascending dose design with independent cohorts ('parallel design') the most frequent design within all therapeutic areas. Parallel designs are likely to be more popular because the study duration for each subject is considerably shorter, reducing the likelihood of premature withdrawal.

More flexible study designs have been proposed for Phase I oncology studies, where the dose level allocated to the next cohort of patients depends on the toxicities observed in the patients to date and where dose levels do not necessarily increase [6–9], but they have not yet been applied very frequently to Phase I healthy volunteer studies.

3. REVIEW OF CURRENTLY USED STATISTICAL ANALYSIS METHODOLOGY FOR DOSE PROPORTIONALITY

3.1. Options

Different statistical analysis approaches can be used for the assessment of dose proportionality [10, 11]. The following options are investigated in more depth in this section:

(a) *Dose normalization* of the PK parameter followed by an analysis of variance (ANOVA) (or an equivalent non-parametric test) on log-transformed data to test for differences between dose levels. This is done either using an overall test (e.g. *F*-test) and/or several pairwise comparisons (which may be presented as confidence intervals (CIs) for the ratios of dose normalized geometric means).

(b) *Weighted simple linear regression* between the PK parameter (y) and dose

$$y = \alpha + \beta \,\text{dose}$$

where the hypothesis that $\alpha = 0$ is tested and the lack of fit of the model is generally tested by adding a quadratic term.

(c) *Power model* proposed by Gough *et al.* [12]. The relationship between the PK parameter (y) and dose is defined as follows:

$$y = \alpha \,\text{dose}^{\beta}$$

This becomes a linear relationship following a logarithmic transformation, to which a linear

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regression approach can be applied:

$$\log(y) = \mu + \beta \log(\text{dose})$$

Assuming that the underlying relationship between $\log(y)$ and $\log(\text{dose})$ is linear, a value of 1 for β indicates perfect dose proportionality. Therefore, the estimate of β together with a suitable CI can be used to quantify dose proportionality.

(d) *Equivalence criterion*: On the basis of the criterion suggested by the FDA and EMEA guidelines for the assessment of bioequivalence [13, 14], Smith *et al.* [15] propose a criterion for dose proportionality based on 90% CI for the ratio of dose normalized means (R_{dnm}) lying within pre-specified limits $(\vartheta_L, \vartheta_U)$. Different approaches can be used to estimate R_{dnm}. In the case of the power model, R_{dnm} can be estimated as $r^{\beta-1}$ where r is the ratio of the highest to the lowest dose, and comparing the 90% CI around R_{dnm} to pre-specified limits $(\vartheta_L, \vartheta_U)$ is mathematically equivalent to comparing the 90% CI around β to the limits

$$(\beta_L, \beta_U) = \left(1 + \frac{\ln(\vartheta_L)}{\ln(r)}, 1 + \frac{\ln(\vartheta_U)}{\ln(r)}\right)$$

While no specific values are advocated for ϑ_L and ϑ_U in [15], the article states the choice should be based on safety, efficacy or drug registration considerations and provides an example using the values 0.8 and 1.25 as in the FDA guideline for bioequivalence.

3.2. Literature review

A list of 85 articles was obtained from a literature search using Pubmed (http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed) with the keyword 'dose proportionality', limited to Humans, language English and publication dates between 1 January 2002 and 31 December 2006. Since we were interested in applications to dose-escalation studies rather than studies that, for example, assessed different formulations, we restricted our review to the 50 articles [16–65] where there were three or more dose levels of the same formulation. A summary of this review is shown in Table I.

Note that some papers used more than one of the approaches (a)–(d). The most commonly used techniques were pair-wise comparisons on dose-normalized data [17–21, 23, 28, 29, 37, 41, 49, 52, 54, 59, 63, 65] and power model approach [18, 19, 22, 25, 27, 28, 38, 42, 44, 45, 48, 51, 52, 55, 5-7, 58, 64] used in 16 and 17 articles, respectively. In six of the articles [42, 45, 55, 57, 58, 64] that utilized the power model, interpretation was based on a hypothesis testing approach with dose proportionality concluded if a suitable CI around β included 1. In a further five articles [18, 19, 22, 25, 48] utilizing the power model the conclusion was based on the equivalence criterion; these criteria were set without consideration to the corresponding power. In four articles [18, 19, 52, 65] the criterion of (0.8, 1.25) or (0.7, 1.43) was applied to pair-wise comparisons resulting from an ANOVA of dose-normalized data.

Analysis of *dose-normalized* data is still widely used in the literature despite this being an inefficient use of data that, therefore, lacks power (see [12]). We consider the *power model* to be the best approach to assess dose proportionality with

Table I. Summary of the literature review.

Methodology	*n*
(a) *Dose-adjusted data analysed*	29
Overall test only	6
Overall test followed by pair-wise comparisons	2
Pair-wise comparisons	14
Descriptive statistics only	7
(b) Weighted simple linear regression	2
(c) *Power model*	17
Interpretation based on CI includes/excludes 1	6
Interpretation based on equivalence criteria	5
Neither of the above	6
(d) *Equivalence criterion*	7
Pair-wise comparisons only	2
Power model approach	3
Power model and pair-wise approach	2
(e) No statistical testing or confidence intervals	12

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an analysis of *dose-normalized* data recommended only where there is evidence for lack of fit of the power model. The *equivalence criterion* applied to the power model is appealing, although it does not yet appear to have been commonly utilized in published work.

4. SUITABILITY OF CURRENTLY USED DOSE PROPORTIONALITY CRITERION

4.1. Sample data set

A sample of 34 Phase I dose-escalation studies conducted in healthy volunteers, for which Aptuit Ltd (a CRO) performed the PK analysis between 2000 and 2006, was chosen to assess the suitability of the *equivalence criterion* with the values 0.8 and 1.25 for ϑ_L and ϑ_U, respectively, for an exploratory assessment of dose proportionality.

Table II presents an outline of the study design of all studies in the sample data set, which were restricted to the more typical 'parallel group' designs and where cohorts had identical dosing intervals and formulations. The median number of subjects on active treatment was 6; however, changes in design sometimes resulted in numbers fluctuating between doses.

The sample of 43 study parts yielded a total of 143 PK analyses, where the power model was used to assess dose proportionality (72 analyses for AUC and 71 analyses for C_{max}). To maintain confidentiality of the individual study results, none of the individual CIs for β are presented. For consistency between studies, AUC was taken as $AUC_{0-\infty}$ unless data were considerably less complete than for AUC_{0-t} and data sets were excluded if there was evidence of lack of fit (see [12]). For some studies, more than one analyte was investigated and analyses were performed after a single dose and at steady state in repeated dose studies.

4.2. Results

Dose proportionality can be claimed over the complete dose range in few of the analyses using the *equivalence criterion* values of 0.8 and 1.25 for ϑ_L and ϑ_U, respectively (Table III). It is recognized that C_{max} is generally more variable than AUC [14], typically leading to wider CIs for β. Hence, the proportion of PK analyses classed as dose proportional is smaller for C_{max} (1/71; 1%) than for AUC (7/72; 10%). Seven of the 8 PK analyses classed as dose proportional had no more than three dose levels and a dose range ratio no greater than 3.

However, the vast majority (88% in our sample) of single dose studies have either more dose levels or a wider dose range ratio. This also applies to the majority (53% in our sample) of repeated dose studies, although to a lesser extent.

5. ALTERNATIVE CRITERION FOR EXPLORATORY ASSESSMENT FOR DOSE PROPORTIONALITY

5.1. Rationale for alternative criterion

The suitability of the *equivalence criterion* (with the values 0.8 and 1.25 for ϑ_L and ϑ_U, respectively) has been acknowledged [11] for definitive dose proportionality assessments in confirmatory studies. However, the above results indicate its limitations for exploratory dose proportionality assessments.

It is important to gain good understanding of the dose proportionality properties of a compound early in the drug development process to facilitate the dose escalation within a study and to assist dose selection for subsequent healthy volunteer and patient studies [66]. While the provision of an estimate of β with a suitable CI may be more appealing than a hypothesis testing approach, the clinical relevance of any deviation from 1 will depend on the dose range investigated. As the therapeutic dose range to be studied in patients is generally unknown at this stage, it will in practice be sufficient in most cases to know whether the compound is approximately dose proportional or clearly more or less than dose proportional.

We use the framework of the conceptually appealing *equivalence criterion* to suggest an alternative criterion for exploratory dose proportionality assessments by determining more suitable

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Table II. Study design outline for the studies in the sample data set.

Study type/study number	Administration route	Total number of subjects	Number of subjects per dose (min/max)	Number of dose levels	Dose range ratio
Parallel single dose studies					
1	Oral	48	6	8	60
2	Oral	24	4	6	20
3	Oral	34	8/18	3	6
4	Oral	48	6	8	60
5	Oral	48	6	8	128
6	Oral	48	6	8	40
7	Oral	48	8	6	32
8	Oral	16	4	4	12
9	Oral	56	8	7	72
10	Oral	42	6	7	72
11	Oral	36	6	6	32
12* (Part 1)	Oral	30	6/12	4	8
12* (Part 2)	Oral	18	6	3	2
13 (Part 1)	Oral	36	6	6	8
14 (Part 1)	Oral	54	6	9	64
15 (Part 1)	Oral	36	6	6	24
16 (Part 1)	Oral	24	4	6	20
17	Intravenous	16	4/6	3	33
18	Intravenous	9	3	3	10
19	Intravenous	36	3/6	7	28
20† (Part 1)	Intravenous	12	6	2	3
20† (Part 2)	Intravenous	18	6	3	10
21	Intravenous	24	6	4	2.33
22	Subcutaneous	18	6	3	3
23 (Part 1)	Subcutaneous	25	5	5	20
24 (Part 1)	Subcutaneous	41	5/6	7	40
Summary single dose ($n = 26$): median (minimum, maximum)		35 (9, 56)	6 (3, 8/18)	6 (2, 9)	22 (2, 128)
Parallel repeated dose studies					
13 (Part 2)	Oral	18	6	3	3
14 (Part 2)	Oral	24	6	4	8
15 (Part 2)	Oral	18	6	3	5
16 (Part 2)	Oral	12	4	3	3.75
25	Oral	24	8	3	3
26	Oral	18	6	3	2
27	Oral	18	6	3	3
28	Oral	24	6	4	8
29	Oral	50	10	5	8
30	Oral	18	6	3	3
31	Oral	18	6	3	8.33
32	Oral	36	9	4	4
33‡ (Part 1)	Intravenous	12	6	2	2
33‡ (Part 2)	Intravenous	12	6	2	2
34	Intravenous	21	7	3	33
22 (Part 2)	Subcutaneous	12	6	2	5
23 (Part 2)	Subcutaneous	18	9	2	2.5
Summary repeated dose ($n = 17$): median (minimum, maximum)		18 (12, 50)	6 (4, 10)	3 (2,5)	3.75 (2, 33)

*Part 1 was conducted under fasted conditions and Part 2 under fed conditions.
†Part 1 was conducted under normal and Part 2 under challenge conditions.
‡Parts 1 and 2 had different frequency of administration of the study drug.

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values for ϑ_L and ϑ_U than 0.8 and 1.25, respectively.

5.2. Power calculations

To explore suitable parameters for ϑ_L and ϑ_U for the *equivalence criterion*, power calculations were performed for a typical repeated dose-escalation study, which (based on the properties of our sample studies in Section 4.1) had a sample size (n) of six subjects at each dose level and three doubling doses ($r = 4$). The power of establishing dose proportionality can be calculated as

$$\text{power} = \max\{\Phi[-U_{\alpha/2} - (\tau - \beta_U)\sqrt{w}] - \Phi[U_{\alpha/2} - (\tau - \beta_L)\sqrt{w}], 0\} \quad (1)$$

where w is the inverse of the variance of the slope estimator (see Technical Appendix for further details). Different calculations were performed for the true slope, $\beta = \tau$, ranging from 1.0 to 1.6, and the lower limit of the *equivalence criterion* ϑ_L ranging from 0.3 to 0.8 (upper limit ϑ_U defined correspondingly). Based on our experience, the variability was set at $\sigma = 0.294$ (equivalent to a geometric CV of 30%).

Table III. Dose proportionality assessment over whole dose range of study using the equivalence criterion with $\vartheta_L = 0.8$ and $\vartheta_U = 1.25$.

	PK parameter	
Dose proportionality criterion	AUC	C_{max}
Met	7 (10%)	1 (1%)
Not met	65 (90%)	70 (99%)
Total	72 (100%)	71 (100%)

The resulting power curves plotted against ϑ_L are shown in Figure 1. As to be expected, the probability of concluding dose proportionality over the whole dose range increased as the *equivalence criterion* widened and as β tended towards one. Calculations using Equation (1) showed that for an underlying perfectly dose proportional compound (i.e. $\beta = 1.0$), the power of concluding dose proportionality using the (0.8, 1.25) criterion was 0% for n up to nine subjects. Similar calculations show that only large n of 30 and 38 subjects would achieve power of at least 80% and 90%, respectively, to conclude dose proportionality over a dose range of 4 using the (0.8, 1.25) criterion.

A practical dose proportionality criterion should conclude dose proportionality in the majority of cases if a compound is truly close to dose proportional and reject dose proportionality in the majority of cases if a compound is markedly

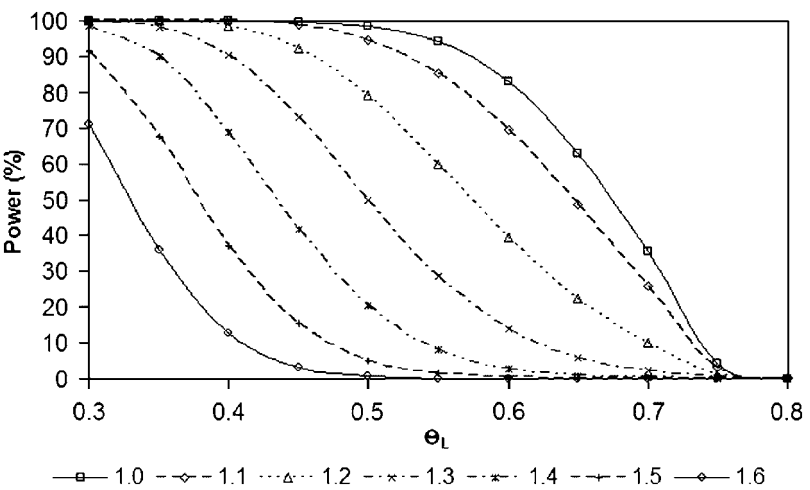

Figure 1. Relationship between Θ_L and power of concluding dose proportionality for β from 1.0 to 1.6 (six subjects at each dose level with values of 1, 2, 4).

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Table IV. Cross-tabulation of dose proportionality assessment by pharmacokineticist for AUC.

		Pharmacokineticist 1			
		AUC		C_{max}	
Dose proportionality criterion		Met	Not met	Met	Not met
Pharmacokineticist 2	Met	17 (24%)	1 (1%)	11 (15%)	0 (0%)
	Not met	15 (21%)	39 (54%)	15 (21%)	45 (63%)
	Total	32 (44%)	40 (56%)	26 (37%)	45 (63%)

non-dose proportional. Clearly the bioequivalence criterion of (0.8, 1.25) is too strict for an exploratory assessment of dose proportionality over the whole dose range as the type II error is extremely high (i.e. low power) and the use of wider criterion should be considered.

Using the wider criterion of (0.5, 2), the power to conclude dose proportionality increased to 98.6% based on $n = 6$. If a compound is truly not dose proportional (underlying $\beta = 1.6$), then the power to conclude dose proportionality should be low, which the wider criterion of (0.5, 2) achieves just as well with a value of only 0.7%.

5.3. Input from pharmacokineticists

Using the sample data set of 143 PK analyses introduced in Section 4.1, two experienced pharmacokineticists independently assessed whether they intuitively regarded a compound as dose proportional for the relevant PK parameter. The only information available to them from each PK analysis was the name of the PK parameter investigated, the estimate and 90% CI for β and basic information on the study design as shown in Table II. Both pharmacokineticists erred on the side of caution in their assessment as they classed a compound only as dose proportional if in their opinion the evidence was beyond reasonable doubt. Table IV summarizes the results of the dose proportionality classifications made by the two pharmacokineticists. Overall Pharmacokineticist 1 was less conservative in the assessment than Pharmacokineticist 2, but both concluded dose proportionality in more analyses than resulted from use of the equivalence criterion of 0.8, 1.25.

We acknowledge the limited size of the sample of experienced pharmacokineticists used, but the above exercise shows that their intuitive dose proportionality criterion appears to be wider than 0.8–1.25.

5.4. Suggested exploratory dose proportionality criterion

Providing a robust criterion for exploratory dose proportionality is difficult as it needs to cover many different compounds and dose-escalation study designs. As such, the choice of the parameters ϑ_L and ϑ_U should be guided by prior information about the compound investigated as well as the variability of its PK parameters (where this is available) and therefore by the power of the study. However, we feel that the predominantly chosen default values of $\vartheta_L = 0.8$ and $\vartheta_U = 1.25$, while useful for a definitive assessment of dose proportionality, are too conservative for an exploratory assessment of dose proportionality. On the basis of the power calculations, but also taking into account the intuitive assessments of pharmacokineticists, we suggest instead the use of the default values $\vartheta_L = 0.50$ and $\vartheta_U = 2$ for typical single and repeated dose studies. This, therefore, leads to the following exploratory criterion: approximate dose proportionality will be concluded if the 90% CI for β is entirely within

$$\left(1 + \frac{\ln(0.5)}{\ln(r)}, 1 + \frac{\ln(2)}{\ln(r)}\right)$$

Table V compares the equivalence criterion with values of (0.8, 1.25) with (0.5, 2) for ϑ_L and ϑ_U as well as with the assessment by the pharmacokineticists and shows that the proposed criterion of

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Table V. Comparison of dose proportionality criteria using sample data set.

Dose proportionality criterion	PK parameter	
	AUC	C_{max}
$(\vartheta_L, \vartheta_U) = (0.8, 1.25)$*	7 (10%)	1 (1%)
Intuitive assessment by pharmacokineticists†	17 (24%)–33 (46%)	11 (15%)–26 (37%)
$(\vartheta_L, \vartheta_U) = (0.5, 2)$‡	32 (44%)	31 (44%)

*Current example using FDA bioequivalence guidelines [13]; source Table III.
†Pharmacokineticist assessment. Lower bound displays studies where both pharmacokineticists concluded dose proportionality, upper bound where at least one did so; source Table IV.
‡Proposed limits for ϑ.

$\vartheta_L = 0.5$ and $\vartheta_U = 2$ broadly agrees with the pharmacokineticists' assessment.

6. SUMMARY AND DISCUSSION

This article promotes the use of the power model (considered to be the best approach provided that there is no evidence of lack of fit) and its conceptually appealing extension suggested by Smith *et al.* [15] by comparing 90% CIs for R_{dnm} to pre-defined equivalence criterion $(\vartheta_L, \vartheta_U)$. The choice of the bioequivalence default values of $\vartheta_L = 0.8$ and $\vartheta_U = 1.25$ seems reasonable for dose levels only a doubling apart but are impractically strict with unacceptably high Type II error when applied over the complete dose range. A more lenient criterion with values $\vartheta_L = 0.5$ and $\vartheta_U = 2$ is proposed for exploratory dose proportionality assessments across the complete dose range, but it is recognized that higher values for ϑ_L (and lower corresponding values for ϑ_U) will be required for studies intending to gain a definitive answer on the dose proportionality of a new compound in the later stage of its development.

TECHNICAL APPENDIX: DERIVATION OF POWER FOR ESTABLISHING DOSE PROPORTIONALITY

Smith *et al.* [15] proposed that to establish dose proportionality, the 90% CI for the ratio of dose normalized means (R_{dnm}) should lie within pre-specified limits $(\vartheta_L, \vartheta_U)$. In the case of applying the power model, this equates to comparing the 90% CI around the slope, β, to limits

$$(\beta_L, \beta_U) = \left(1 + \frac{\ln(\vartheta_L)}{\ln(r)}, 1 + \frac{\ln(\vartheta_U)}{\ln(r)}\right)$$

where r is the dose range.

This in turn can be formulated as rejecting the following two one-sided hypotheses (H_{01} and H_{02}) in favour of their alternative hypotheses (H_{A1} and H_{A2}, respectively):

H_{01} $\beta \leqslant \beta_L$ versus H_{A1} $\beta > \beta_L$;
H_{02} $\beta \geqslant \beta_U$ versus H_{A2} $\beta < \beta_U$.

To simplify the subsequent mathematics, we introduce w as the inverse of the variance of the slope estimator. For a parallel group design, w is a function of the number of subjects per dose (n_i), residual variability (σ^2) and distribution of log doses (d_i) about their mean in the study design

$$\left(S_{dd} = \sum_{i=1}^{k} n_i (d_i - \bar{d})^2\right)$$

Thus, the variance of the slope is expressed as

$$\mathrm{var}(\hat{\beta}) = \frac{1}{w} = \frac{\sigma^2}{S_{dd}}$$

(see [67]).

For a true underlying slope of $\beta = \tau$, the power of establishing dose proportionality can be

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expressed as

$$\begin{aligned}\text{Power} &= P(\text{reject } H_{01} \text{ and reject } H_{02})\\ &= P[(\hat{\beta}-\beta_{\mathrm{L}})\sqrt{w} > \mathrm{U}_{\alpha/2} \text{ and}\\ &\quad (\hat{\beta}-\beta_{\mathrm{U}})\sqrt{w} < -\mathrm{U}_{\alpha/2} | \beta=\tau]\\ &= P\left[(\hat{\beta}-\tau) > \frac{\mathrm{U}_{\alpha/2}}{\sqrt{w}} - (\tau-\beta_{\mathrm{L}}) \text{ and}\right.\\ &\quad \left.(\hat{\beta}-\tau) < -\frac{\mathrm{U}_{\alpha/2}}{\sqrt{w}} - (\tau-\beta_{\mathrm{U}}) | \beta=\tau\right]\\ &= P[(\hat{\beta}-\tau)\sqrt{w} > \mathrm{U}_{\alpha/2} - (\tau-\beta_{\mathrm{L}})\sqrt{w} \text{ and}\\ &\quad (\hat{\beta}-\tau)\sqrt{w} < -\mathrm{U}_{\alpha/2} - (\tau-\beta_{\mathrm{U}})\sqrt{w} | \beta=\tau]\end{aligned}$$

Given a true slope of τ, $(\hat{\beta}-\tau)\sqrt{w}$ is expected to be distributed $N(0,1)$. The probability of lying between two quantities a and b on the normal curve for $b > a$ is expressed as $\Phi[b] - \Phi[a]$, where Φ represents the cumulative Normal (i.e. area under the curve up to that point). Thus, the power for establishing dose proportionality simplifies to the probability of meeting the upper criterion minus the probability of failing the lower criterion or

$$\begin{aligned}\text{power} = \max\{&\Phi[-U_{\alpha/2} - (\tau-\beta_{\mathrm{U}})\sqrt{w}]\\ &- \Phi[U_{\alpha/2} - (\tau-\beta_{\mathrm{L}})\sqrt{w}], 0\}\end{aligned} \quad (1)$$

Note that the maximum of this quantity or zero is introduced to guard against a negative power (i.e. the situation where the probability of meeting the upper criterion is smaller than the probability of failing the lower criterion).

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REFERENCES

1. Patterson S, Jones B. *Bioequivalence and statistics in clinical pharmacology*. Chapman & Hall: Boca Raton, FL, 2006; pp. 189–242.
2. US Food and Drug Administration (FDA). *Guidance for industry and reviewers on estimating the safe starting dose in clinical trials for therapeutics in adult healthy volunteers*. FDA: Rockville, 2005.
3. Royal Statistical Society. *Report of the working party on statistical issues in first in man studies*. Royal Statistical Society. Available at: http://www.rss.org.uk/first-in-man-report (accessed 22 June 2007).
4. Julious S. A personal perspective on the Royal Statistical Society report of the working party on statistical issues in first-in-man studies. *Pharmaceutical Statistics* 2007; **6**:75–78.
5. Buoen C, Bjerrum OJ, Thomsen MS. How first-time-in-human studies are being performed: a survey of Phase I dose-escalation trials in healthy volunteers published between 1995 and 2004. *Journal of Clinical Pharmacology* 2005; **45**:1123–1136.
6. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for Phase 1 clinical trials in cancer. *Biometrics* 1990; **46**:33–48.
7. O'Quigley J, Shen LZ. Continual reassessment method: a likelihood approach. *Biometrics* 1996; **52**:673–684.
8. Whitehead J, Zhou Y, Patterson S, Webber D, Francis S. Easy-to-implement Bayesian methods for dose-escalation studies in healthy volunteers. *Biostatistics* 2001; **2**:47–61.
9. Zhou Y, Lucini M. Gaining acceptability for the Bayesian decision-theoretic approach in dose-escalation studies. *Pharmaceutical Statistics* 2005; **4**:161–171.
10. Smith B. Assessment of dose proportionality. In *Pharmacokinetics in drug development*: *clinical study design and analysis*, Bonate P, Howard D (eds). AAPS Press: USA, 2004; pp. 363–382.
11. Sethuraman VS, Leonov S, Squassante L, Mitchell TR, Hale MD. Sample size calculation for the power model for dose proportionality studies. *Pharmaceutical Statistics* 2007; **6**:35–41.
12. Gough K, Hutchison M, Keene O, Byrom B, Ellis S, Lacey L, McKellar J. Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry/pharmaceutics UK joint working party. *Drug Information Journal* 1995; **29**:1039–1048.
13. US Food and Drug Administration (FDA). *Guidance for industry*: *statistical approaches to establishing bioequivalence*. FDA: Rockville, 2001.
14. Committee for Proprietary Medicinal Products (CPMP). *Note for guidance on the investigation of bioavailability and bioequivalence*. EMEA: London, 2001.
15. Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. *Pharmaceutical Research* 2000; **17**:1278–1283.

DOI: 10.1002/pst

16. Surolia I, Reddy GB, Sinha S. Hierarchy and the mechanism of fibril formation in ADan peptides. *Journal of Neurochemistry* 2006; **99**:537–548.
17. Glue P, Fang A, Gandelman K, Klee B. Pharmacokinetics of an extended release formulation of alprazolam (Xanax XR) in healthy normal adolescent and adult volunteers. *American Journal of Therapeutics* 2006; **13**:418–422.
18. Darwish M, Tempero K, Kirby M, Thompson J. Relative bioavailability of the fentanyl effervescent buccal tablet (FEBT) 1,080 pg versus oral transmucosal fentanyl citrate 1,600 pg and dose proportionality of FEBT 270 to 1,300 microg: a single-dose, randomized, open-label, three-period study in healthy adult volunteers. *Clinical Therapeutics* 2006; **28**:715–724.
19. Darwish M, Kirby M, Robertson Jr P, Tracewell W, Jiang JG. Pharmacokinetic properties of fentanyl effervescent buccal tablets: a phase I, open-label, crossover study of single-dose 100, 200, 400, and 800 microg in healthy adult volunteers. *Clinical Therapeutics* 2006; **28**:707–714.
20. Valles J, Artigas R, Crea A, Muller F, Paredes I, Zapata A, Capriati A. Clinical pharmacokinetics of parenteral dexketoprofen trometamol in healthy subjects. *Methods and Findings in Experimental and Clinical Pharmacol*ogy 2006; **28** (Suppl. A): 7–12.
21. Modi NB, Dresser MJ, Simon M, Lin D, Desai D, Gupta S. Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. *Journal of Clinical Pharmacology* 2006; **46**:301–309.
22. Forgue ST, Patterson BE, Bedding AW, Payne CD, Phillips DL, Wrishko RE, Mitchell MI. Tadalafil pharmacokinetics in healthy subjects. *British Journal of Clinical Pharmacology* 2006; **61**:280–288.
23. Ciraulo DA, Hitzemann RJ, Somoza E, Knapp CM, Rotrosen J, Sarid-Segal O, Ciraulo AM, Greenblatt DJ, Chiang CN. Pharmacokinetics and pharmacodynamics of multiple sublingual buprenorphine tablets in dose-escalation trials. *Journal of Clinical Pharmacology* 2006; **46**:179–192.
24. Marmarou A, Guy M, Murphey L, Roy F, Layani L, Combal JP, Marquer C, American Brain Injury Consortium. A single dose, three-arm, placebo-controlled, phase I study of the bradykinin B2 receptor antagonist Anatibant (LF16-0687Ms) in patients with severe traumatic brain injury. *Journal of Neurotrauma* 2005; **22**:1444–1455.
25. Darwish M, Tempero K, Kirby M, Thompson J. Pharmacokinetics and dose proportionality of fentanyl effervescent buccal tablets in healthy volunteers. *Clinical Pharmacokinetics* 2005; **44**: 1279–1286.
26. Clausen SB, Read SC, Tulloch SJ. Single- and multiple-dose pharmacokinetics of an oral mixed amphetamine salts extended-release formulation in adults. *CNS Spectrums* 2005; **10**:6–15.
27. Bronstein M, Musolino N, Jallad R, Cendros JM, Ramis J, Obach R, Leselbaum A, Catus F. Pharmacokinetic profile of lanreotide Autogel in patients with acromegaly after four deep subcutaneous injections of 60, 90 or 120 mg every 28 days. *Clinical Endocrinology* 2005; **63**:514–519.
28. Swaisland HC, Smith RP, Laight A, Kerr DJ, Ranson M, Wilder-Smith CH, Duvauchelle T. Single-dose clinical pharmacokinetic studies of gefitinib. *Clinical Pharmacokinetics* 2005; **44**: 1165–1177.
29. Persiani S, Roda E, Rovati LC, Locatelli M, Giacovelli G, Roda A. Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. *Osteoarthritis Cartilage* 2005; **13**:1041–1049.
30. Budde K, Fritsche L, Waiser J, Glander P, Slowinski T, Neumayer HH, RADW 102 Renal Transplant Study Group. Pharmacokinetics of the immunosuppressant everolimus in maintenance renal transplant patients. *European Journal of Medical Research* 2005; **10**:169–174.
31. Fridberg MJ, Hedner U, Roberts HR, Erhardtsen E. A study of the pharmacokinetics and safety of recombinant activated factor VII in healthy Caucasian and Japanese subjects. *Blood Coagulation and Fibrinolysis* 2005; **16**:259–266.
32. Einecke G, Schutz M, Mai I, Fritsche L, Giessing M, Glander P, Neumayer HH, Budde K. Limitations of C2 monitoring in renal transplant recipients. *Nephrology*, *Dialysis*, *Transplantation* 2005; **20**:1463–1470.
33. Adams MP, Ahdieh H. Single- and multiple-dose pharmacokinetic and dose-proportionality study of oxymorphone immediate-release tablets. *Drugs in R&D* 2005; **6**:91–99.
34. Lennernas B, Hedner T, Holmberg M, Bredenberg S, Nystrom C, Lennernas H. Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: a new approach to treatment of incident pain. *British Journal of Clinical Pharmacology* 2005; **59**:249–253.
35. McEwen J, Salva M, Jansat JM, Cabarrocas X. Pharmacokinetics and safety of oral almotriptan in healthy male volunteers. *Biopharmaceutics and Drug Disposition* 2004; **25**:303–311.
36. Otulana B, Okikawa J, Linn L, Morishige R, Thipphawong J. Safety and pharmacokinetics of inhaled morphine delivered using the AERx system in patients with moderate-to-severe asthma. *International Journal of Clinical Pharmacology Therapeutics* 2004; **42**:456–462.

DOI: 10.1002/pst

37. Cullen E, Liao J, Lukacsko P, Niecestro R, Friedhoff L. Pharmacokinetics and dose proportionality of extended-release metformin following administration of 1000, 1500, 2000 and 2500 mg in healthy volunteers. *Biopharmaceutics and Drug Disposition* 2004; **25**:261–263.
38. Budde K, Neumayer HH, Lehne G, Winkler M, Hauser IA, Lison A, Fritsche L, Soulillou JP, Fauchald P, Dantal J, RADW 102 Renal Transplant Study Group. Tolerability and steady-state pharmacokinetics of everolimus in maintenance renal transplant patients. *Nephrology, Dialysis, Transplantation* 2004; **19**:2606–2614.
39. Rochdi M, Gonzalez MA, Dirksen SJ. Dose-proportional pharmacokinetics of a methylphenidate extended-release capsule. *International Journal of Clinical Pharmacology Therapeutics* 2004; **42**: 285–292.
40. Adams MP, Ahdieh H. Pharmacokinetics and dose-proportionality of oxymorphone extended release and its metabolites: results of a randomized cross-over study. *Pharmacotherapy* 2004; **24**:468–476.
41. Harris DS, Mendelson JE, Lin ET, Upton RA, Jones RT. Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone: lack of dose proportionality. *Clinical Pharmacokinetics* 2004; **43**:329–340.
42. Lin CC, Philips L, Xu C, Yeh LT. Pharmacokinetics and safety of viramidine, a prodrug of ribavirin, in healthy volunteers. *Journal of Clinical Pharmacology* 2004; **44**:265–275.
43. Sobue S, Sekiguchi K, Shimatani K, Tan K. Pharmacokinetics and safety of Fosfluconazole after single intravenous bolus injection in healthy male Japanese volunteers. *Journal of Clinical Pharmacology* 2004; **44**:284–292.
44. Wang LH, Wiznia AA, Rathore MH, Chittick GE, Bakshi SS, Emmanuel PJ, Flynn PM. Pharmacokinetics and safety of single oral doses of emtricitabine in human immunodeficiency virus-infected children. *Antimicrobial Agents and Chemotherapy* 2004; **48**:183–191.
45. Forouzesh B, Takimoto CH, Goetz A, Diab S, Hammond LA, Smetzer L, Schwartz G, Gazak R, Callaghan JT, Von Hoff DD, Rowinsky EK. A phase I and pharmacokinetic study of ILX-295501, an oral diarylsulfonylurea, on a weekly for 3 weeks every 4-week schedule in patients with advanced solid malignancies. *Clinical Cancer Research* 2003; **15**(9):5540–5549.
46. Houwing NS, Maris F, Schnabel PG, Bagchus WM. Pharmacokinetic study in women of three different doses of a new formulation of oral testosterone undecanoate, Andriol Testocaps. *Pharmacotherapy* 2003; **23**:1257–1265.
47. Hossain M, Quebe-Fehling E, Sergejew T, Schmidt G, Skerjanec A, Ibarra de Palacios P, Krinsky L. Dose proportionality study of four doses of an estradiol transdermal system, Estradot. *Maturitas* 2003; **46**:173–185.
48. Martin PD, Warwick MJ, Dane AL, Cantarini MV. A double-blind, randomized, incomplete crossover trial to assess the dose proportionality of rosuvastatin in healthy volunteers. *Clinical Therapeutics* 2003; **25**:2215–2224.
49. Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrobial Agents and Chemotherapy* 2003; **47**:2788–2795.
50. Dandekar PK, Maglio D, Sutherland CA, Nightingale CH, Nicolau DP. Pharmacokinetics of meropenem 0.5 and 2 g every 8 hours as a 3-hour infusion. *Pharmacotherapy* 2003; **23**:988–991.
51. Sathirakul K, Chan C, Teng L, Bergstrom RF, Yeo KP, Wise SD. Olanzapine pharmacokinetics are similar in Chinese and Caucasian subjects. *British Journal of Clinical Pharmacology* 2003; **56**:184–187.
52. Agrawal NG, Porras AG, Matthews CZ, Rose MJ, Woolf EJ, Musser BJ, Dynder AL, Mazina KE, Lasseter KC, Hunt TL, Schwartz JI, McCrea JB, Gottesdiener KM. Single- and multiple-dose pharmacokinetics of etoricoxib, a selective inhibitor of cyclooxygenase-2, in man. *Journal of Clinical Pharmacology* 2003; **43**:268–276.
53. Kantarjian HM, Gandhi V, Kozuch P, Faderl S, Giles F, Cortes J, O'Brien S, Ibrahim N, Khuri F, Du M, Rios MB, Jeha S, McLaughlin P, Plunkett W, Keating M. Phase I clinical and pharmacology study of clofarabine in patients with solid and hematologic cancers. *Journal of Clinical Oncology* 2003; **21**:1167–1173.
54. Zobrist RH, Quan D, Thomas HM, Stanworth S, Sanders SW. Pharmacokinetics and metabolism of transdermal oxybutynin: in vitro and in vivo performance of a novel delivery system. *Pharmaceutical Research* 2003; **20**:103–109.
55. Da Ros L, Squassante L, Milleri S. Dose linearity of lacidipine pharmacokinetics after single and repeated oral doses in healthy volunteers. *Clinical Pharmacokinetics* 2003; **42**:99–106.
56. Nolting A, Abramowitz W. Multiple-dose proportionality study of flunisolide hydrofluoroalkane. *Allergy and Asthma Proceedings* 2002; **23**:311–318.
57. Yates R, Nairn K, Dixon R, Kemp JV, Dane AL. Pharmacokinetics, dose proportionality, and tolerability of single and repeat doses of a nasal spray formulation of zolmitriptan in healthy volunteers. *Journal of Clinical Pharmacology* 2002; **42**: 1244–1250.

DOI: 10.1002/pst

58. Prasad PP, Yeh CM, Gurrieri P, Glazer R, McLeod J. Pharmacokinetics of multiple doses of valsartan in patients with heart failure. *Journal of Cardiovascular Pharmacology* 2002; **40**:801–807.
59. Kienzler JL, Sallin D, Schifflers MH, Ghika A. Pharmacokinetics of mono-3′- and mono-4′-0-(beta-hydroxyethyl)-rutoside derivatives, after single doses of Venoruton powder in healthy volunteers. *European Journal of Clinical Pharmacology* 2002; **58**:395–402.
60. Duijkers IJ, Klipping C, Boerrigter PJ, Machielsen CS, De Bie JJ, Voortman G. Single dose pharmacokinetics and effects on follicular growth and serum hormones of a long-acting recombinant FSH preparation (FSH-CTP) in healthy pituitary-suppressed females. *Human Reproduction* 2002; **17**:1987–1993.
61. Crul M, Rosing H, de Klerk GJ, Dubbelman R, Traiser M, Reichert S, Knebel NG, Schellens JH, Beijnen JH, ten Bokkel Huinink WW. Phase I and pharmacological study of daily oral administration of perifosine (D-21266) in patients with advanced solid tumours. *European Journal of Cancer* 2002; **38**:1615–1621.
62. Lamson M, Phillips G, Shen J, Lukacsko P, Friedhoff L, Niecestro RM. Pharmacokinetics of lovastatin extended-release dosage form (Lovastatin XL) in healthy volunteers. *Biopharmaceutics and Drug Disposition* 2002; **23**:143–149.
63. Timmer CJ, Houwing NS. Dose proportionality of three different doses of tibolone. *Pharmacotherapy* 2002; **22**:6–13.
64. Gupta S, Banfield C, Affrime M, Marco A, Cayen M, Herron J, Padhi D. Desloratadine demonstrates dose proportionality in healthy adults after single doses. *Clinical Pharmacokinetics* 2002; **41**:1–6.
65. Nichols DJ, Muirhead GJ, Harness JA. Comparison of systemic exposure to nemifitide following two methods of subcutaneous administration to healthy volunteers. *Biopharmaceutics and Drug Disposition* 2005; **26**:379–385.
66. Yin Y, Chen C. Optimizing first-time-in-human trial design for studying dose proportionality. *Drug Information Journal* 2001; **35**:1065–1078.
67. Armitage P, Berry G. *Statistical methods in medical research*. Blackwell: Oxford, 1987; p. 153.

DOI: 10.1002/pst